biology of exhaustion in human T cells expressing CAR receptors, experiments were conducted during development of examples herein using a model system employing a tonically signaling CAR, which induces hallmarks of exhaustion described in other settings. Results demonstrate that exhaustion was associated with a profound defect in IL-2 production alongside increased chromatin accessibility of AP-1 transcription factor motifs, and overexpression of numerous bZIP and IRF transcription factors that have been implicated in inhibitory activity. Engineering CAR T cells to overexpress an AP-1 factor (e.g., c-Jun) enhanced expansion potential, increased functional capacity, diminished terminal differentiation, and improved antitumor potency in numerous in vivo tumor models.

Experiments conducted during development of examples herein additionally demonstrate that functional deficiency in an AP-1 factor (e.g., c-Jun) mediates dysfunction in exhausted human T cells and that engineering CAR T cells to overexpress an AP-1 factor (e.g., c-Jun) renders them exhaustion-resistant, thereby addressing a major barrier to progress for this emerging class of therapeutics.

Experiments conducted during development of examples herein additionally demonstrate that knockdown of IRF4 dramatically increases functional activity of exhausted HA-28z CAR T cells, that the enhanced *in vivo* function of c-Jun modified HA-28z CAR T cells can not be replicated by ex vivo provision of IL-2, that c-Jun enhanced Her2-BBz CAR T cell activity within a suppressive solid tumor microenvironment, that c-Jun overexpression increases resistance to TGFβ-mediated suppression of exhausted HA-28z CAR T cells, and that transcriptional changes in c-Jun modified cells are consistent with reduced exhaustion and increased memory formation.

As described herein, engineered T cells (e.g., T cells engineered to express a synthetic receptor such as an engineered T cell receptor or a CAR), as well as non-engineered (e.g., native, natural) T cells are provided that are modified to overexpress and/or contain elevated levels (e.g., are made to have physiologically elevated levels) of one or more activator protein 1 (AP-1) transcription factors (e.g., c-Fos, c-Jun, Activating transcription factor (ATF) and Jun dimerization protein (JDP) families) and/or modified (e.g., genetically) for reduced expression and/or activity of one or more AP-1 inhibitory complex members (e.g., JunB and BATF3 and other BATF family members, IRF4, and ATF family members).

In one aspect, provided herein is a composition comprising isolated T cells modified to selectively overexpress c-Jun~~and/or contain elevated levels of one or more AP-1 transcription factors~~.

In another aspect, provided herein is a use of ~~a~~the composition as described herein~~comprising T cells modified to express and/or contain elevated levels of one or more AP-1~~

~~transcription factors~~ in the manufacture of a medicament for treating a disease or pathologic condition in a subject.

In another aspect, provided herein is a use of the~~a~~ composition as described herein~~comprising T cells modified to express and/or contain elevated levels of one or more AP-1 transcription factors and to express a chimeric antigen receptor (CAR) specific for a tumor antigen~~ in the manufacture of a medicament for treating a viral, bacterial, and/or parasitic infection~~or delaying the progression of cancer in a patient, wherein the medicament is to be administered to the patient~~.

~~In another aspect, provided herein is a therapeutically effective amount of a composition comprising T cells modified to express and/or contain elevated levels of one or more AP-1 transcription factors and to express a chimeric antigen receptor (CAR) specific for a tumor antigen for use as a medicament.~~

~~In another aspect, provided herein is a use of a composition comprising T cells modified to reduce and/or eliminate expression and/or activity of one or more AP-1 inhibitory complex members in the manufacture of a medicament for treating a disease or condition in a patient.~~

~~In another aspect, provided herein is a composition comprising isolated T cells modified to reduce and/or eliminate expression and/or activity of one or more AP-1 inhibitory complex members~~

~~In another aspect, provided herein is a composition comprising T cells modified to express and/or contain elevated levels of one or more AP-1 transcription factors for use as a medicament.~~

~~In another aspect, provided herein is a composition comprising T cells modified to reduce and/or eliminate expression and/or activity of one or more AP-1 inhibitory complex members for use as a medicament.~~

Accordingly, in one example, the disclosure provides T cells modified to overexpress and/or contain elevated levels of one or more AP-1 transcription factors. For example, in one example, c-Jun is expressed in T cells that are engineered to express a synthetic receptor

CLAIMS

What Is Claimed Is:

1. A composition comprising isolated T cells modified to selectively overexpress c-Junand/or contain elevated levels of one or more AP-1 transcription factors.

