

stimulatory signals during activation of exogenously expressed TCRs by antigens. However, existing recombinant DNA strategies often suffer from reduced cell surface expression of the chimeric proteins combining two co-stimulatory signaling domains, preventing realization of the functional potential of the chimeric proteins. The present application addresses such needs.

SUMMARY

Provided herein are novel chimeric co-stimulatory intracellular domains. The chimeric co-stimulatory intracellular domains provided herein comprise: (a) a first signaling domain that is based on the intracellular signaling domain of a CD28 family protein; and (b) at least a second signaling domain that comprises a mutant intracellular signaling domain of a tumor necrosis factor receptor (TNFR) family protein.

In some examples, the first signaling domain that is based on the intracellular signaling domain of a CD28 family proteins is selected from a CD28 protein, ICOS protein or a combination thereof. In some examples, the at least second signaling domain is based on a mutant of the intracellular signaling domain of a TNFR family protein selected from CD137 (4-1BB) and CD134 (OX-40).

The chimeric co-stimulatory intracellular domains provided herein comprise: (a) a first signaling domain that is based on the intracellular signaling domain of a CD28 protein, ICOS protein or a combination thereof; and (b) at least a second signaling domain that comprises a mutant CD137 (4-1BB) intracellular domain or a mutant CD134 (OX-40) intracellular domain.

wherein the at least second signal transduction domain comprises a mutant intracellular signaling domain of a tumor necrosis factor receptor (TNFR) family protein.

The present disclosure provides a recombinant T cell co-stimulatory receptor (RTCR), comprising: (a) an extracellular domain; (b) a transmembrane domain; and (c) a chimeric intracellular domain comprising a first and at least a second signal transduction domains, wherein the first and the at least second signal transduction domains are non-identical; and wherein the at least second signal transduction domain comprises a mutant CD137 (4-1BB) intracellular domain or a mutant CD134 (OX-40) intracellular domain.

The present disclosure also provides a nucleic acid encoding the RTCR disclosed herein.

The present disclosure also provides a vector comprising the nucleic acid disclosed herein. The present disclosure also provides a cell comprising the nucleic acid or the vector disclosed herein. In another aspect, the present disclosure refers to a cell comprising the nucleic acid or the vector as described herein, optionally wherein the cell is a modified T cell, or a modified natural killer T cell (NK-T cell), optionally wherein the modified T cell is an allogenic T cell or an autologous T cell, optionally wherein the modified T cell is a naïve T cell, an early memory T cell, a stem cell-like T cell, a stem memory T cell (TSCM), a central memory T cell (TCM), or a regulatory T cell (Treg), optionally wherein the cell further comprises a sequence encoding an artificial antigen receptor, a therapeutic polypeptide, an immune cell modulatory protein, or a combination thereof, optionally wherein the artificial antigen receptor comprises a chimeric antigen receptor (CAR), optionally wherein the cell expresses the RTCR either transiently or stably, and optionally wherein the cell co-expresses with the RTCR at least one or more of the endogenous co-stimulatory molecules selected from CD28, CD2, OX-40, ICOS, CD28, CD3, CD4, CD8, CD40L, and a combination thereof.

The present disclosure also provides a modified T lymphocyte (T cell), comprising: (a) a modification of an endogenous sequence encoding a T cell Receptor (TCR), wherein the modification reduces or eliminates a level of expression or activity of the TCR; and (b) a recombinant T cell co-stimulatory receptor (RTCR) disclosed herein. In another aspect, the present disclosure refers to a modified T cell, comprising: (a) a modification of an endogenous sequence encoding a TCR, wherein the modification reduces or eliminates a level of expression or activity of the TCR; and (b) a recombinant RTCR as described herein, optionally further comprising a modification of an endogenous sequence encoding a component of major

histocompatibility complex class I (MHC-I), wherein the modification reduces or eliminates a level of expression or activity of the MHC-I, and optionally wherein the modified T cell co-expresses with the RTCR at least one of the endogenous co-stimulatory molecules CD28, CD2, OX-40, ICOS, CD28, CD3, CD4, CD8, CD40L, or a combination thereof.

