

CLAIMS

What is claimed is:

1. An immune effector cell, wherein the cell produces a composition comprising:
 - (a) one or more tumor cell binding domains or target cell binding domains, and
 - (b) one or more cytokine domains comprising
 - (i) one or more cytokines or one or more functional fragments thereof; or
 - (ii) one or more cytokine receptors or one or more functional fragments thereof;
or
 - (iii) a combination of both (i) and (ii);
 - (c) optionally further comprising one or more antigen receptor target domains;
optionally wherein the cell comprises one or more engineered antigen receptors
against one or more tumor target antigens or target antigens.
2. The cell of claim 1, wherein the one or more tumor cell binding domains comprise an antibody, an antibody fragment or a non-antibody scaffold.
3. The cell of claim 1 or 2, wherein the one or more tumor cell binding domains comprise an scFv.
4. The cell of claim 1, 2, or 3, wherein the one or more tumor cell binding domains target an antigen expressed on the surface of a tumor cell, such as GD2, BCMA, CD56, CD24, L1CAM, GPC2, GPC3, CSPG4, HER2, CD19, CD22, CD30, CD71, B7-H3, B7-H4, PD-L1, or PDL-2.
5. The cell of any one of the preceding claims, wherein said one or more cytokines are selected from the group consisting of IL7, IL12, IL15, IL18, IL27, IL33, IL21 and a combination thereof.
6. The cell of any one of claims 1-5, wherein the cytokine is IL15 and/or the cytokine receptor is IL15R or the alpha subunit thereof (IL15RA).

7. The cell of any one of the preceding claims, wherein the one or more antigen receptor target domains comprise one or more tumor antigens or one or more functional fragments thereof.
8. The cell of claim 7, wherein the composition comprises

one or more tumor cell binding domains targeting a first antigen on the tumor cell and

one or more antigen receptor target domains comprising a second tumor antigen or
functional fragments thereof.
9. The cell of any one of the preceding claims, wherein the one or more antigen receptor target domains comprises CD19.
10. The cell of any one of the preceding claims, wherein the one or more engineered antigen receptors is a non-natural T cell receptor (TCR) or a chimeric antigen receptor (CAR).
11. The cell of any one of the preceding claims, wherein said cell

produces a composition targeting one or more first tumor antigens and comprises one
or more antigen receptors targeting the one or more first tumor antigens;

produces a composition targeting one or more second tumor antigens and comprises
one or more antigen receptors targeting the one or more first tumor antigens; or

produces a composition targeting one or more first tumor antigens, said composition
comprising one or more antigen receptor target domains that are targeted by one
or more antigen receptors expressed on the surface of the cell.
12. The cell of any one of the preceding claims, wherein the one or more tumor cell binding domains and the one or more antigen receptor target domains are linked by a hinge region and/or linker.
13. The cell of claim 12, wherein the hinge region is from IgG1, IgG2, IgG3, or IgG4.
14. The cell of any one of the preceding claims, comprising an expression vector or RNA encoding said composition and optionally said one or more engineered antigen receptors.

15. The cell of claim 14, wherein the expression vector is a viral vector or a non-viral vector.
16. The cell of claim 15, wherein the viral vector is a retroviral, lentiviral, adenoviral, or adeno-associated viral vector.
17. The cell of any one of claims 1-16, wherein the cell is an NK cell, an NKT cell, a T cell, a $\gamma\delta$ T cell, a Mucosal-associated invariant T (MAIT) cell, a macrophage, an innate lymphoid (IL) cell, cytokine-induced killer (CIK) cell, or a mixture thereof.
18. A composition for redirecting cells expressing one or more engineered antigen receptors, comprising:
 - (a) one or more tumor cell binding domains,
 - (b) one or more cytokine domains comprising
 - (i) one or more cytokines or one or more functional fragments thereof; or
 - (ii) one or more cytokine receptors or one or more functional fragments thereof;or
 - (iii) a combination of both (i) and (ii).
19. The composition of claim 18, wherein the composition further comprises (c) one or more antigen receptor target domains.
20. The composition of claim 18 or 19, wherein the one or more cytokine domains in the composition are positioned between the one or more tumor cell binding domains and the one or more antigen receptor domains.
21. A non-natural antigen receptor directed against the composition of any one of claims 18-20.
22. A polynucleotide encoding the composition of any one of claims 18-20.
23. An expression vector comprising the polynucleotide of claim 22.
24. The expression vector of claim 23, further comprising a sequence that encodes one or more antigen receptors.

25. An expression vector encoding:
- (a) a composition comprising:
 - (i) one or more tumor cell binding domains, and
 - (ii) one or more cytokine domains; and
 - (b) one or more antigen receptors.
26. The expression vector of any one of claims 23-25, wherein an IRES element or a 2A sequence is located between the composition and the one or more antigen receptors.
27. The expression vector of any one of claims 23-26, wherein said expression vector is a viral vector or a non-viral vector.
28. The expression vector of claim 27, wherein the viral vector is a retroviral, lentiviral, adenoviral, or adeno-associated viral vector.
29. A cell comprising the expression vector of any one of claims 21-26.
30. A method of treating cancer in an individual, comprising the step of administering to the individual a therapeutically effective amount of the cells of any one of claims 1-17.
31. A method of treating cancer in an individual, comprising administering a therapeutically effective amount of the composition of any one of claims 18-20 and/or a therapeutically effective amount of cells expressing one or more antigen receptors of claim 29.
32. A method of treating cancer in an individual, comprising administering to the individual a therapeutically effective amount of:
- a composition comprising one or more tumor cell binding domains targeting a first or a second antigen on a tumor cell and one or more cytokine domains, and
 - cells expressing one or more antigen receptors against a first antigen on the tumor cell.
33. The method of any one of claims 31-32, wherein the composition and/or the cells are administered to the individual by intraperitoneal or intravenous injection.