2. The composition according to claim 1, wherein the c-Jun is wildtype c-Jun.

3. The composition according to claim 1, wherein the c-Jun is a mutated/truncated c-Jun, and optionally wherein the mutated/truncated c-Jun comprises

(i) an N-terminal deletion;

(ii) lacks a transactivation domain and/or delta domain; or

(iii) comprises an inactive transactivation domain and/or delta domain.

4. The composition according to claim 1 or 3, wherein the c-Jun comprises (i) S63A and S73A mutations or (ii) a deletion between residues 2 and 102 or between residues 30 and 50 as compared to wildtype c-Jun.

52. The composition according to of any one of claims 1-4, wherein the isolated T cells are further modified to express a recombinant receptor, optionally .

3, The composition of claim 2, wherein the recombinant receptor is a T cell receptor (TCR) or .

4. The composition of claim 2, wherein the recombinant receptor is a chimeric antigen receptor (CAR).

6. The composition according to any one of claims 1-5, wherein the c-Jun is expressed from an expression vector encoding c-Jun.

7. The composition according to claim 5 or 6, wherein the isolated T cells co-express the c-Jun and a recombinant receptor; optionally wherein:

(i) the c-Jun and the recombinant receptor are expressed from separate expression vector constructs; or

(ii) the c-Jun and the recombinant receptor are co-expressed from a single expression vector construct.

8. The composition according to claim 6 or 7, wherein the expression vector is a viral vector, optionally a lentiviral, retroviral, adenoviral, or adeno-associated viral vector.

9~~5~~. The composition according to any one of claims 5-8~~of claim 2~~, wherein the recombinant receptor is specific for a tumor antigen.

10~~6~~. The composition according to ~~of~~ claim 9~~5~~, wherein the tumor antigen is selected from the group consisting of CD19, CD20, CD22, ROR1, GD2, EBV protein or antigen, folate receptor, Mesothelin, human carcinoembryonic antigen, CD33/IL3Ra, c-Met, PSMA, Glycolipid F77, EGFRvIII, NY-ESO-1, MAGE-A3, MART-1, GP1000 and p53.

11~~7~~. The composition according to ~~of~~ any one of claims 1-10, wherein the isolated T cells are native, naturally occurring T cells, optionally ~~.~~

~~8. The composition of claim 7, wherein the native, naturally occurring T cells are~~ obtained from resected tumors ~~.~~

~~9. The composition of claim 7, wherein the native, naturally occurring T cells are~~ or obtained by leukapheresis of a blood sample, optionally ~~.~~

~~10. The composition of claim 9,~~ wherein the T cells are expanded ex vivo.

12. The composition according to any one of claims 1-11, wherein the T cells are autologous T cells.

13~~1~~. The composition of any one of claims 1-12, wherein the T cells are selected from the group consisting of CD3+ T cells, CD8+ T cells, CD4+ T cells, natural killer (NK) T cells, gamma delta T cells, a combination of CD4+ and CD8 T+ cells, memory T cells, cytokine-induced killer cells, tumor infiltrating lymphocytes, and combinations thereof.

14. The composition according to claim 13, wherein the T cells are a combination of CD4+ and CD8 T+ cells.

~~12. The composition of claim 1, wherein the one or more AP-1 transcription factors are selected from the group consisting of c-Fos, c-Jun, Activating transcription factor (ATF) and Jun dimerization protein (JDP).~~

~~13. The composition of claim 1, wherein the AP-1 transcription factor is c-Jun.~~

~~14. The composition of claim 1, wherein the AP-1 transcription factor is a mutated/truncated AP-1 transcription factor.~~

~~15. The composition of claim 1, wherein the mutated/truncated AP-1 transcription factor comprises an N-terminal deletion.~~

~~16. The composition of claim 1, wherein the mutated/truncated AP-1 transcription factor (i) lacks a transactivation domain or (ii) comprises an inactive transactication domain.~~

~~17. The composition of claim 1, wherein the isolated T cells co-express c-Jun and an engineered receptor.~~

~~18. The composition of claim 17, wherein c-Jun and the engineered receptor are expressed from separate expression vector constructs.~~

~~19. The composition of claim 17, wherein c-Jun and the engineered receptor are co-expressed from a single expression vector construct.~~

15. The composition according to any one of claims 1-14, wherein the T cells are modified by CRISPR-Cas9, shRNA, siRNA, RNAi, micro-RNA, degron, regulatable promoter, or pharmacological inhibition.

