cell malignancies, but long-term disease control occurs in only approximately 50% of patients with B- ALL1 and large B cell lymphoma (Ref. 2; herein incorporated by reference in its entirety), and is even less frequent in CLL (Ref. 3; herein incorporated by reference in its entirety). Moreover, despite numerous trials, CAR T cells have not mediated sustained antitumor effects in solid tumors (Ref. 4; herein incorporated by reference in its entirety). Numerous factors limit the efficacy of CAR T cells, including heterogeneous antigen expression and a requirement for high antigen density for optimal CAR function enabling rapid selection of antigen loss variants (Refs. 5-7; herein incorporated by reference in their entireties), the suppressive tumor microenvironment (Ref. 8; herein incorporated by reference in its entirety) and intrinsic T cell dysfunction as a result of T cell exhaustion (Refs. 3,9,10; herein incorporated by reference in their entireties). T cell exhaustion has been increasingly incriminated as a cause of T cell dysfunction in CAR T cells. Tonic antigen-independent signaling, due to scFv aggregation, commonly occurs in T cells expressing CARs and can induce rapid exhaustion (Ref. 9; herein incorporated by reference in its entirety). Integration of the CD28 endodomain into second generation CAR T cell receptors enhances expansion, but also predisposes CAR T cells to exhaustion, both in the setting of tonically signaling receptors and in CD19-28z CAR T cells exposed to high tumor burdens (Ref. 9; herein incorporated by reference in its entirety). Increased frequency of T cells bearing exhaustion characteristics contained within CD19-BBz CAR grafts were recently demonstrated to distinguish non-responding from responding patients treated for CLL3. A broad base of data from diverse studies implicates intrinsic T cell dysfunction due to T cell exhaustion as a major factor limiting the efficacy of CAR T cell therapeutics and raises the prospect that engineering exhaustion-resistant CAR T cells could substantially improve clinical outcomes.

SUMMARY

The present disclosure relates to compositions and methods for use in preventing exhaustion of engineered (e.g., T cells engineered to express a synthetic receptor such as an engineered T cell receptor or a chimeric antigen receptor (CAR)) as well as non-engineered (e.g., native) T cells. T cells modified (e.g., to prevent T cell exhaustion) according to the disclosure, compositions containing same, and methods of using same enhance T cell functionality (e.g., activity against cancer or infectious disease).

CAR T cells mediate antitumor effects in a small subset of cancer patients, but dysfunction due to T cell exhaustion is an important barrier to progress. To investigate the

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 overexpress and/or contain elevated levels of one or more AP-1 transcription factors.

In another aspect, provided herein is a use of a composition 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 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.

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

such as an engineered T cell receptor or a chimeric antigen receptor (CAR). In another example, c-Jun is expressed in T cells with a native, natural T cell receptor. The disclosure is not limited by the means of expressing one or more AP-1 transcription factors. In one example, when co-expressed with an engineered TCR or CAR, c-Jun (and/or other AP-1 transcription factor) and the engineered receptor are co-expressed from distinct viral vectors. In another example, they are expressed from a single vector construct using a bicistronic vector. C-Jun (and/or other AP-1 transcription factor) may be expressed constitutively or in a regulated fashion (e.g., using a system to regulate expression remotely via a small molecule or using an endogenously regulated system). c-Jun and/or other AP-1 transcription factor genes may, in another example, be genetically integrated into the cellular DNA using a retroviral, lentiviral or other viral vector or via CRISPR/Cas9 based system. In yet another example, c-Jun and/or other AP-1 transcription factors is/are expressed via RNA or an oncolytic virus or other transient expression system known in the art. C-Jun and/or other AP-1 transcription factors can be delivered ex vivo into T cells for adoptive transfer, or delivered via in vivo genetic transfer.

