

SUMMARY

[0007] Examples of the disclosure include methods and compositions related to cell therapy for a mammalian individual in need thereof. The cell therapy includes cells that are engineered by the hand of man to be effective as a therapy for a medical condition, such as cancer. The cell therapy includes immune effector cells, such as T cells or NK cells that have a receptor that targets an antigen, and the receptor may be endogenous and native to the cell or may be engineered by the hand of man. In certain examples, the cells of the cell therapy are modified to express a protein that enhances the efficacy of the cells for the therapy, and in particular the cells also express a receptor (native to the cell or not) that targets a particular antigen. The antigen to which the receptor is targeted is a cancer antigen, in specific examples. Although the receptor is a T cell receptor (TCR) in at least some cases, in alternative cases the receptor is a chimeric antigen receptor (CAR), or the cell may express both.

[0008] In particular examples, the protein that enhances the efficacy of the cells for the therapy is cluster of differentiation 8 (CD8) comprising CD8- α and/or CD8- β chain. T cells are modified to express CD8 $\alpha\beta$ whether or not they are CD4+ T cells or CD8+ T cells. For CD8+ T cells, the increase in level of expression of CD8 $\alpha\beta$ co-receptor in the CD8+ T cells enhances the ability of native TCRs in the cells to be effective and also enhances the ability of engineered TCRs in transgenic CD8+ T cells to be effective. In cases wherein CD4+ T cells, which are naturally helper T cells, are modified to express CD8 $\alpha\beta$, the transgenic expression allows the CD4+ T cells also to have cytotoxic activity.

[0008a] In one aspect, the present disclosure refers to use of one or both of the following: CD8+ cells that express an exogenous CD8 $\alpha\beta$ co-receptor and optionally express one or more exogenous engineered antigen receptors; and CD4+ cells that express an exogenous CD8 $\alpha\beta$ co-receptor and one or more exogenous engineered antigen receptors, in the manufacture of a medicament for enhancing an immune effector cell therapy for an individual.

[0009] Examples of the disclosure include methods of enhancing an immune effector cell therapy for an individual, comprising the steps of: providing to the individual an effective amount of one or both of the following: CD8+ cells that express an exogenous CD8 $\alpha\beta$ co-receptor and optionally express one or more exogenous engineered antigen receptors; and CD4+ cells that express an exogenous CD8 $\alpha\beta$ co-receptor and one or more exogenous engineered antigen receptors. In specific cases, the engineered antigen receptor is a T cell receptor (TCR), a chimeric antigen receptor (CAR) or both. The CD8+ cells, CD4+ cells, or both may be autologous or allogeneic with respect to the individual. In some cases, the exogenous engineered antigen receptor and the exogenous CD8 $\alpha\beta$ co-receptor are expressed from the same vector in the cells, and the vector may comprise one or more expression constructs that separately express the exogenous engineered antigen receptor and the exogenous CD8 $\alpha\beta$ co-receptor. In specific

examples, the expression construct that expresses the exogenous engineered antigen receptor and the expression construct that expresses the exogenous CD8 $\alpha\beta$ co-receptor are separated by a 2A element or an IRES element. In some cases, the exogenous engineered antigen receptor and the exogenous CD8 $\alpha\beta$ co-receptor are expressed from different vectors in the cells. In any case, the vector may be a viral vector (adenoviral vector, an adeno-associated viral vector, a retroviral vector, or a lentiviral vector) or non-viral vector.

[0010] In particular examples of the method, the antigen is a tumor antigen or a pathogen antigen. Examples of tumor antigens include those selected from the group consisting of survivin, PRAME, CD 19, CD20, CD22, Kappa or light chain, CD30, CD33, CD 123, CD38, ROR1, ErbB2, ErbB3/4, EGFR vIII, carcinoembryonic antigen, EGP2, EGP40, mesothelin, TAG72, PSMA, NKG2D ligands, B7-H6, IL-13 receptor cc2, IL-11 receptor R a, MUC1, MUC16, CA9, GD2, GD3, HMW-MAA, CD171, Lewis Y, G250/CAIX, HLA-AI MAGE A1, HLA-A2 NY-ESO-1, PSC1, folate receptor- a, CD44v7/8, 8H9, NCAM, VEGF receptors, 5T4, Fetal AchR, NKG2D ligands, HER2, BCMA, CD44v6, and a combination thereof.

[0011] Methods of the disclosure may further comprise the step of providing to the individual an effective amount of the CD4+ T cells, the CD8+ T cells, or a mixture thereof. In such cases, the method may further comprise the step of providing to the individual an additional cancer therapy.

