iNKT cell, B cell, regulatory T cell, monocyte, macrophage, dendritic cell, or mesenchymal stromal cell. The cell may or may not express one or more exogenously provided cytokines, such as IL-15, IL-12, IL-18, IL-21 or combination thereof. The cytokine may or may not be encoded from the same vector as the TNF-alpha mutant gene. In specific cases, the cytokine is expressed as a separate polypeptide molecule as the TNF-alpha mutant and as an engineered receptor of the cell.

[0009] In particular examples of the disclosure, the TNF-alpha mutant polypeptide comprises SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:39. The TNF-alpha mutant polypeptide may be encoded by a sequence that comprises SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, or SEQ ID NO:38. In certain examples, the TNF-alpha mutant polypeptide lacks one or more further mutations that prevent binding of the TNF-alpha mutant polypeptide to a TNF receptor.

[0010] Examples of the disclosure include methods of inducing death for a transduced cell expressing at least an engineered nonsecretable TNF-alpha mutant polypeptide and optionally expressing a therapeutic gene, such as an engineered receptor, the methods comprising the step of providing an effective amount of at least one agent that binds the TNF-alpha mutant on the transduced cell. ~~In another aspect, the present disclosure refers to an *in vitro* method of inducing death for a transduced cell expressing an engineered nonsecretable TNF-alpha mutant polypeptide, comprising the step of providing an effective amount of at least one agent that binds the TNF-alpha mutant on the transduced cell. In another aspect, the present disclosure refers to use of at least one agent that binds an engineered nonsecretable TNF-alpha mutant polypeptide on a transduced cell in the manufacture of a medicament for inducing death for the transduced cell expressing the TNF-alpha mutant polypeptide.~~ An agent that binds TNF-alpha may be an antibody, small molecule, polypeptide, nucleic acid, or combination thereof, for example. When the agent is an antibody, the antibody may be of any kind, including at least a monoclonal antibody. In the methods, the cell may further express an engineered receptor, including a T-cell receptor, a chimeric antigen receptor (CAR), cytokine receptor, homing receptor, or chemokine receptor. Any of the engineered receptors may bind a cancer or other antigen. In specific cases, the method occurs *in vivo* in an individual with a medical condition and when the individual has been provided a therapy for the medical condition that comprises a plurality of the transduced cells. Although the medical condition may be of any kind, in specific cases the medical condition is cancer. The agent may be provided to the individual upon onset of one or more adverse events from the therapy or when an adverse event is suspected of occurring. The individual may exhibit one or more symptoms of cytokine release syndrome, neurotoxicity, anaphylaxis/allergy, and/or on-target/off tumor toxicity. In some cases, the individual has been provided, is provided, and/or will be provided an additional therapy for the medical condition. In particular examples of the disclosure, the TNF-alpha mutant polypeptide lacks or comprises one or more further mutations

that prevent binding of the TNF-alpha mutant polypeptide to a TNF receptor or prevents reverse signaling.

[0011] Examples of the disclosure include methods of reducing the effects of cytokine release syndrome in an individual that has received and/or who is receiving cell therapy with cells that express a nonsecretable TNF-alpha mutant, comprising the step of providing an effective amount of one or more agents that bind the mutant to cause in the individual (a) elimination of at least some of the cells of the cell therapy; and (b) reduction in the level of soluble TNF-alpha.

~~**[0011a]** In another aspect, the present disclosure refers to use of one or more agents that bind a nonsecretable TNF-alpha mutant in the manufacture of a medicament, for reducing the effects of cytokine release syndrome in an individual who has received and/or who is receiving cell therapy with cells that express the TNF-alpha mutant, to cause in the individual (a) elimination of at least some of the cells of the cell therapy; and (b) reduction in the level of soluble TNF-alpha.~~

[0012] Examples of the disclosure include methods of reducing the risk of toxicity of a cell therapy for an individual, comprising the step of modifying the cells of the cell therapy to express a nonsecretable TNF-alpha mutant. The cell therapy may be for cancer, for example. The cell therapy may comprise an engineered receptor that targets an antigen.

~~**[0012a]** In another aspect, the present disclosure refers to an *in vitro* method of reducing the risk of toxicity of a cell therapy for an individual, comprising the step of modifying the cells of the cell therapy to express a nonsecretable TNF-alpha mutant.~~

~~**[0012b]** In another aspect, the present disclosure refers to use of cells of a cell therapy modified to express a nonsecretable TNF-alpha mutant in the manufacture of a medicament for reducing the risk of toxicity of the cell therapy for an individual.~~

[0013] In another ~~aspect~~example, the present disclosure refers to a vector, comprising a sequence that encodes a nonsecretable TNF-alpha mutant and that encodes an engineered receptor. The nonsecretable TNF-alpha mutant and the engineered receptor may or may not be encoded from the vector as separate polypeptides. In specific cases, sequence of the vector that encodes the nonsecretable TNF-alpha mutant and sequence of the vector that encodes the engineered receptor are separated on the vector by a 2A element or an IRES element. The vector may or may not further encode a cytokine, such as IL-15, IL-12, IL-18, IL-2, IL-7, or IL-21. The cytokine may be expressed from the vector as a separate polypeptide as the TNF-alpha mutant and the engineered receptor.