Similarly, the disclosure is not limited by the type of T cell modified to overexpress and/or contain elevated levels of one or more AP-1 transcription factors 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 some examples, the T cells are CD3+ T cells (e.g., a combination of CD4+ and CD8+ T cells). In certain examples, the T cells are CD8+ T cells. In other examples, the T cells are CD4+ T cells. In some examples, the T cells are natural killer (NK) T cells. In some examples, the T cells are alpha beta T cells. In some examples, the T cells are gamma delta T cells. In some examples, the T cells are a combination of CD4+ and CD8 T+ cells (e.g., that are CD3+). In certain examples, the T cells are memory T cells. In certain examples, the memory T cells are central memory T cells. In certain examples, the memory T cells are effector memory T cells. In some examples, the T cells are tumor infiltrating lymphocytes. In certain examples, the T cells are a combination of CD8+ T cells, CD4+ T cells, NK T cells, memory T cells, and/or gamma delta T cells. In some examples, the T cells are cytokine-induced killer cells.

In some examples, the T cell is an anti-tumor T cell (e.g., a T cell with activity against a tumor (e.g., an autologous tumor) that becomes activated and expands in response to antigen). Anti-tumor T cells (e.g., useful for adoptive T cell transfer) include, in one

example, peripheral blood derived T cells genetically modified with receptors that recognize and respond to tumor antigens. Such receptors are generally composed of extracellular domains comprising a single-chain antibody (scFv) specific for tumor antigen, linked to intracellular T cell signaling motifs (See, e.g., Westwood, J. A. et al, 2005, Proc. Natl. Acad. Sci., USA, 102(52):19051-19056). Other anti-tumor T cells include T cells obtained from resected tumors or tumor biopsies (e.g., tumor infiltrating lymphocytes (TILs). In another example, the T cell is a polyclonal or monoclonal tumor-reactive T cell (e.g., obtained by apheresis, expanded ex vivo against tumor antigens presented by autologous or artificial antigen-presenting cells). In another example, the T cell is engineered to express a T cell receptor of human or murine origin that recognizes a tumor antigen. The disclosure is not limited by the type of tumor antigen so recognized. Indeed, any T cell containing a receptor that recognizes a tumor antigen finds use in the compositions and methods of the disclosure. Examples include, but are not limited to, T cells expressing a receptor (e.g., a native or naturally occurring receptor, or a receptor engineered to express a synthetic receptor such as an engineered T cell receptor or a CAR) that recognize an antigen selected from CD19, CD20, CD22, receptor tyrosine kinase-like orphan receptor 1 (ROR1), disialoganglioside 2 (GD2), Epstein-Barr Virus (EBV) protein or antigen, folate receptor, mesothelin, human carcinoembryonic antigen (CEA), CD33/IL3Rα, tyrosine protein kinase Met (c-Met) or hepatocyte growth factor receptor (HGFR), prostate-specific membrane antigen (PSMA), Glycolipid F77, epidermal growth factor receptor variant III (EGFRvIII), NY-ESO-1, melanoma antigen gene (MAGE) Family Member A3 (MAGE-A3), melanoma antigen recognized by T cells 1 (MART-1), GP1000, p53, or other tumor antigen described herein.

In some examples, the T cell is engineered to express a CAR. The disclosure is not limited by the type CAR. Indeed, any CAR that binds with specificity to a desired antigen (e.g., tumor antigen) may be modified as disclosed and described herein to overexpress and/or contain elevated levels (e.g., are made to have physiologically elevated levels) of one or more AP-1 transcription factors (e.g., c-Jun). In certain examples, the CAR comprises an antigen-binding domain. In certain examples, the antigen-binding domain is a single-chain variable fragment (scFv) containing heavy and light chain variable regions that bind with specificity to the desired antigen. In some examples, the CAR further comprises a transmembrane domain (e.g., a T cell transmembrane domain (e.g., a CD28 transmembrane domain)) and a signaling domain comprising one or more

immunoreceptor tyrosine-based activation motifs (ITAMs)(e.g., a T cell receptor signaling domain (e.g., TCR zeta chain). In some examples, the CAR comprises one or more co-stimulatory domains (e.g., domains that provide a second signal to stimulate T cell activation). The disclosure is not limited by the type of co-stimulatory domain. Indeed, any co-stimulatory domain known in the art may be used including, but not limited to, CD28, OX40/CD134, 4-1BB/CD137/TNFRSF9, the high affinity immunoglobulin E receptor-gamma subunit (FcERIγ, ICOS/CD278, interleukin 2 subunit beta (ILRβ) or CD122, cytokine receptor common subunit gamma (IL-2Rγ) or CD132, and CD40. In one example, the co-stimulatory domain is 4-1BB.