5 The present disclosure also provides a composition comprising the RTCR disclosed herein. The present disclosure also provides a composition comprising the nucleic acid encoding the RTCR disclosed herein. The present disclosure also provides a composition comprising the vector comprising the nucleic acid disclosed herein. The present disclosure also provides a composition comprising the cell disclosed herein. The present disclosure also provides a
10 composition comprising the modified T cell disclosed herein.

 The present disclosure also provides a composition comprising a population of cells, wherein the population comprises a plurality of the cell comprising the nucleic acid encoding or a vector comprising the nucleic acid encoding the RTCR disclosed herein. The present disclosure also provides a composition comprising a population of cells, wherein the population comprises
15 a plurality of the modified T cell disclosed herein.

 The present disclosure provides a method of producing a plurality of modified T cells, wherein the method comprises: a) providing a plurality of primary T cells disclosed herein; b) providing a composition comprising the RTCR disclosed herein, the nucleic acid encoding the RTCR disclosed herein, or the vector comprising the nucleic acid encoding the RTCR disclosed
20 herein; and c) introducing into the plurality of primary T cells of (a) the composition of (b), to

produce a plurality of modified T cells under conditions that stably express the RTCR within the plurality of modified T cells. In some examples, the method of producing a plurality of modified T cells disclosed herein, further comprises a step of modifying an endogenous sequence encoding an endogenous T cell Receptor (TCR), wherein the modification reduces or eliminates a level of expression or activity of the endogenous TCR. In some examples, the method of producing a plurality of modified T cells disclosed herein, further comprises a step of modifying an endogenous sequence, wherein the modification reduces or eliminates a level of expression or activity of a major histocompatibility complex (MHC) class I (MHC-I). In some examples, the method of producing a plurality of modified T cells disclosed herein, further comprises: d) maintaining the plurality of modified T cells in a suitable cell culture media; and e) either: i) cryopreserving the plurality of modified T cells in a suitable cell freezing media; or ii) preparing the plurality of modified T cells for administering to a subject suffering from a disease or disorder.

The present disclosure also provides a method of treating a disease or disorder, comprising administering to a subject in need thereof a therapeutically effective number of the cell comprising the nucleic acid encoding or the vector comprising the nucleic acid encoding the RTCR disclosed herein, a therapeutically effective number of any one of the modified T cell disclosed herein, a therapeutically effective amount of any one of the compositions disclosed herein, or a therapeutically effective number of the plurality of modified T cells produced by the method disclosed herein. In another aspect, the present disclosure refers to a use of a therapeutically effective number of the cell as described herein, a therapeutically effective number of the modified T cell as described herein, a therapeutically effective amount of the composition as described herein, or a therapeutically effective number of the plurality of modified T cells produced by the method as described herein in the manufacture of a medicament for treating a disease or disorder, optionally wherein the subject is a mammal, and optionally wherein the mammal is a human, wherein the disease or disorder is a cancer, an autoimmune disease or disorder, an infectious disease, an inflammatory disease, a renal disease or disorder, a lung disease or disorder, a liver disease or disorder, a cardiovascular system disease or disorder, a neurodegenerative disease or disorder, or a metabolic disease or disorder, optionally wherein the cancer is a solid tumor or a hematologic cancer, optionally wherein the solid cancer is a sarcoma, a carcinoma or a melanoma or wherein the hematological cancer is a

leukemia, a lymphoma or a myeloma, and optionally wherein a) the cancer is selected from acute leukemia, acute lymphoblastic leukemia (ALL), acute lymphocytic leukemia, B cell, T cell or FAB ALL, acute myeloid leukemia (AML), acute myelogenous leukemia, chronic myelocytic leukemia (CML), chronic lymphocytic leukemia (CLL), hairy cell leukemia, myelodysplastic syndrome (MDS), Hodgkin's lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, colorectal carcinoma, pancreatic carcinoma, nasopharyngeal carcinoma, malignant histiocytosis, paraneoplastic syndrome/hypercalcemia of malignancy, bladder cancer, breast cancer, colorectal cancer, endometrial cancer, head cancer, neck cancer, hereditary nonpolyposis cancer, liver cancer, lung cancer, non-small cell lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cell carcinoma, testicular cancer, adenocarcinomas, sarcomas, malignant melanoma, and hemangioma; b) the infectious disease is caused by a bacteria, a virus, a fungus, a protozoa, or a parasite; c) the neurodegenerative disorder is Alzheimer's disease (AD) and other dementias, Parkinson's disease (PD) and PD-related disorders, prion disease, Motor neuron diseases (MND), Huntington's disease (HD), Spinocerebellar ataxia (SCA), or Spinal muscular atrophy (SMA); or d) the inflammatory disease is systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, or multiple sclerosis.