34. The method of claims 31-33, wherein a second dose of the composition is administered after an initial dose.

35. The method of any one of claims 30-34, wherein the individual is receiving, has received, and/or will receive an additional cancer therapy.

36. The method of claim 35, wherein the additional cancer therapy is surgery, radiation, chemotherapy, immunotherapy, hormone therapy, or a combination thereof.

37. A pharmaceutical composition comprising the immune effector cell of claims 1-17 or the composition of any one of claims 18-20.

38. A method of adapting a cancer therapy to a cancer expressing a first tumor antigen, comprising the steps of:

(a) providing or obtaining an immune effector cell or plurality thereof comprising one or more non-natural antigen receptors that targets a second tumor antigen; and

(b) providing or obtaining a composition comprising one or more tumor cell binding domains that binds the first tumor antigen and one or more antigen receptor target domains that binds the antigen receptor that targets a second tumor antigen,

optionally wherein the composition comprises (i) one or more cytokines or one or more functional fragments thereof; or (ii) one or more cytokine receptors or one or more functional fragments thereof; or (iii) a combination of both (i) and (ii),

and wherein the providing or obtaining of the composition in step (b) is determined by the presence of expression of the first antigen in the cancer cells of the cancer being treated.

39. A method of adapting a cancer therapy to a cancer expressing a first tumor antigen, comprising the steps of:

(a) providing or obtaining an immune effector cell or plurality thereof comprising one or more non-natural antigen receptors that targets a second tumor antigen; and

(b) transfecting said cells with a polynucleotide that encodes a composition comprising:

- (1) one or more tumor cell binding domains that targets the first antigen, and
 - (2) one or more cytokine domains comprising:
 - (i) one or more cytokines or one or more functional fragments thereof; or
 - (ii) one or more cytokine receptors or one or more functional fragments thereof; or
 - (iii) a combination of both (i) and (ii).
40. An immune effector cell, separately producing proteins comprising:
- (a) one or more engineered antigen receptors against one or more tumor target antigens;
 - (b) one or more recombinant cytokines or one or more functional fragments thereof; and
 - (c) one or more recombinant cytokine receptors or one or more functional fragments thereof.
41. The cell of claim 40, wherein the one or more engineered antigen receptors is a non-natural T cell receptor (TCR) or a chimeric antigen receptor (CAR).
42. The cell of claim 40 or 41, wherein the one or more components are on an expression vector or RNA.
43. The cell of claim 42, wherein the one or more components are provided by the same expression vector or RNA.
44. The cell of claim 43, wherein at least two or more of the components, if provided by the same vector, are separable by a 2A self-cleavage site or an IRES element.
45. The cell of claim 42, wherein the one or more components are provided by a different expression vector or RNA.

46. The cell of claim 45, wherein two or more components are provided on a different expression vector or RNA, and at least two of the components are provided on different types of vectors.

47. The cell of any one of claims 42-45, wherein the expression vector is a viral vector or a non-viral vector.

48. The cell of claim 46, wherein the viral vector is a retroviral, lentiviral, adenoviral, or adeno-associated viral vector.

49. The cell of any one of claims 40-48, wherein the cell is an NK cell, an NKT cell, a T cell, a $\gamma\delta$ T cell, a Mucosal-associated invariant T (MAIT) cell, a macrophage, an innate lymphoid (IL) cell, cytokine-induced killer (CIK) cell, or a mixture thereof.

50. The cell of any one of claims 40-48, wherein the one or more tumor target antigens is GD2, BCMA, CD56, CD24, L1CAM, GPC2, GPC3, CSPG4, HER2, CD19, CD22, CD30, CD71, B7-H3, B7-H4, PD-L1, or PDL-2.

51. The cell of any one of claims 40-50, wherein said one or more cytokines are selected from the group consisting of IL7, IL12, IL15, IL18, IL27, IL33, IL21, and a combination thereof.

52. The cell of any one of claims 40-51, wherein the cytokine is IL-15 and/or the cytokine receptor is IL15R or the alpha subunit thereof (IL15RA).

53. The cell of any one of claims 40-52, wherein the one or more engineered antigen receptors is a chimeric antigen receptor (CAR).

54. The cell of claim 53, wherein the CAR comprises one or more costimulatory domains selected from the group consisting of CD27, CD28, 4-1BB, ICOS, OX40, and a combination thereof.

55. The cell of claim 54, wherein the CAR comprises 4-1BB costimulatory domain.

56. A method of treating cancer in an individual, comprising administering to the individual a therapeutically effective amount of the cells of any one of claims 40-55.

57. The method of claim 56, wherein the cells are administered to the individual by intraperitoneal or intravenous injection.

58. The method of claim 56 or 57, wherein the individual is receiving, has received, and/or will receive an additional cancer therapy.

59. The method of claim 58, wherein the additional cancer therapy is surgery, radiation, chemotherapy, immunotherapy, hormone therapy, or a combination thereof.