In one example, the disclosure provides a method of treating a disease or condition in a subject comprising administering to the subject (e.g., a patient) having a disease or condition an effective amount of T cells modified to express and/or contain elevated levels of one or more AP-1 transcription factors 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). The disclosure is not limited by the type of disease or condition treated. Indeed, any disease or condition that is treatable (e.g., for which signs or symptoms of the disease are ameliorated upon treatment) via administration of T cells can be treated in an improved and more effective manner using compositions and methods of the disclosure (e.g., containing and/or using T cells modified to express and/or contain elevated levels of one or more AP-1 transcription factors). In one example, the disease or condition is cancer. In another example, the disease or condition is an infectious disease. The disclosure is not limited by the type of cancer or by the type of infectious disease. Indeed, any cancer known in the art for which T cell therapy is used for treatment may be treated with the compositions and methods of the disclosure. In like manner, any infectious disease known in the art for which T cell therapy is used for treatment may be treated with the compositions and methods of the disclosure. In one example, administration to a subject (e.g., a patient) having a disease or condition of an effective amount of T cells modified to express and/or contain elevated levels of one or more AP-1 transcription factors and/or reduced expression and/or activity of one or more AP-1 inhibitory complex members inhibits T cell exhaustion (e.g., compared to a subject receiving the same amount of engineered T cells (e.g., CAR T cells or T cells comprising a recombinant TCR) not modified to express and/or contain elevated levels of one or more AP-

1 transcription factors or to have reduced expression and/or activity of one or more AP-1 inhibitory complex members).

Thus, the disclosure provides, in one example, a method of inhibiting T cell exhaustion (e.g. maintaining functionality of T cells exposed to excessive antigen (e.g., in the context of treating a disease or condition)) via modification of T cells to express and/or contain elevated levels of one or more AP-1 transcription factors and/or reduced expression and/or activity of one or more AP-1 inhibitory complex members (e.g., compared to control T cells not so modified). In one example, T cells modified to express and/or contain elevated levels of one or more AP-1 transcription factors (e.g., c-Jun) display increased functionality and/or activity (e.g., increased antigen induced cytokine production, enhanced killing capacity (e.g., increased recognition of tumor targets with low surface antigen), increased memory cell formation, and/or enhanced proliferation in response to antigen) and/or reduced features of exhaustion (e.g., lower levels of markers indicative of exhaustion (e.g., PD-1, TIM-3, LAG-3) and/or lower levels of programmed cell death). In some examples, T cells modified to express and/or contain elevated levels of one or more AP-1 transcription factors and/or reduced expression and/or activity of one or more AP-1 inhibitory complex members described herein significantly enhance clinical efficacy (e.g., of engineered T cells (e.g., CAR T cells) and/or non-engineered natural T cells).

In certain examples, the present disclosure demonstrates that treatment of a subject having cancer with 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 is superior to treatment of a subject having cancer with T cells expressing normal amounts of one or more AP-1 transcription factors. In some examples, treatment of animals (e.g., humans) suffering from cancer with therapeutically effective amounts of immunotherapeutic compositions comprising T cells modified to express and/or contain elevated levels of one or more AP-1 transcription factors inhibits the development or growth of cancer cells or and/or renders the cancer cells as a population more susceptible to other treatments (e.g., the cell death-inducing activity of cancer therapeutic drugs or radiation therapies). Accordingly, compositions and methods of the disclosure may be used as a monotherapy (e.g., to kill cancer cells, and/or reduce or inhibit cancer cell growth, induce apoptosis and/or cell cycle arrest in cancer cells), or when administered in combination with one or more additional agent(s), such as other anti-cancer agents (e.g., cell death-inducing or cell cycle-disrupting cancer therapeutic drugs or radiation therapies) to render a greater proportion of the cancer cells

susceptible to killing, inhibited cancer cell growth, induced apoptosis and/or cell cycle arrest compared to the corresponding proportion of cells in an animal treated only with the cancer therapeutic drug or radiation therapy alone.