The present disclosure also provides a chimeric co-stimulatory intracellular protein (CIP) comprising a first and at least a second signal transduction domains, wherein the first and the at least second signal transduction domains are non-identical; and wherein the at least second signal transduction domain comprises a mutant intracellular signaling domain of a tumor necrosis factor receptor (TNFR) family protein.

The present disclosure also provides a chimeric co-stimulatory intracellular protein (CIP) comprising a first and at least a second signal transduction domains, wherein the first and the at least second signal transduction domains are non-identical; and wherein the at least second signal transduction domain comprises a mutant CD137 (4-1BB) intracellular domain or a mutant CD134 (OX-40) intracellular domain. In another aspect, the present disclosure refers to a chimeric co-stimulatory intracellular protein (CIP) comprising a first and at least a second signal transduction domain, wherein the first and the at least second signal transduction domains are non-identical; and wherein the at least second signal transduction domain comprises a mutant intracellular signaling domain of a tumor necrosis factor receptor (TNFR) family protein, wherein the mutant intracellular signaling domain of the TNFR family protein is a mutant

CD137 (4-1BB) intracellular domain or a mutant CD134 (OX-40) intracellular domain, and optionally wherein the CIP further comprises a transmembrane domain.

CLAIMS

1. A recombinant T cell co-stimulatory receptor (RTCR), comprising:
 - (a) an extracellular domain;
 - (b) a transmembrane domain; and
 - (c) a chimeric intracellular domain comprising a first and at least a second signal transduction domain,wherein the first and the at least second signal transduction domains are non-identical; and
wherein the at least second signal transduction domain comprises a mutant CD137 (4-1BB) intracellular domain or a mutant CD134 (OX-40) intracellular domain.
2. The RTCR of claim 1, wherein the mutant CD137 intracellular domain comprises
 - (1) a truncated CD137 intracellular domain comprising:
 - 1a) an amino acid sequence according to amino acid position 13 to amino acid position 42 of the CD137 intracellular domain;
 - 1b) a deletion of a continuous stretch of one, two, three, four, five, six, seven, eight, nine, ten or more amino acids from the N-terminus of the CD137 intracellular domain;
 - 1c) a deletion of one, two, three, four, five, six, seven, eight, nine, ten or more amino acids from amino acid position 1 to amino acid position 12 of the N-terminus of the CD137 intracellular domain; and/or
 - 1d) an amino acid sequence according to SEQ ID NO: 3;
 - (2) a deletion of one, two, three, or four lysine residue(s) from amino acid position 1 to amino acid position 12 of the N-terminus of the CD137 intracellular domain;
 - (3) one or more lysine mutation(s) from amino acid position 1 to amino acid position 12 of the N-terminus of the CD137 intracellular domain, optionally one or more lysine mutation(s) at amino acid positions selected from amino acid positions 1, 5, 6 and 12 of the N-terminus of the CD137 intracellular domain;
 - (4) a deletion of one or more proximal basic amino acids from amino acid position 1 to amino acid position 12 of the N-terminus of the CD137 intracellular domain; and/or
 - (5) one or more proximal basic amino acid mutation(s) from amino acid position 1 to amino acid position 12 of the N-terminus of the CD137 intracellular domain, optionally one or

more proximal basic amino acid mutation(s) at amino acid positions selected from amino acid positions 1, 2, 3, 4, 5 and 6 of the N-terminus of the CD137 intracellular domain, and

optionally a lysine mutation at amino acid position 12 of the N-terminus of the CD137 intracellular domain.