[0014] Examples of the disclosure include compositions of matter including a nucleic acid sequence comprising SEQ ID NO:15 or SEQ ID NO:16.

[0014a] In another aspect, the present disclosure refers to as a composition of matter, a nucleic acid sequence comprising SEQ ID NO:15.

[0014b] In another aspect, the present disclosure refers to as a composition of matter, a nucleic acid sequence comprising SEQ ID NO:16.

[0015] 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 Brief Summary, Detailed Description, Claims, and Brief Description of Drawings.

CLAIMS

What is claimed is:

1. A composition comprising a transduced cell comprising a nucleic acid that encodes one or more engineered nonsecretable tumor necrosis factor (TNF)-alpha mutant polypeptides and a nucleic acid that encodes one or more therapeutic gene products.

2. The composition of claim 1, wherein the TNF-alpha mutant polypeptide comprises a deletion with respect to SEQ ID NO:8 of the following:

amino acid residue 1 and amino acid residue 12;

amino acid residue 1 and amino acid residue 13;

amino acid residues 1-12;

amino acid residues 1-13; or

amino acid residues -1 to 13.

3. The composition of claim 1 or 2, wherein the therapeutic gene product is an engineered receptor.

4. The composition of any one of claims 1, 2, or 3, wherein the engineered receptor is a T-cell receptor, chimeric antigen receptor (CAR), cytokine receptor, homing receptor, or chemokine receptor.

5. The composition of claim 3 or 4, wherein the engineered receptor targets a cancer antigen.

6. The composition of any one of claims 3-5, wherein the engineered receptor is a CAR that comprises one or more costimulatory domains.

7. The composition of claim 6, wherein the one or more costimulatory domains comprises the costimulatory domain of CD28, DAP12, CD137 (4-1BB), CD134 (OX40), Dap10, CD27, CD2, CD5, ICAM-1, LFA-1 (CD11a/CD18), Lck, TNFR-I, TNFR-II, Fas, CD30, CD40 or a combination thereof.

8. The composition of any one of claims 1-7, wherein the nucleic acid that encodes the TNF-alpha mutant polypeptide and the nucleic acid that encodes the therapeutic gene product are within the same nucleic acid molecule.

9. The composition of any one of claims 1-7, wherein the nucleic acid that encodes the TNF-alpha mutant polypeptide and the nucleic acid that encodes the therapeutic gene product are ~~different~~ not within the same nucleic acid molecule~~s~~.

10. The composition of claim 8 or 9, wherein the nucleic acid molecule is a vector.

11. The composition of claim 10, wherein the vector is a viral vector or a non-viral vector.

12. The composition of claim 11, wherein the viral vector is a retroviral vector, lentiviral vector, adenoviral vector, or adeno-associated viral vector.

13. The composition of claim 11, wherein the non-viral vector is a plasmid, lipid, or transposon.

14. The composition of any one of claims 1-13, wherein the cell is an immune cell or a stem cell.

15. The composition of claim 14, wherein the immune cell is a T cell, a NK cell, NKT cell, iNKT cell, B cell, regulatory T cell, monocyte, macrophage, dendritic cell, or mesenchymal stromal cell..

16. The composition of any one of claims 1-15, wherein the TNF-alpha mutant polypeptide comprises SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:39 or SEQ ID NO:41.

17. The composition of any one of claims 1-16, wherein the TNF-alpha mutant polypeptide is encoded by a sequence that comprises SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:38, or SEQ ID NO:40.

18. The composition of any one of claims 1-17, wherein the cell expresses an exogenously provided cytokine.

19. The composition of claim 18, wherein the cytokine is IL-7, IL-2, IL-15, IL-12, IL-18, IL-21 or a combination thereof.

20. The composition of claim 18 or 19, wherein the cytokine is encoded from the same vector as the TNF-alpha mutant gene.

21. The composition of any one of claims 18-20, wherein the cytokine is expressed as a separate polypeptide molecule as the TNF-alpha mutant and as a separate polypeptide molecule as an engineered receptor of the cell.