[0012] In another aspect, the present disclosure refers to a method of producing a CD4+ T cell having cytotoxic effector cell function and helper function, comprising the step of transfecting the CD4+ T cell with an exogenous CD8 $\alpha\beta$ co-receptor and an exogenous engineered antigen receptor. The engineered antigen receptor may be a T cell receptor (TCR), a chimeric antigen receptor (CAR) or both. The exogenous engineered antigen receptor and the exogenous CD8 $\alpha\beta$ co-receptor may or may not be expressed from the same vector in the cells. In particular, the vector comprises one or more expression constructs that separately express the exogenous engineered antigen receptor and the exogenous CD8 $\alpha\beta$ co-receptor. The expression construct that expresses the exogenous engineered antigen receptor and the expression construct that expresses the exogenous CD8 $\alpha\beta$ co-receptor may be separated by a 2A element or an IRES element. Vectors include viral vectors (adenoviral vector, an adeno-associated viral vector, a retroviral vector, or a lentiviral vector) or non-viral vectors.

[0013] The antigen may be a tumor antigen or a pathogen antigen. In some cases, the tumor antigen is selected from the group consisting of survivin, PRAME, CD 19, CD20, CD22, Kappa or light chain, CD30, CD33, CD 123, CD38, ROR1, ErbB2, ErbB3/4, EGFR vIII, carcinoembryonic antigen, EGP2, EGP40, mesothelin, TAG72, PSMA, NKG2D ligands, B7-H6, IL-13 receptor cc2, IL-11 receptor R a, MUC1, MUC16, CA9, GD2, GD3, HMW-MAA, CD171, Lewis Y, G250/CAIX, HLA-AI MAGE A1, HLA-A2 NY-ESO-1, PSC1, folate receptor-a, CD44v7/8, 8H9, NCAM, VEGF receptors, 5T4, Fetal AchR, NKG2D ligands, HER2, BCMA, CD44v6, and a combination thereof.

[0014] Methods of the disclosure may further comprise the step of providing to the individual an effective amount of the CD4+ T cells to an individual in need thereof, such as one who has cancer. An effective amount of CD8+ T cells expressing an exogenous CD8 $\alpha\beta$ co-receptor, an exogenous engineered antigen receptor, or both may be provided to the individual, the individual may also be receiving an additional cancer therapy.

[0014a] In yet another aspect, the present disclosure refers to use of the CD4+ T cells produced by the methods as disclosed herein, in the manufacture of a medicament for providing an effective amount of the CD4+ T cells to an individual in need thereof.

[0015] In yet another aspect, the present disclosure refers to a method of enhancing cytotoxicity of CD8+ T cells, comprising the step of transfecting the CD8+ T cell with an exogenous CD8 $\alpha\beta$ co-receptor. The CD8+ T cells may also express an exogenous engineered antigen receptor, such as a T cell receptor (TCR), a chimeric antigen receptor (CAR) or both. The exogenous engineered antigen receptor and the exogenous CD8 $\alpha\beta$ co-receptor are expressed from the same vector in the cells. The vector may comprise one or more expression constructs that separately express the exogenous engineered antigen receptor and the exogenous CD8 $\alpha\beta$ co-receptor. In some cases, the expression construct that expresses the exogenous engineered antigen receptor and the expression construct that expresses the exogenous CD8 $\alpha\beta$ co-receptor are separated by a 2A element or an IRES element. The exogenous engineered antigen receptor and the exogenous CD8 $\alpha\beta$ co-receptor may be expressed from different vectors in the cells. Viral vectors (adenoviral vector, an adeno-associated viral vector, a retroviral vector, or a lentiviral vector) or non-viral vectors may be utilized.

[0015a] In yet another aspect, the present disclosure refers to use of the CD8+ T cells whose cytotoxicity is enhanced by the methods as disclosed herein, in the manufacture of a medicament for providing an effective amount of the CD8+ T cells to an individual in need thereof.