3. The RTCR of claim 1, wherein the mutant CD134 intracellular domain comprises
(1) a truncated CD134 intracellular domain comprising:

1a) an amino acid sequence according to amino acid position 15 to amino acid position 37 of the CD134 intracellular domain;

1b) a deletion of a continuous stretch of one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen or more amino acids from the N-terminus of the CD134 intracellular domain;

1c) a deletion of one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen or more amino acids from amino acid position 1 to amino acid position 14 of the N-terminus of the CD134 intracellular domain; and/or

1d) an amino acid sequence according to SEQ ID NO: 6;

(2) a deletion of a lysine residue from amino acid position 1 to amino acid position 14 of the N-terminus of the CD134 intracellular domain;

(3) a lysine mutation at amino acid position 12 of the N-terminus of the CD134 intracellular domain;

(4) a deletion of one or more proximal basic amino acids from amino acid position 1 to amino acid position 14 of the N-terminus of the CD134 intracellular domain; and/or

(5) one or more proximal basic amino acid mutation(s) from amino acid position 1 to amino acid position 14 of the N-terminus of the CD134 intracellular domain, optionally one or more proximal basic amino acid mutation(s) at amino acid positions selected from amino acid positions 1, 2, and 5 of the N-terminus of the CD134 intracellular domain, and

optionally wherein the mutant CD134 intracellular domain further comprises a lysine mutation at amino acid position 12 of the N-terminus of the CD137 intracellular domain.

4. The RTCR of any one of claims 1-3, wherein the chimeric intracellular domain comprises a first signal transduction domain derived from a protein of the CD28 family, optionally wherein

the first signal transduction domain is derived from CD28, CD28H, ICOS, or a combination thereof, and optionally wherein:

a) the first signal transduction domain is derived from ICOS and optionally comprises an amino acid sequence according to SEQ ID NO: 9, optionally wherein the chimeric intracellular domain comprises a first signal transduction domain comprising a portion of a CD28 intracellular domain combined with an ICOS domain according to SEQ ID NO: 9, and optionally wherein the first signal transduction domain comprises an amino acid sequence according to any one of SEQ ID NOs: 12 and 109; or

b) the first signal transduction domain is derived from CD28 and optionally comprises an amino acid sequence according to SEQ ID NO: 10, optionally wherein the first signal transduction domain comprises an amino acid sequence according to any one of SEQ ID NOs: 121-122, and

optionally wherein the chimeric intracellular domain comprises an amino acid sequence according to any one of SEQ ID NOs: 14-17.

5. The RTCR of any one of claims 1-4, wherein the chimeric intracellular domain further comprises a third signal transduction domain, optionally wherein the third signal transduction domain is derived from a CD3 signaling domain, a CD2 signaling domain, an interleukin 2 receptor binding (IL-2RB) protein signaling domain, or a combination thereof, and optionally wherein:

a) the CD3 signaling domain is derived from a CD3 ζ or a CD3 ϵ domain, or a combination thereof, optionally wherein the CD3 signaling domain comprises an amino acid sequence according to any one of SEQ ID NOs: 18, 45, 46, 47, and 48;

b) the CD2 signaling domain is a mutant CD2 signaling domain, optionally wherein the mutant CD2 signaling domain is a truncated CD2 signaling domain, and optionally wherein the CD2 signaling domain comprises an amino acid sequence according to SEQ ID NO: 49; or

c) the IL-2RB protein signaling domain comprises an amino acid sequence according to SEQ ID NO: 50.

6. The RTCR of any one of claims 1-5, wherein the chimeric intracellular domain further comprises a fourth signal transduction domain, optionally wherein the fourth signal transduction

domain is derived from a CD3 signaling domain, a CD2 signaling domain, an interleukin 2 receptor binding (IL-2RB) protein signaling domain, or a combination thereof, wherein the third and the fourth signal transduction domain are not identical, and optionally wherein:

- a) the CD3 signaling domain is derived from a CD3 ζ or a CD3 ϵ domain, or a combination thereof, optionally wherein the CD3 signaling domain comprises an amino acid sequence according to any one of SEQ ID NOs: 18, 45, 46, 47, and 48;
- b) the CD2 signaling domain is a mutant CD2 signaling domain, optionally wherein the mutant CD2 signaling domain is a truncated CD2 signaling domain, and optionally wherein the CD2 signaling domain comprises an amino acid sequence according to SEQ ID NO: 49; or
- c) the IL-2RB protein signaling domain comprises an amino acid sequence according to SEQ ID NO: 50.