~~20. The composition of claim 1, wherein the isolated T cells are T cells with specificity for and activity against a tumor.~~

~~21. The composition of claim 20, wherein the T cells are peripheral blood derived T cells genetically modified to express a receptor that recognizes and responds to tumor.~~

~~22. The composition of claim 1, wherein the T cells are further modified to reduce and/or eliminate expression and/or activity of one or more AP-1 inhibitory complex members.~~

~~23. The composition of claim 22, wherein the AP-1 inhibitory complex member is selected from the group consisting of JunB, a BATF family member, IRF4, an ATF family member, or a combination thereof.~~

~~24. The composition of claim 22, wherein the AP-1 inhibitory complex member is JunB and/or BATF3.~~

16~~25~~. Use of the~~a~~ composition of any one of claims 1-15 ~~comprising T cells modified to express and/or contain elevated levels of one or more AP-1 transcription factors~~ in the manufacture of a medicament for treating a disease or pathologic condition in a subject.

~~26. The use of claim 25, wherein the AP-1 transcription factor is c-Jun.~~

~~27. The use of claim 26, wherein the AP-1 transcription factor is a mutated/truncated transcription factor.~~

~~28. The use of claim 26, wherein the T cells are further modified to express a recombinant receptor.~~

~~29. The use of claim 28,~~

~~wherein c-Jun and the recombinant receptor are expressed from separate expression vector constructs, or~~

~~wherein c-Jun and the recombinant receptor are co-expressed from a single expression vector construct.~~

~~30. The use of claim 25, wherein the T cells modified to express and/or contain elevated levels of one or more AP-1 transcription factors are less susceptible to experiencing T cell exhaustion.~~

~~31. The use of claim 25, wherein the T cells modified to express and/or contain elevated levels of one or more AP-1 transcription factors have increased reactivity against low antigen density on target cells of the T cells.~~

~~32. The use of claim 25, wherein the T cells modified to express and/or contain elevated levels of one or more AP-1 transcription factors are less susceptible to experiencing diminished memory formation.~~

~~33. The use of claim 25, wherein the T cells modified to express and/or contain elevated levels of one or more AP-1 transcription factors are less susceptible to experiencing diminished proliferative capacity.~~

17~~34~~. The use of claim 16~~25~~, wherein the disease or condition is a tumor or cancer.

~~35. The use of claim 34, wherein the T cells are modified to express a recombinant receptor specific for the tumor or cancer.~~

~~36. The use of claim 35, wherein the recombinant receptor is a chimeric antigen receptor (CAR).~~

~~37. The use of claim 36, wherein the CAR is specific for a tumor antigen selected from the group consisting of CD19, CD20, CD22, ROR1, GD2, EBV protein or antigen, folate receptor, Mesothelin, human carcinoembryonic antigen, CD33/IL3Ra, c-Met, PSMA, Glycolipid F77, EGFRvIII, NY-ESO-1, MAGE-A3, MART-1, GP1000 and p53.~~

~~38. The use of claim 25, wherein the disease or condition is a viral, bacterial and/or parasitic infection.~~

~~39. The use of claim 25, wherein the T cells are further modified to reduce and/or eliminate expression and/or activity of one or more AP-1 inhibitory complex members.~~

~~40. The use of claim 39, wherein the AP-1 inhibitory complex member is selected from the group consisting of JunB, a BATF family member, IRF4, an ATF family member, or a combination thereof.~~

~~41. The use of claim 40, wherein the AP-1 inhibitory complex member is JunB and/or BATF3.~~

~~42. Use of a composition comprising T cells modified to express and/or contain elevated levels of one or more AP-1 transcription factors and to express a chimeric antigen receptor (CAR) specific for a tumor antigen in the manufacture of a medicament for treating or delaying the progression of cancer in a patient, wherein the medicament is to be administered to the patient.~~

~~43. The use of claim 42, wherein the number of cancerous cells in the patient is reduced.~~

~~44. The use of claim 42, wherein tumor burden in the patient is reduced and/or cleared.~~

18.~~45~~ The use of claim 17~~42~~, wherein one or more anticancer agents and/or one or more chemotherapeutic agents is to be further administered to the patient.