[0016] Antigens include tumor antigens or pathogen antigens. Tumor antigens include those selected from the group consisting of CD 19, CD20, CD22, Kappa or light chain, CD30, CD33, CD 123, CD38, ROR1, ErbB2, ErbB3/4, EGFR vIII, carcinoembryonic antigen, EGP2, EGP40, mesothelin, TAG72, PSMA, NKG2D ligands, B7-H6, IL-13 receptor cc2, IL-11 receptor R a, MUC1, MUC16, CA9, GD2, GD3, HMW-MAA, CD171, Lewis Y, G250/CAIX,

HLA-AI MAGE A1, HLA-A2 NY-ESO-1, PSC1, folate receptor- a, CD44v7/8, 8H9, NCAM, VEGF receptors, 5T4, Fetal AchR, NKG2D ligands, HER2, BCMA, CD44v6, and a combination thereof. The method may further comprise the step of providing to the individual an effective amount of the CD8+ T cells to an individual in need thereof. The method may further comprise the step of providing to the individual an effective amount of CD4+ T cells to an individual in need thereof. The CD4+ T cells may be engineered to express an exogenous CD8 $\alpha\beta$ co-receptor, an exogenous engineered antigen receptor, or both. The individual may have cancer, and the method may further comprise the step of providing to the individual an additional cancer therapy.

[0017] In yet another aspect, the present disclosure refers to a composition comprising CD4+ T cells transgenically expressing CD8 $\alpha\beta$ co-receptor. The CD4+ T cells may also transgenically express one or more exogenous engineered antigen receptors, such as a TCR, a CAR, or both. The composition may further comprise CD8+ T cells of any kind, including CD8+ T cells that transgenically express CD8 $\alpha\beta$ co-receptor, one or more exogenous engineered antigen receptors, or both.

[0018] In yet another aspect, the present disclosure refers to a composition comprising CD8+ T cells transgenically expressing CD8 $\alpha\beta$ co-receptor and optionally one or more exogenous engineered antigen receptors. The engineered antigen receptor may be a TCR, a CAR, or both. The composition may further comprise CD4+ T cells of any kind, including CD4+ T cells that transgenically express CD8 $\alpha\beta$ co-receptor, one or more exogenous engineered antigen receptors, or both.

[0019] It is specifically contemplated that any limitation discussed with respect to one example of the disclosure may apply to any other example of the disclosure. Furthermore, any composition of the disclosure may be used in any method of the disclosure, and any method of the disclosure may be used to produce or to utilize any composition of the disclosure. Aspects of an example set forth in the Examples are also examples that may be implemented in the context of examples discussed elsewhere in a different Example or elsewhere in the application, such as in the Summary of Disclosure, Detailed Description of the Examples, Claims, and description of Figure Legends.

[0020] The foregoing has outlined rather broadly the features and technical advantages of the present disclosure in order that the detailed description that follows may be better understood. Additional features and advantages will be described hereinafter which form the subject of the claims herein. It should be appreciated by those skilled in the art that the conception and specific examples disclosed may be readily utilized as a basis for modifying or designing other structures for carrying out the same purposes of the present designs. It should also be realized by those skilled in the art that such equivalent constructions do not depart from the spirit and scope as set forth in the appended claims. The novel features which are believed to be characteristic of the designs disclosed herein, both as to the 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. Additional objects, features, aspects and advantages of the present disclosure will be set forth in part in the description which follows, and in part will be obvious from the description or may be learned by practice of the disclosure. Various examples of the disclosure will be described in sufficient detail to enable those skilled in the art to practice the disclosure, and it is to be understood that other examples may be utilized and that changes may be made without departing from the scope of the disclosure. The following detailed description is, therefore, not to be taken in a limiting sense, and the scope of the present disclosure is best defined by the appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0021] 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:

[0022] **FIGS. 1A-1E: CD4⁺ T cells convert to a hybrid phenotype upon transduction with a class I TCR and CD8 $\alpha\beta$.** (FIG. 1A) Schemes of retroviral vectors. (FIG. 1B) Transduction efficiency of CD4⁺ (red squares) or CD8⁺ (black circles) T cells with TCR or T8 vectors compared to NT controls, n=6. Representative histograms of CD8 α expression (FIG. 1C), CD8 β expression (FIG. 1D) and survivin LML dextramer staining (FIG. 1E) in CD4⁺ and CD8⁺ T cells (upper panels), and MFI summaries (lower panels), n=5-7 donors. (FIGS. 1C, 1D,

CLAIMS

What is claimed is:

1. Use of one or both of the following:

CD8+ cells that express an exogenous CD8 $\alpha\beta$ co-receptor and optionally express one or more exogenous engineered antigen receptors; and

CD4+ cells that express an exogenous CD8 $\alpha\beta$ co-receptor and one or more exogenous engineered antigen receptors, in the manufacture of a medicament for enhancing an immune effector cell therapy for an individual.

2. The use of claim 1, wherein the engineered antigen receptor is a T cell receptor (TCR), a chimeric antigen receptor (CAR) or both.

