[0006] Despite effective localization to the tumor site, the functionality and therapeutic efficacy of NKT cells are inhibited by hypoxic TME. NKT cells can be rescued from hypoxia-mediated suppression by IL-15 so that NKT cells engineered to express IL15 showed increased anti-tumor activity in a NB model in mice (9). Furthermore, NKT cells that co-express a CARGD2 and IL15 in the same construct (CARGD2.IL15) undergo *in vivo* expansion in NB-bearing mice and have a higher anti-tumor activity compared with NKTs expressing either CARGD2 or IL15 alone. In addition, NK cell proliferation, survival, and antibody-mediated cytotoxicity can be increased in the presence of a chimeric protein of the sushi domain of IL15Ra, IL15, and apolipoprotein (10).

[0007] The present disclosure provides solutions to long-felt needs in the art of adoptive immunotherapy for the treatment of cancer.

SUMMARY

[0008] The present disclosure is directed to systems, compositions, and methods that expand the use of engineered immune cells having a receptor that targets an antigen. In particular examples, the disclosure concerns cancer immunotherapy and configuring the immunotherapy with modular molecular adaptors that allow for interchangeable use depending upon the cancer to be treated and its particular expression of tumor antigen(s). In some examples, the disclosure concerns cancer immunotherapy and molecular adaptors that at least in some cases allow for utilizing pre-existing immune effector cells that target a first antigen to also target a second (or more) antigen.

[0008a] In one aspect, the present disclosure refers to 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.

[0008b] In another aspect, the present disclosure refers to 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).

[0009] Examples of the disclosure include the engineering of immune effector cells to express an engineered antigen receptor and to secrete a molecular adaptor with an antigen-cytokine complex for effective cancer immunotherapy. In particular examples, the molecular adaptor in comprising a cytokine domain (cytokine, a cytokine receptor, and/or a cytokine and its receptor) allows for use of immunotherapy in suppressive microenvironments of solid tumors.

[0009a] In another aspect, the present disclosure refers to a non-natural antigen receptor directed against the composition as disclosed herein.

[0010] In a certain example, there is an immune effector cell, wherein the cell produces a molecular adaptor comprising: (a) a tumor cell binding domain, and (b) a cytokine domain comprising (i) a cytokine or a functional fragment thereof; or (ii) a cytokine receptor or a functional fragment thereof; or (iii) a combination of both (i) and (ii); (c) optionally further

comprising an antigen receptor target domain; optionally wherein the cell comprises one or more engineered antigen receptors against one or more tumor target antigens. Thus, the immune effector cell is engineered and therefore non-natural.

[0011] In a certain example, there is an immune effector cell, wherein the cell produces a molecular adaptor comprising: (a) a target cell binding domain, and (b) a cytokine domain comprising (i) a cytokine or a functional fragment thereof; or (ii) a cytokine receptor or a functional fragment thereof; or (iii) a combination of both (i) and (ii); (c) optionally further comprising an antigen receptor target domain; optionally wherein the cell comprises one or more engineered antigen receptors against one or more target antigens. Thus, the immune effector cell is engineered and therefore non-natural.

[0012] In one example, a molecular adaptor is provided that comprises a) a tumor cell binding domain, (b) a cytokine domain comprising (i) a cytokine or a functional fragment thereof; or (ii) a cytokine receptor or a functional fragment thereof; or (iii) a combination of both (i) and (ii), and optionally (c) an antigen receptor target domain. Such molecular adaptors can be provided in combination with engineered immune effector cells comprising one or more engineered antigen receptors against one or more tumor target antigens to improve efficacy of the immunotherapy.

[0013] Examples of the disclosure include an immune effector cell, wherein the cell produces a molecular adaptor comprising: (a) a tumor cell binding domain, and (b) a cytokine domain comprising (i) a cytokine or a functional fragment thereof; or (ii) a cytokine receptor or a functional fragment thereof; or (iii) a combination of both (i) and (ii); (c) optionally (or not) further comprising an antigen receptor target domain; optionally (or not) wherein the cell comprises one or more engineered antigen receptors against one or more tumor target antigens. In specific examples, the tumor cell binding domain comprises an antibody, an antibody fragment or a non-antibody scaffold. The tumor cell binding domain may comprise an scFv. The tumor cell binding domain may target an antigen expressed on the surface of a tumor cell, such as GD2, CD56, CD24, L1CAM, GPC2, GPC3, CSPG4, HER2, CD19, CD22, CD30, CD71, B7-H3, B7-H4, BCMA, PD-L1, or PDL-2. In some cases, the cytokine is selected from the group consisting of IL7, IL12, IL15, IL18, IL27, IL33, IL21, and a combination thereof. In specific cases, the cytokine is IL15 and/or the cytokine receptor is IL15R or the alpha subunit thereof (IL15RA). The antigen receptor target domain may comprise a tumor antigen or a

functional fragment thereof, or the antigen receptor target domain could also be an antigen (or a functional fragment thereof) that is not considered a tumor antigen.