7. The RTCR of any one of claims 1-6, wherein the extracellular domain comprises a protein or a portion thereof that induces activation and/or proliferation of an immune cell, optionally wherein the extracellular domain comprises any one of:

- a) a component of a T cell Receptor (TCR) complex;
- b) a component of a chimeric antigen receptor (CAR);
- c) a component of a T cell co-receptor, wherein the T cell co-receptor is a T cell co-stimulatory protein or a T cell inhibitory protein;
- d) a ligand that binds to a cell surface receptor or a component thereof;
- e) a component of a cytokine receptor;
- f) a component of a chemokine receptor;
- g) a component of an integrin receptor;
- h) a component of an endothelial cell surface protein receptor or a fragment thereof;
- i) a component of a neuronal guidance protein receptor; and
- j) a component of a complement receptor.

8. The RTCR of claim 7, wherein the extracellular domain comprises any one of:

- a) the component of the T cell co-receptor or the CAR is a component of PD1, CD28, CD2, OX-40, ICOS, CTLA-4, CD28, CD3, CD4, CD8, CD40L, Lag-3, Tim-3, TIGIT, or a combination thereof;

b) the component of T cell co-receptor or the CAR binds to CD19, B cell maturation Ag (BCMA), PD-L1, PD-L2, IL-10, a proliferation-inducing ligand (APRIL), BAFF, OX-40L, ICOS-L, B7-1, B7-2, CD40, CD58, CD59, nectin, CD155, or CD112, or a combination thereof;

c) the cytokine receptor binds to IL-10, IL-27, TGF- β , IL-12, IL-1, IL-2, IL-4, IL-5, IFN- γ , IFN- α/β , or a combination thereof;

d) the component of the complement receptor is a component of C3aR, C5aR, CD46/MCP, CD55, CD97, or DAF, or a combination thereof; and/or

e) the extracellular domain comprises an amino acid sequence of a component of epithelial growth factor receptor (EGFR), vascular-endothelial growth factor receptor (VEGFR), chemokine receptor (CCR) 4, CCR5, CCR7, CCR10, netrin-1 receptor, semaphorin receptor, lymphocyte function-associated antigen-1 (LFA-1), leukocyte-specific β 2 integrin (α L β 2, α M β 2, α X β 2, or α D β 2), β 7 integrin (α 4 β 7 or α E β 7), extracellular matrix (ECM)-binding β 1 integrin (α 1- α 6 β 1), L-selectin, or sialyl Lewis^x,

optionally wherein the extracellular domain is a polypeptide, a glycoprotein, or an antibody or a fragment thereof, optionally wherein the antibody or fragment thereof is a Fab fragment, a F(ab)₂ fragment, a diabody, a nanobody, a sdAb, Fv, a V_HH fragment, or a single chain Fv fragment, and

further optionally wherein the extracellular domain binds to a target selected from a tumor antigen, a pathogen associated protein, and an antigen associated with an autoimmune, an inflammatory, a metabolic, or a neurodegenerative condition or disorder, optionally wherein the tumor antigen is a tumor associated antigen (TAA), a tumor secreted antigen (TSA) or an unconventional antigen (UCA), optionally wherein the extracellular domain binds to a target with a binding affinity of 1 fM to 100 μ M, optionally wherein the extracellular domain binds to a target with a binding affinity of 1 μ M to 10 μ M, and

further optionally wherein the extracellular domain comprises:

a) a signal peptide at the N-terminus, wherein the signal peptide is derived from a surface or a secretory protein, optionally wherein the signal peptide comprises:

i) PD-1 signal peptide (PD-1 SP); or

ii) an HLA class I histocompatibility antigen or a portion thereof; and/or

b) a hinge region, optionally wherein the hinge region is derived from CD8, PD-1, CD28, ICOS, or IgG.