3. The use of claim 1 or 2, wherein the CD8+ cells, CD4+ cells, or both are autologous with respect to the individual.

4. The use of claim 1 or 2, wherein the CD8+ cells, CD4+ cells, or both are allogeneic with respect to the individual.

5. The use of any one of claims 2-4, wherein the exogenous engineered antigen receptor and the exogenous CD8 $\alpha\beta$ co-receptor are expressed from the same vector in the cells.

6. The use of claim 5, wherein the vector comprises one or more expression constructs that separately express the exogenous engineered antigen receptor and the exogenous CD8 $\alpha\beta$ co-receptor.

7. The use of claim 6, wherein the expression construct that expresses the exogenous engineered antigen receptor and the expression construct that expresses the exogenous CD8 $\alpha\beta$ co-receptor are separated by a 2A element or an IRES element.

8. The use of any one of claims 2-4, wherein the exogenous engineered antigen receptor and the exogenous CD8 $\alpha\beta$ co-receptor are expressed from different vectors in the cells.

9. The use of any one of claims 5-8, wherein the vector is a viral vector or non-viral vector.

10. The use of claim 9, wherein the viral vector is an adenoviral vector, an adeno-associated viral vector, a retroviral vector, or a lentiviral vector.
11. The use of any one of claims 1-10, wherein the antigen is a tumor antigen.
12. The use of claim 11, wherein the tumor antigen is selected from the group consisting of survivin, PRAME, CD 19, CD20, CD22, Kappa or light chain, CD30, CD33, CD 123, CD38, ROR1, ErbB2, ErbB3/4, EGFR vIII, carcinoembryonic antigen, EGP2, EGP40, mesothelin, TAG72, PSMA, NKG2D ligands, B7-H6, IL-13 receptor cc2, IL-11 receptor R a, MUC1, MUC16, CA9, GD2, GD3, HMW-MAA, CD171, Lewis Y, G250/CAIX, HLA-AI MAGE A1, HLA-A2 NY-ESO-1, PSC1, folate receptor- a, CD44v7/8, 8H9, NCAM, VEGF receptors, 5T4, Fetal AchR, NKG2D ligands, HER2, BCMA, CD44v6, and a combination thereof.
13. The use of any one of claims 1-12, wherein the CD4+ T cells, the CD8+ T cells, or a mixture thereof are to be further provided to the individual.
14. The use of claim 13, wherein an additional cancer therapy is to be further provided to the individual.
15. A method of producing a CD4+ T cell having cytotoxic effector cell function and helper function, comprising the step of transfecting the CD4+ T cell with an exogenous CD8 $\alpha\beta$ co-receptor and an exogenous engineered antigen receptor.
16. The method of claim 15, wherein the engineered antigen receptor is a T cell receptor (TCR), a chimeric antigen receptor (CAR) or both.
17. The method of claim 15 or 16, wherein the exogenous engineered antigen receptor and the exogenous CD8 $\alpha\beta$ co-receptor are expressed from the same vector in the cells.
18. The method of claim 17, wherein the vector comprises one or more expression constructs that separately express the exogenous engineered antigen receptor and the exogenous CD8 $\alpha\beta$ co-receptor.
19. The method of claim 18, wherein the expression construct that expresses the exogenous engineered antigen receptor and the expression construct that expresses the exogenous CD8 $\alpha\beta$ co-receptor are separated by a 2A element or an IRES element.

20. The method of claim 15 or 16, wherein the exogenous engineered antigen receptor and the exogenous CD8 $\alpha\beta$ co-receptor are expressed from different vectors in the cells.
21. The method of any one of claims 17-20, wherein the vector is a viral vector or non-viral vector.
22. The method of claim 21, wherein the viral vector is an adenoviral vector, an adeno-associated viral vector, a retroviral vector, or a lentiviral vector.
23. The method of any one of claims 15-22, wherein the antigen is a tumor antigen.
24. The method of claim 23, wherein the tumor antigen is selected from the group consisting of survivin, PRAME, CD 19, CD20, CD22, Kappa or light chain, CD30, CD33, CD 123, CD38, ROR1, ErbB2, ErbB3/4, EGFR vIII, carcinoembryonic antigen, EGP2, EGP40, mesothelin, TAG72, PSMA, NKG2D ligands, B7-H6, IL-13 receptor cc2, IL-11 receptor R a, MUC1, MUC16, CA9, GD2, GD3, HMW-MAA, CD171, Lewis Y, G250/CAIX, HLA-AI MAGE A1, HLA-A2 NY-ESO-1, PSC1, folate receptor- a, CD44v7/8, 8H9, NCAM, VEGF receptors, 5T4, Fetal AchR, NKG2D ligands, HER2, BCMA, CD44v6, and a combination thereof.
25. Use of the CD4+ T cells produced by the method of any one of claims 15-24, in the manufacture of a medicament for providing an effective amount of the CD4+ T cells to an individual in need thereof.
26. The use of claim 25, wherein the individual has cancer.
27. The use of claim 25 or 26, wherein CD8+ T cells expressing an exogenous CD8 $\alpha\beta$ co-receptor, an exogenous engineered antigen receptor, or both are to be provided to the individual.
28. The use of claim 25, 26, or 27, wherein an additional cancer therapy is to be further provided to the individual.
29. A method of enhancing cytotoxicity of CD8+ T cells, comprising the step of transfecting the CD8+ T cell with an exogenous CD8 $\alpha\beta$ co-receptor.
30. The method of claim 29, wherein the CD8+ T cells also express an exogenous engineered antigen receptor.