[0014] In particular examples, the molecular adaptor comprises a tumor cell binding domain targeting a first antigen on the tumor cell and an antigen receptor target domain comprising a second tumor antigen or functional fragment thereof. In specific examples, the antigen receptor target domain comprises CD19. Any cell of the disclosure may comprise one or more engineered antigen receptors that are a recombinant T cell receptor (TCR) or a chimeric antigen receptor (CAR). The cell may comprise an engineered TCR by virtue of transduction with a vector that encodes a TCR, including encodes a TCR from a natural source.

[0015] In particular examples, a cell of the disclosure produces a molecular adaptor targeting a first tumor antigen and comprises an antigen receptor targeting a first tumor antigen; produces a molecular adaptor targeting a second tumor antigen and comprises an antigen receptor targeting a first tumor antigen; or produces a molecular adaptor targeting a first tumor antigen, said molecular adaptor comprising an antigen receptor target domain that is targeted by an antigen receptor expressed on the surface of the cell. In specific examples, the tumor cell binding domain and the antigen receptor target domain are linked by a hinge region and/or linker. The hinge region may be from IgG1, IgG2, IgG3, IgG4, or CD8. In specific examples, the cell comprises an expression vector (viral vector or a non-viral vector) or RNA encoding said molecular adaptor and optionally said engineered antigen receptor. Examples of viral vectors include retroviral, lentiviral, adenoviral, or adeno-associated viral vector. Examples of non-viral vectors include plasmids and transposons. In specific examples, the cell is an NK cell, an NKT cell, a T cell, a γδ T cell, a Mucosal-associated invariant T (MAIT) cell, an innate lymphoid (IL) cell, cytokine-induced killer (CIK) cell, macrophage, a stem cell, or a mixture thereof.

[0015a] In another aspect, the present disclosure refers to a polynucleotide encoding the composition as disclosed herein.

[0015b] In another aspect, the present disclosure refers to an expression vector comprising the polynucleotide as disclosed herein. **[0015c]** In another aspect, the present disclosure refers to 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.

[0015d] In another aspect, the present disclosure refers to a cell comprising the expression vector as disclosed herein.

[0016] In one example, there is a molecular adaptor for redirecting cells expressing engineered antigen receptors, comprising: (a) a tumor cell binding domain, (b) a cytokine domain comprising (i) a cytokine or a functional fragment thereof; or (ii) a cytokine receptor or a functional fragment thereof; or (iii) a combination of both (i) and (ii), and (c) an antigen receptor target domain. In specific examples, the cytokine domain in the molecular adaptor is positioned between the tumor cell binding domain and the antigen receptor domain.

[0017] In one example, there is a molecular adaptor for redirecting cells expressing engineered antigen receptors, comprising: (a) a target cell binding domain, (b) a cytokine domain comprising (i) a cytokine or a functional fragment thereof; or (ii) a cytokine receptor or a functional fragment thereof; or (iii) a combination of both (i) and (ii), and (c) an antigen receptor target domain. In specific examples, the cytokine domain in the molecular adaptor is positioned between the target cell binding domain and the antigen receptor domain.

[0018] Examples of the disclosure include non-natural antigen receptors directed against a molecular adaptor encompassed by the disclosure.

[0019] In one example, there is an expression vector encoding a molecular adaptor of the disclosure. In some cases the expression vector comprises sequence that encodes an antigen receptor. Particular examples include an expression vector encoding: a molecular adaptor comprising: (i) a tumor cell binding domain, and (ii) a cytokine domain; and (b) an antigen receptor. In a specific examples, an IRES element or a 2A sequence is located between the molecular adaptor and the antigen receptor. Such an expression vector may be a viral vector (retroviral, lentiviral, adenoviral, or adeno-associated viral vector) or a non-viral vector.

[0020] In one example, there is an expression vector encoding a molecular adaptor of the disclosure. In some cases the expression vector comprises sequence that encodes an antigen receptor. Particular examples include an expression vector encoding: a molecular adaptor comprising: (i) a target cell binding domain, and (ii) a cytokine domain; and (b) an antigen receptor. In a specific examples, an IRES element or a 2A sequence is located between the molecular adaptor and the antigen receptor. Such an expression vector may be a viral vector (retroviral, lentiviral, adenoviral, or adeno-associated viral vector) or a non-viral vector.