9. The RTCR of any one of claims 1-8, wherein the transmembrane domain is derived from CD8, PD1, CD28, COS, or IgG.
10. The RTCR of any one of claims 1-9, wherein the RTCR is for expression in a T cell, wherein the T cell co-expresses at least one of the endogenous co-stimulatory molecules selected from CD28, CD2, OX-40, ICOS, CD28, CD3, CD4, CD8, CD40L, and a combination thereof.
11. A nucleic acid encoding the RTCR of any one of claims 1-10, or a vector comprising said nucleic acid.
12. A cell comprising the nucleic acid or the vector of claim 11, optionally wherein the cell is a modified T cell, or a modified natural killer T cell (NK-T cell), optionally wherein the modified T cell is an allogenic T cell or an autologous T cell, optionally wherein the modified T cell is a naïve T cell, an early memory T cell, a stem cell-like T cell, a stem memory T cell (T_{SCM}), a central memory T cell (T_{CM}), or a regulatory T cell (T_{reg}),
 optionally wherein the cell further comprises a sequence encoding an artificial antigen receptor, a therapeutic polypeptide, an immune cell modulatory protein, or a combination thereof, optionally wherein the artificial antigen receptor comprises a chimeric antigen receptor (CAR),
 optionally wherein the cell expresses the RTCR either transiently or stably, and
 optionally wherein the cell co-expresses with the RTCR at least one or more of the endogenous co-stimulatory molecules selected from CD28, CD2, OX-40, ICOS, CD28, CD3, CD4, CD8, CD40L, and a combination thereof.
13. A modified T lymphocyte (T cell), comprising:
 - (a) a modification of an endogenous sequence encoding a T cell Receptor (TCR), wherein the modification reduces or eliminates a level of expression or activity of the TCR; and
 - (b) a recombinant T cell co-stimulatory receptor (RTCR) according to any one of claims 1-10, optionally further comprising a modification of an endogenous sequence encoding a component of major histocompatibility complex (MHC) class I (MHC-I), wherein the

modification reduces or eliminates a level of expression or activity of the MHC-I, and optionally wherein the modified T cell co-expresses with the RTCR at least one of the endogenous co-stimulatory molecules CD28, CD2, OX-40, ICOS, CD28, CD3, CD4, CD8, CD40L, or a combination thereof.

14. A composition comprising:
 - a) the RTCR of any one of claims 1-10;
 - b) the nucleic acid of claim 11;
 - c) the vector of claim 11;
 - d) the cell of claim 12;
 - e) the modified T cell of claim 13; and/or
 - f) a population of cells, wherein the population comprises a plurality of the cell of claim 12 or wherein the population comprises a plurality of the modified T cell of claim 13.

15. A method of producing a plurality of modified T cells, wherein the method comprises:
 - a) providing a plurality of primary T cells;
 - b) providing a composition comprising the RTCR of any one of claims 1-10, the nucleic acid or the vector of claim 11; and
 - c) introducing into the plurality of primary T cells of (a) the composition of (b), to produce a plurality of modified T cells under conditions that stably express the RTCR within the plurality of modified T cells,

optionally wherein the method further comprises a step of modifying an endogenous sequence encoding an endogenous T cell Receptor (TCR), wherein the modification reduces or eliminates a level of expression or activity of the endogenous TCR,

optionally wherein the method further comprises a step of modifying an endogenous sequence of the plurality of primary T cells, wherein the modification reduces or eliminates a level of expression or activity of a major histocompatibility complex (MHC) class I (MHC-I),

optionally wherein the method further comprises:

 - d) maintaining or expanding the plurality of modified T cells in a suitable cell culture media; and
 - e) either:

- i) cryopreserving the plurality of modified T cells in a suitable cell freezing media; or
- ii) preparing the plurality of modified T cells for administration to a subject in need thereof.