19~~46~~. The use of claim 17~~42~~, wherein the medicament is to be administered before, at the same time, and/or after the patient has received radiation therapy.

20. Use of the composition of any one of claims 1-8 and 11-15 in the manufacture of a medicament for treating a viral, bacterial, and/or parasitic infection.

~~47. The use of claim 42, wherein the T cells modified to express and/or contain elevated levels of one or more AP-1 transcription factors and to express a chimeric antigen receptor (CAR) specific for a tumor antigen are less susceptible to experiencing T cell exhaustion.~~

~~48. The use of claim 42, wherein the T cells modified to express and/or contain elevated levels of one or more AP-1 transcription factors and to express a chimeric antigen receptor~~

~~(CAR) specific for a tumor antigen have increased reactivity against low antigen density on target cells of the T cells.~~

~~49. The use of claim 42, wherein the T cells modified to express and/or contain elevated levels of one or more AP-1 transcription factors and to express a chimeric antigen receptor (CAR) specific for a tumor antigen are less susceptible to experiencing diminished memory formation.~~

~~50. The use of claim 42, wherein the T cells modified to express and/or contain elevated levels of one or more AP-1 transcription factors and to express a chimeric antigen receptor (CAR) specific for a tumor antigen are less susceptible to experiencing diminished proliferative capacity.~~

~~51. A therapeutically effective amount of a composition comprising T cells modified to express and/or contain elevated levels of one or more AP-1 transcription factors and to express a chimeric antigen receptor (CAR) specific for a tumor antigen for use as a medicament.~~

~~52. The composition for use of claim 51, further comprising one or more anticancer agents and/or one or more chemotherapeutic agents.~~

~~53. Use of a composition comprising T cells modified to reduce and/or eliminate expression and/or activity of one or more AP-1 inhibitory complex members in the manufacture of a medicament for treating a disease or condition in a patient.~~

~~54. The use of claim 53, wherein the disease or condition is cancer.~~

~~55. The use of claim 54, wherein the AP-1 inhibitory complex member is selected from the group consisting of JunB, BATF3, a BATF family member, IRF4, an IRF family member, an ATF family member, or a combination thereof.~~

~~56. The use of claim 53, wherein the AP-1 inhibitory complex member is JunB, BATF3, and/or IRF4.~~

~~57. The use of claim 53, wherein the T cells are modified by CRISPR-Cas9, shRNA, siRNA, RNAi, micro-RNA, degron, regulatable promoter, or pharmacological inhibition.~~

~~58. A composition comprising isolated T cells modified to reduce and/or eliminate expression and/or activity of one or more AP-1 inhibitory complex members.~~

~~59. The composition of claim 58, wherein the AP-1 inhibitory complex member is selected from the group consisting of JunB, BATF3, a BATF family member, IRF4, an IRF family member, an ATF family member, or a combination thereof.~~

~~60. The composition of claim 58, wherein the AP-1 inhibitory complex member is JunB, BATF3, and/or IRF4.~~

~~61. The composition of claim 1, wherein the isolated T cells modified to overexpress and/or contain elevated levels of one or more AP-1 transcription factors are less susceptible to experiencing T cell exhaustion .~~

~~62. The composition of claim 1, wherein the isolated T cells modified to overexpress and/or contain elevated levels of one or more AP-1 transcription factors have increased reactivity against low antigen density on target cells of the T cells.~~

~~63. The composition of claim 1, wherein the isolated T cells modified to overexpress and/or contain elevated levels of one or more AP-1 transcription factors are less susceptible to experiencing diminished memory formation.~~

~~64. The composition of claim 1, wherein the isolated T cells modified to overexpress and/or contain elevated levels of one or more AP-1 transcription factors are less susceptible to experiencing diminished proliferative capacity.~~

~~65. A composition comprising T cells modified to express and/or contain elevated levels of one or more AP-1 transcription factors for use as a medicament.~~

~~66. A composition comprising T cells modified to reduce and/or eliminate expression and/or activity of one or more AP-1 inhibitory complex members for use as a medicament.~~