[0021] Examples of the disclosure encompass cells comprising an expression vector encompassed by the disclosure.

[0022] In one example, there is a method of treating cancer or other disease (autoimmune disease, for example) in an individual, comprising the step of administering to the individual a therapeutically effective amount of the cells of the disclosure. In cases wherein the disease is not cancer, the disease may have conditions where it is desirable to kill a population of cells that can be targeted through one or more antigens associated with the disease.

[0022a] In another aspect, the present disclosure refers to use of the cells as disclosed herein in the manufacture of a medicament for treating cancer in an individual.

[0022b] In another aspect, the present disclosure refers to use of the composition as disclosed herein and/or cells expressing one or more antigen receptors as disclosed herein in the manufacture of a medicament for treating cancer in an individual.

[0022c] In another aspect, the present disclosure refers to use 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, in the manufacture of a medicament for treating cancer in an individual, wherein the medicament is to be administered with cells expressing one or more antigen receptors against a first antigen on the tumor cell.

[0023] In a particular example, there is a method of treating cancer or other disease in an individual, comprising administering a therapeutically effective amount of a molecular adaptor of the disclosure and/or a therapeutically effective amount of cells expressing an antigen receptor of the disclosure.

[0024] In a certain example, there is a method of treating cancer in an individual, comprising administering to the individual a therapeutically effective amount of: a molecular adaptor comprising a tumor cell binding domain targeting a first or a second antigen on a tumor cell and a cytokine domain, and cells expressing an antigen receptor against a first antigen on the tumor cell. In specific examples, the molecular adaptor and/or the cells are administered to the individual by intraperitoneal or intravenous injection. In some cases, a second dose of the molecular adaptor is administered after the initial dose. The individual may be receiving, has received, and/or will receive an additional cancer therapy. An additional cancer therapy may be surgery, radiation, chemotherapy, immunotherapy, hormone therapy, or a combination thereof.

[0025] In a certain example, there is a method of treating a disease in an individual, comprising administering to the individual a therapeutically effective amount of: a molecular adaptor comprising a target cell binding domain targeting a first or a second antigen on a target cell and a cytokine domain, and cells expressing an antigen receptor against a first antigen on the target cell. In specific examples, the molecular adaptor and/or the cells are administered to the individual by intraperitoneal or intravenous injection. In some cases, a second dose of the molecular adaptor is administered after the initial dose. The individual may be receiving, has received, and/or will receive an additional therapy for the disease.

[0026] In some examples, there is a pharmaceutical composition comprising immune effector cells encompassed herein and/or a molecular adaptor encompassed herein.

[0026a] In another aspect, the present disclosure refers to a pharmaceutical composition comprising the immune effector cell as disclosed herein or the composition as disclosed herein.

[0027] In one example, there is 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 a non-natural antigen receptor that targets a second tumor antigen; and (b) providing or obtaining a molecular adaptor comprising a tumor cell binding domain that binds the first tumor antigen and an antigen receptor target domain that binds the antigen receptor that targets a second tumor antigen, optionally (or not) wherein the molecular adaptor comprises (i) a cytokine or a functional fragment thereof; or (ii) a cytokine receptor or a functional fragment thereof; or (iii) a combination of both (i) and (ii), and wherein

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

[0027a] In another aspect, the present disclosure refers to a method of adapting a cancer therapy to a cancer expressing a first tumor antigen, comprising the steps of:

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

(b) providing 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 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.

[0028] In a certain example, there is 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 a non-natural antigen receptor that targets a second tumor antigen; and (b) transfecting said cells with a polynucleotide that encodes a molecular adaptor comprising: (1) a tumor cell binding domain that targets the first antigen, and (2) a cytokine domain comprising: (i) a cytokine or a functional fragment thereof; or (ii) a cytokine receptor or a functional fragment thereof; or (iii) a combination of both (i) and (ii).

[0028a] In another aspect, the present disclosure refers to a method of adapting a cancer therapy to a cancer expressing a first tumor antigen, comprising the steps of:

(a) providing 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).