16. Use of a therapeutically effective number of the cell of claim 12, a therapeutically effective number of the modified T cell of claim 13, a therapeutically effective amount of the composition of claim 14, or a therapeutically effective number of the plurality of modified T cells produced by the method of claim 15 in the manufacture of a medicament for treating a disease or disorder,

optionally wherein the subject is a mammal, and optionally wherein the mammal is a human,

wherein the disease or disorder is a cancer, an autoimmune disease or disorder, an infectious disease, an inflammatory disease, a renal disease or disorder, a lung disease or disorder, a liver disease or disorder, a cardiovascular system disease or disorder, a neurodegenerative disease or disorder, or a metabolic disease or disorder, optionally wherein the cancer is a solid tumor or a hematologic cancer,

optionally wherein the solid cancer is a sarcoma, a carcinoma or a melanoma or wherein the hematological cancer is a leukemia, a lymphoma or a myeloma,

and optionally wherein

a) the cancer is selected from acute leukemia, acute lymphoblastic leukemia (ALL), acute lymphocytic leukemia, B cell, T cell or FAB ALL, acute myeloid leukemia (AML), acute myelogenous leukemia, chronic myelocytic leukemia (CML), chronic lymphocytic leukemia (CLL), hairy cell leukemia, myelodysplastic syndrome (MDS), Hodgkin's lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, colorectal carcinoma, pancreatic carcinoma, nasopharyngeal carcinoma, malignant histiocytosis, paraneoplastic syndrome/hypercalcemia of malignancy, bladder cancer, breast cancer, colorectal cancer, endometrial cancer, head cancer, neck cancer, hereditary nonpolyposis cancer, liver cancer, lung cancer, non-small cell lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cell carcinoma, testicular cancer, adenocarcinomas, sarcomas, malignant melanoma, and hemangioma;

b) the infectious disease is caused by a bacteria, a virus, a fungus, a protozoa, or a parasite;

c) the neurodegenerative disorder is Alzheimer's disease (AD) and other dementias, Parkinson's disease (PD) and PD-related disorders, prion disease, Motor neuron diseases (MND), Huntington's disease (HD), Spinocerebellar ataxia (SCA), or Spinal muscular atrophy (SMA); or

d) the inflammatory disease is systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, or multiple sclerosis.

17. A chimeric co-stimulatory intracellular protein (CIP) comprising a first and at least a second signal transduction domain,

wherein the first and the at least second signal transduction domains are non-identical; and

wherein the at least second signal transduction domain comprises a mutant intracellular signaling domain of a tumor necrosis factor receptor (TNFR) family protein,

wherein the mutant intracellular signaling domain of the TNFR family protein is a mutant CD137 (4-1BB) intracellular domain or a mutant CD134 (OX-40) intracellular domain, and optionally wherein the CIP further comprises a transmembrane domain.

18. The CIP of claim 17, wherein:

a) the mutant CD137 intracellular domain comprises

(1) a truncated CD137 intracellular domain, optionally wherein the truncated CD137 intracellular domain comprises:

1i) an amino acid sequence according to amino acid position 13 to amino acid position 42 of the CD137 intracellular domain;

1ii) a deletion of a continuous stretch of one, two, three, four, five, six, seven, eight, nine, ten or more amino acids from the N-terminus the CD137 intracellular domain;

1iii) a deletion of one, two, three, four, five, six, seven, eight, nine, ten or more amino acids from amino acid position 1 to amino acid position 12 of the N-terminus of the CD137 intracellular domain; and/or

(1) an amino acid sequence according to SEQ ID NO: 3;

(2) a deletion of one, two, three or four lysine residue(s) from amino acid position 1 to amino acid position 12 of the N-terminus of the CD137 intracellular domain;

(3) one or more lysine mutation(s) from amino acid position 1 to amino acid position 12 of the N-terminus of the CD137 intracellular domain, optionally one or more lysine mutation(s) at amino acid positions selected from amino acid positions 1, 5, 6 and 12 of the N-terminus of the CD137 intracellular domain;

(4) a deletion of one or more proximal basic amino acids from amino acid position 1 to amino acid position 12 of the N-terminus of the CD137 intracellular domain; and/or

(5) one or more proximal basic amino acid mutation(s) from amino acid position 1 to amino acid position 12 of the N-terminus of the CD137 intracellular domain optionally one or more proximal basic amino acid mutation(s) at amino acid positions selected from amino acid positions 1, 2, 3, 4, 5 and 6 of the N-terminus of the CD137 intracellular domain, and

optionally a lysine mutation at amino acid position 12 of the N-terminus of the CD137 intracellular domain; or

b) the mutant CD134 intracellular domain comprises

(1) a truncated CD134 intracellular domain, optionally wherein the truncated CD134 intracellular domain comprises:

