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 comprising an introduced nucleic acid for overexpressing ~~modified to selectively overexpress~~ c-Jun.

In another aspect, provided herein is ~~a use of~~ the composition as described herein for use in therapy

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

In another aspect, provided herein is use of the composition as described herein in the manufacture of a medicament for the treatment of a tumor or cancer, and wherein the composition comprises T cells specific for an antigen associated with the tumor or cancer.

In another aspect, provided herein is a use of the composition as described herein in the manufacture of a medicament for treating a viral, bacterial, and/or parasitic infection, wherein the composition comprises T cells specific for an antigen associated with the viral, bacterial and/or parasitic infection.

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 comprising an introduced nucleic acid for overexpressing ~~modified to selectively overexpress~~ c-Jun.

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) comprises 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.

5. The composition according to any one of claims 1-4, wherein the isolated T cells are further modified to express a recombinant receptor, optionally wherein the recombinant receptor is a T cell receptor (TCR) or 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 6, wherein the expression vector is a viral vector, optionally a lentiviral, retroviral, adenoviral, or adeno-associated viral vector.

8~~7~~. The composition according to claim 5~~ or 6~~, wherein the isolated T cells co-express the c-Jun and ~~a~~ the 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~~9. The composition according to claim 8~~6 or 7~~, wherein:

(i) the c-Jun and the recombinant receptor are expressed from separate expression vector constructs and at least one of the separate expression vector constructs is a viral vector, optionally a lentiviral, retroviral, adenoviral, or adeno-associated viral vector; or

(ii) the c-Jun and the recombinant receptor are co-expressed from a single expression vector construct and the single expression vector construct is a viral vector, optionally a lentiviral, retroviral, adenoviral, or adeno-associated viral vector.

10~~9~~. The composition according to ~~any one of claims 5-8~~claim 8 or 9, wherein the recombinant receptor is specific for a tumor antigen.

~~10~~11. The composition according to claim ~~9~~10, 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~~12. The composition according to any one of claims 1-~~10~~11, wherein the isolated T cells are derived from native, naturally occurring T cells, optionally obtained from resected tumors or obtained by leukapheresis of a blood sample, optionally wherein the T cells are expanded ex vivo.

~~12~~13. The composition according to any one of claims 1-~~11~~12, wherein the T cells are autologous T cells.

~~13~~14. The composition of any one of claims 1-~~12~~13, 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~~15. The composition according to claim 1~~43~~, wherein the T cells are a combination of CD4+ and CD8 T+ cells.

~~15~~16. The composition according to any one of claims 1-~~14~~15, wherein the T cells are modified to reduce and/or eliminate expression and/or activity of one or more AP-l inhibitory complex members by CRISPR-Cas9, shRNA, siRNA, RNAi, micro-RNA, ~~degron, regulatable promoter,~~ or ~~pharmacological inhibition~~protein inhibitors targeting one or more AP-l inhibitory complex members.

~~16~~17. The ~~Use of the~~ composition of any one of claims 1-~~15~~ 16 ~~in the manufacture of a medicament for treating a disease or pathologic condition in a subject~~ for use in therapy.

187. Use of Tthe composition of any one of claims 1-16use of claim 16, in the manufacture of a medicament for the treatment of wherein the disease or condition is a tumor or cancer, and wherein the composition comprises T cells specific for an antigen associated with the tumor or cancer.

1819. The use of claim 1718, wherein one or more anticancer agents and/or one or more chemotherapeutic agents is to be further administered to the patient.

1920. The use of claim 1718, wherein the medicament is to be administered before, at the same time, and/or after the patient has received radiation therapy.

2021. Use of the composition of any one of claims 1-8 9 and 1112-15 16 in the manufacture of a medicament for treating a viral, bacterial, and/or parasitic infection, wherein the composition comprises T cells specific for an antigen associated with the viral, bacterial, and/or parasitic infection.