~~22. The composition of any one of claims 1-21, wherein the TNF-alpha mutant polypeptide lacks one or more further mutations that prevent binding of the TNF-alpha mutant polypeptide to a TNF receptor.~~

~~23. An *in vitro* method of inducing death for a transduced cell expressing an engineered nonsecretable TNF-alpha mutant polypeptide, comprising the step of providing an effective amount of at least one agent that binds the TNF-alpha mutant on the transduced cell.~~

~~24. Use of at least one agent that binds an engineered nonsecretable TNF-alpha mutant polypeptide on a transduced cell in the manufacture of a medicament for inducing death for the transduced cell expressing the TNF-alpha mutant polypeptide.~~

~~25. The method of claim 23 or the use of claim 24, wherein the agent that binds TNF-alpha is an antibody, small molecule, polypeptide, nucleic acid, or combination thereof.~~

~~26. The method or use of claim 25, wherein the antibody is a monoclonal antibody.~~

~~27. The method of any one of claims 23 or 25-26, or the use of any one of claims 24-26, wherein the cell further expresses an engineered receptor.~~

~~28. The method or use of claim 27, wherein the engineered receptor is a T-cell receptor or a CAR.~~

~~29. The method or use of claim 27 or 28, wherein the engineered receptor targets a cancer antigen.~~

~~30. The method of any one of claims 23 or 25-29, wherein the method occurs on the transduced cell obtained from an individual with a medical condition and the individual has been provided a therapy for the medical condition that comprises a plurality of the transduced cells.~~

~~31. The use of any one of claims 24-29, wherein the medicament is to be provided to an individual with a medical condition and the individual has been provided a therapy for the medical condition that comprises a plurality of the transduced cells.~~

~~32. The method of claim 30 or the use of claim 31, wherein the medical condition is cancer.~~

~~33. The method of claim 30 or 32, or the use of claim 31 or 32, wherein the agent is to be provided to the individual upon onset of one or more adverse events from the therapy.~~

~~34. The method or use of claim 33, wherein the individual exhibits one or more symptoms of cytokine release syndrome, neurotoxicity, anaphylaxis/allergy, and/or on-target/off tumor toxicity.~~

~~35. The method of any one of claims 30 or 32-34, or the use of any one of claims 31-34, wherein the individual has been provided, is provided, and/or will be provided an additional therapy for the medical condition.~~

~~36. The method of any one of claims 23 or 25-30 or 32-35, or the use of any one of claims 24-29 or 31-35, wherein the TNF-alpha mutant polypeptide lacks one or more further mutations that prevent binding of the TNF-alpha mutant polypeptide to a TNF receptor or prevents reverse signaling.~~

~~37. Use of one or more agents that bind a nonsecretable TNF-alpha mutant in the manufacture of a medicament, for reducing the effects of cytokine release syndrome in an individual who has received and/or who is receiving cell therapy with cells that express the TNF-alpha mutant, to cause in the individual (a) elimination of at least some of the cells of the cell therapy; and (b) reduction in the level of soluble TNF-alpha.~~

~~38. An *in vitro* method of reducing the risk of toxicity of a cell therapy for an individual, comprising the step of modifying the cells of the cell therapy to express a nonsecretable TNF-alpha mutant.~~

~~39. Use of cells of a cell therapy modified to express a nonsecretable TNF-alpha mutant in the manufacture of a medicament for reducing the risk of toxicity of the cell therapy for an individual.~~

~~40. The method of claim 38 or the use of claim 39, wherein the cell therapy is for cancer.~~

~~41. The method of claim 38 or 40, or the use of claim 39 or 40, wherein the cell therapy comprises an engineered receptor that targets an antigen.~~

~~42. A vector, comprising a sequence that encodes a nonsecretable TNF-alpha mutant and that encodes an engineered receptor.~~

~~43. The vector of claim 42, wherein the nonsecretable TNF-alpha mutant and the engineered receptor are encoded from the vector as separate polypeptides.~~

~~44. The vector of claim 42 or 43, wherein sequence of the vector that encodes the nonsecretable TNF-alpha mutant and sequence of the vector that encodes the engineered receptor are separated on the vector by a 2A element or an IRES element.~~

~~45. The vector of any one of claims 42-44, wherein the engineered receptor is a CAR.~~

~~46. The vector of any one of claims 42-45, wherein the vector further encodes a cytokine.~~

~~47. The vector of claim 46, wherein the cytokine is IL-7, IL-2, IL-15, IL-12, IL-18, or IL-21.~~

~~48. The vector of claim 46 or 47, wherein the cytokine is expressed from the vector as a separate polypeptide as the TNF-alpha mutant and the engineered receptor.~~

~~49.~~22. As a composition of matter, a nucleic acid sequence comprising SEQ ID NO:15.

~~50.~~23. As a composition of matter, a nucleic acid sequence comprising SEQ ID NO:16.