31. The method of claim 30, wherein the engineered antigen receptor is a T cell receptor (TCR), a chimeric antigen receptor (CAR) or both.

32. The method of claim 30 or 31, wherein the exogenous engineered antigen receptor and the exogenous CD8 α β co-receptor are expressed from the same vector in the cells.

33. The method of claim 32, wherein the vector comprises one or more expression constructs that separately express the exogenous engineered antigen receptor and the exogenous CD8 α β co-receptor.

34. The method of claim 33, wherein the expression construct that expresses the exogenous engineered antigen receptor and the expression construct that expresses the exogenous CD8 α β co-receptor are separated by a 2A element or an IRES element.

35. The method of claim 30 or 31, wherein the exogenous engineered antigen receptor and the exogenous CD8 α β co-receptor are expressed from different vectors in the cells.

36. The method of any one of claims 32-35, wherein the vector is a viral vector or non-viral vector.

37. The method of claim 36, wherein the viral vector is an adenoviral vector, an adeno-associated viral vector, a retroviral vector, or a lentiviral vector.

38. The method of any one of claims 30-37, wherein the antigen is a tumor antigen.

39. The method of claim 38, wherein the tumor antigen is selected from the group consisting of CD 19, CD20, CD22, Kappa or light chain, CD30, CD33, CD 123, CD38, ROR1, ErbB2, ErbB3/4, EGFR vIII, carcinoembryonic antigen, EGP2, EGP40, mesothelin, TAG72, PSMA, NKG2D ligands, B7-H6, IL-13 receptor cc2, IL-11 receptor R a, MUC1, MUC16, CA9, GD2, GD3, HMW-MAA, CD171, Lewis Y, G250/CAIX, HLA-AI MAGE A1, HLA-A2 NY-ESO-1, PSC1, folate receptor- a, CD44v7/8, 8H9, NCAM, VEGF receptors, 5T4, Fetal AchR, NKG2D ligands, HER2, BCMA, CD44v6, and a combination thereof.

40. Use of the CD8+ T cells whose cytotoxicity is enhanced by the method of any one of claims 29-39, in the manufacture of a medicament for providing an effective amount of the CD8+ T cells to an individual in need thereof.

41. The use of claim 40, wherein CD4+ T cells are to be further provided to the individual in need thereof.
42. The use of claim 40, wherein the CD4+ T cells are engineered to express an exogenous CD8 $\alpha\beta$ co-receptor, an exogenous engineered antigen receptor, or both.
43. The use of any one of claims 40-42, wherein the individual has cancer.
44. The use of claim 43, wherein an additional cancer therapy is to be further provided to the individual.
45. A composition comprising CD4+ T cells transgenically expressing CD8 $\alpha\beta$ co-receptor.
46. The composition of claim 45, wherein the CD4+ T cells also transgenically express one or more exogenous engineered antigen receptors.
47. The composition of claim 46, wherein the engineered antigen receptor is a TCR, a CAR, or both.
48. The composition of any one of claims 45-47, wherein the composition further comprises CD8+ T cells.
49. The composition of claim 48, wherein the CD8+ T cells transgenically express CD8 $\alpha\beta$ co-receptor, one or more exogenous engineered antigen receptors, or both.
50. A composition comprising CD8+ T cells transgenically expressing CD8 $\alpha\beta$ co-receptor and optionally one or more exogenous engineered antigen receptors.
51. The composition of claim 50, wherein the engineered antigen receptor is a TCR, a CAR, or both.
52. The composition of claim 50 or 51, wherein the composition further comprises CD4+ T cells.
53. The composition of claim 52, wherein the CD4+ T cells transgenically express CD8 $\alpha\beta$ co-receptor, one or more exogenous engineered antigen receptors, or both.