[0029] In one example, there is a method of adapting a disease therapy to a diseased cell expressing a first target cell antigen (that may also be the diseased cell antigen), comprising the steps of: (a) providing or obtaining an immune effector cell or plurality thereof comprising a non-natural antigen receptor that targets a second antigen; and (b) providing or obtaining a molecular adaptor comprising a target cell binding domain that binds the first antigen and an antigen receptor target domain that binds the antigen receptor that targets a second antigen, optionally (or not) wherein the molecular adaptor comprises (i) a cytokine or a functional fragment thereof; or (ii) a cytokine receptor or a functional fragment thereof; or (iii) a combination of both (i) and (ii), and wherein the providing or obtaining of the molecular adaptor in step (b) is determined by the presence of expression of the first antigen in the target cells of the disease being treated.

[0030] In a certain example, there is a method of adapting a disease therapy to a cancer expressing a first antigen, comprising the steps of: (a) providing or obtaining an immune effector cell or plurality thereof comprising a non-natural antigen receptor that targets a second antigen; and (b) transfecting said cells with a polynucleotide that encodes a molecular adaptor comprising: (1) a target cell binding domain that targets the first antigen, and (2) a cytokine domain comprising: (i) a cytokine or a functional fragment thereof; or (ii) a cytokine receptor or a functional fragment thereof; or (iii) a combination of both (i) and (ii).

[0031] Examples of the disclosure include immune effector cells and methods of use thereof wherein the cells separately produce or express recombinant cytokine, cytokine receptor, or one or more engineered antigen receptors against one or more tumor target antigens, or a combination of any of these. In these cells, the produced cytokine and cytokine receptor may be

expressed as separate proteins or protein fragments or as a single protein. Such cells may be used in methods of treating individuals for cancers, including cancers with cells that express the tumor target antigen(s).

[0031a] In another aspect, the present disclosure refers to 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.

[0032] The foregoing has outlined rather broadly the features and technical advantages of the present disclosure in order that the detailed description of the disclosure that follows may be better understood. Additional features and advantages of the disclosure will be described hereinafter which form the subject of the claims of the disclosure. It should be appreciated by those skilled in the art that the conception and specific example disclosed may be readily utilized as a basis for modifying or designing other structures for carrying out the same purposes of the present disclosure. It should also be realized by those skilled in the art that such equivalent constructions do not depart from the spirit and scope of the disclosure as set forth in the appended claims. The novel features which are believed to be characteristic of the disclosure, both as to its organization and method of operation, together with further objects and advantages will be better understood from the following description when considered in connection with the accompanying figures. It is to be expressly understood, however, that each of the figures is provided for the purpose of illustration and description only and is not intended as a definition of the limits of the present disclosure.

BRIEF DESCRIPTION OF THE DRAWINGS

[0033] For a more complete understanding of the present disclosure, reference is now made to the following descriptions taken in conjunction with the accompanying drawing, in which:

[0034] FIG. 1. Schematic Diagram of Examples of Molecular Adaptor Constructs: "FMC63 scFv" is an anti-CD19 scFv domain, "CD8 H-TM" is the human CD8 hinge region and CD8 transmembrane domain, "CD28" is the costimulatory domain from CD28, "CD3ζ" is the CD3ζ T-cell activation domain, "14g2a scFv" is an anti-GD2 scFv domain, "IgG4 H" is the hinge region from human IgG4, "P2A" is the self-cleaving viral P2A sequence, "CAR19" is the full length CD19 CAR construct shown at the top of the Figure, "CD19 extracellular" is the human CD19 extracellular domain or antigen for the CAR19, "Linker 1" is a 20 amino acid linker, "IL15" is human IL15, "Linker 2" is a 26 amino acid linker, "IL15Ra" is the human IL15 receptor alpha subunit, "T2A" is the self-cleaving viral T2A sequence, "5' LTR is the 5' long terminal repeat; and "3' LTR" is the 3' long terminal repeat;

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 anyone 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 γδ 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. Use of the cells of any one of claims 1-17 in the manufacture of a medicament for treating cancer in an individual.

31. Use of the composition of any one of claims 18-20 and/or cells expressing one or more antigen receptors of claim 29 in the manufacture of a medicament for treating cancer in an individual.

32. Use 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, in the manufacture of a medicament for treating cancer in an individual, wherein the medicament is to be administered with cells expressing one or more antigen receptors against a first antigen on the tumor cell.

33. The use of any one of claims 31-32, wherein the composition and/or the cells are to be administered to the individual by intraperitoneal or intravenous injection.

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

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

36. The use 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 an immune effector cell or plurality thereof comprising one or more non-natural antigen receptors that targets a second tumor antigen; and

(b) providing 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 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 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 γδ 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. Use of the cells of any one of claims 40-55 in the manufacture of a medicament for treating cancer in an individual.

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

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

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