Accordingly, in certain examples, the disclosure provides methods of treating or delaying the progression of cancer in a patient comprising administering to the patient a therapeutically effective amount of a composition comprising T cells modified (e.g., genetically) to express and/or contain elevated levels of one or more AP-1 transcription factors (e.g., c-Jun) 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 certain examples, the therapeutically effective amount of the modified T cell composition reduces the number of cancer cells in the patient following such treatment. In certain examples, the therapeutically effective amount of the modified T cell composition reduces and/or eliminates the tumor burden in the patient following such treatment. In certain examples, the method further comprises administering radiation therapy to the patient. In certain examples, the radiation therapy is administered before, at the same time as, and/or after the patient receives the therapeutically effective amount of the modified T cell composition. In certain examples, the method further comprises administering to the patient one or more anticancer agents and/or one or more chemotherapeutic agents. In certain examples, the one or more anticancer agents and/or one or more chemotherapeutic agents are administered before, at the same time as, and/or after the patient receives the therapeutically effective amount of the modified T cell composition. In certain examples, combination treatment of a patient with a therapeutically effective amount of modified T cells and a course of an anticancer agent produces a greater tumor response and clinical benefit in such patient compared to those treated with the modified T cells or anticancer drugs/radiation alone. Since the doses for all approved anticancer drugs and radiation treatments are known, the present disclosure contemplates the various combinations of them with the modified T cells.

In certain examples, the disclosure provides a therapeutically effective amount of a composition (e.g., an immunotherapeutic composition) comprising T cells modified according to the present disclosure (e.g., for use in treating or delaying the progression of cancer in a subject). As described herein, the composition may further comprise one or more anticancer agents, for example one or more chemotherapeutic agents. The disclosure also

provides the use of the composition to induce cell cycle arrest and/or apoptosis. The disclosure also relates to the use of the compositions for sensitizing cells to additional agent(s), such as inducers of apoptosis and/or cell cycle arrest, and chemoprotection of normal cells through the induction of cell cycle arrest prior to treatment with chemotherapeutic agents. Compositions of the disclosure are useful for the treatment, amelioration, or prevention of disorders, such as any type of cancer or infectious disease and additionally any cells responsive to induction of apoptotic cell death (e.g., disorders characterized by dysregulation of apoptosis, including hyperproliferative diseases such as cancer). In certain examples, the compositions can be used to treat, ameliorate, or prevent a cancer that additionally is characterized by resistance to cancer therapies (e.g., those cancer cells which are chemoresistant, radiation resistant, hormone resistant, and the like). The disclosure also provides pharmaceutical compositions comprising the composition (e.g., immunotherapeutic compositions) comprising modified T cells of the disclosure in a pharmaceutically acceptable carrier.

In another example, the disclosure provides a method of treating or delaying the progression of cancer in a patient comprising administering to the patient a therapeutically effective amount of a composition comprising T cells modified (e.g., genetically) to express and/or contain elevated levels of one or more AP-1 transcription factors (e.g., c-Jun) in combination with a therapeutically effective amount of an inhibitor of TCR signaling (e.g., in order to prevent T cell exhaustion). In certain examples, the inhibitor of TCR signaling is a tyrosine kinase inhibitor. In another example, the tyrosine kinase inhibitor inhibits Lck kinase. An inhibitor of TCR signaling may be administered by any suitable mode of administration, but is typically administered orally. Multiple cycles of treatment may be administered to a subject. In certain examples, the inhibitor of TCR signaling is administered according to a standard dosing regimen (*e.g.*, daily or intermittently). In another example, the inhibitor of TCR signaling is administered for a period of time sufficient to restore at least partial T cell function, then discontinued.

These and other examples of the subject disclosure will readily occur to those of skill in the art in view of the disclosure herein.

DESCRIPTION OF THE DRAWINGS

FIG. 1A-B shows AP-1 transcription factors c-Fos and c-Jun are downregulated in GD2-28Z exhausted CAR T cells.

CLAIMS

What Is Claimed Is:

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

2. The composition of claim 1, wherein the isolated T cells are further modified to express a recombinant receptor.

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

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

5. The composition of claim 2, wherein the recombinant receptor is specific for a tumor antigen.

6. The composition of claim 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.

7. The composition of claim 1, wherein the isolated T cells are native, naturally occurring T cells.

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 obtained by leukapheresis of a blood sample.

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

11. The composition of claim 1, 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, and combinations thereof.

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.

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.

25. Use of a composition 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.

34. The use of claim 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.

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

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

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.