1i) an amino acid sequence according to amino acid position 15 to amino acid position 37 of the CD134 intracellular domain;

1ii) a deletion of a continuous stretch of one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen or more amino acids from the N-terminus of the CD134 intracellular domain;

1iii) a deletion of one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen or more amino acids from amino acid position 1 to amino acid position 14 of the N-terminus of the CD134 intracellular domain; and/or

1iv) an amino acid sequence according to SEQ ID NO: 6;

(2) a deletion of a lysine residue from amino acid position 1 to amino acid position 14 of the N-terminus of the CD134 intracellular domain;

(3) a lysine mutation at amino acid position 12 of the N-terminus of the CD134 intracellular domain;

(4) a deletion of one or more proximal basic amino acids from amino acid position 1 to amino acid position 14 of the N-terminus of the CD134 intracellular domain; and/or

(5) one or more proximal basic amino acid mutation(s) from amino acid position 1 to amino acid position 14 of the N-terminus of the CD134 intracellular domain, optionally one or more proximal basic amino acid mutation(s) at amino acid positions selected from amino acid positions 1, 2, and 5 of the N-terminus of the CD134 intracellular domain, and

optionally wherein the mutant CD134 intracellular domain further comprises a lysine mutation at amino acid position 12 of the N-terminus of the CD134 intracellular domain.

19. The CIP of claim 17 or 18, wherein the chimeric intracellular domain comprises a first signal transduction domain derived from a protein of the CD28 family, optionally wherein the first signal transduction domain is derived from CD28, CD28H, ICOS, or a combination thereof, and optionally wherein:

a) the first signal transduction domain is derived from ICOS, optionally wherein

i) the first signal transduction domain derived from ICOS comprises an amino acid sequence according to SEQ ID NO: 9;

ii) the first signal transduction domain comprises a portion of a CD28 intracellular domain combined with an ICOS domain according to SEQ ID NO: 9; or

iii) the first signal transduction domain comprises an amino acid sequence according to any one of SEQ ID NOs: 12 or 109; or

b) the first signal transduction domain is derived from CD28, optionally wherein

i) the first signal transduction domain derived from CD28 comprises an amino acid sequence according to SEQ ID NO: 10; or

ii) the first signal transduction domain comprises an amino acid sequence according to any one of SEQ ID NOs: 121-122;

and further optionally wherein the CIP comprises an amino acid sequence according to any one of SEQ ID NOs: 14-17.

20. The CIP of any one of claims 17-19, wherein the CIP further comprises a third signal transduction domain, optionally wherein the third signal transduction domain is derived from a

CD3 signaling domain, a CD2 signaling domain, an interleukin 2 receptor binding (IL-2RB) protein signaling domain, or a combination thereof, and optionally wherein:

- a) the CD3 signaling domain is derived from a CD3 ζ or a CD3 ϵ domain, or a combination thereof, optionally wherein the CD3 signaling domain comprises an amino acid sequence according to any one of SEQ ID NOs: 18, 45, 46, 47, and 48;
- b) the CD2 signaling domain comprises a mutant CD2 signaling domain, optionally wherein the mutant CD2 signaling domain is a truncated CD2 signaling domain, and optionally wherein the CD2 signaling domain comprises an amino acid sequence according to SEQ ID NO: 49; or
- c) the IL-2RB protein signaling domain comprises an amino acid sequence according to SEQ ID NO: 50.

21. The CIP of any one of claims 17-20, wherein the chimeric intracellular domain further comprises a fourth signal transduction domain, optionally wherein the fourth signal transduction domain is derived from a CD3 signaling domain, a CD2 signaling domain or an interleukin 2 receptor binding (IL-2RB) protein signaling domain or a combination thereof, wherein the third and the fourth signal transduction domain are not identical, optionally wherein

- a) the CD3 signaling domain is derived from a CD3 ζ or a CD3 ϵ domain, or a combination thereof, and optionally wherein the CD3 signaling domain comprises an amino acid sequence according to any one of SEQ ID NOs: 18, 45, 46, 47, and 48;
- b) the CD2 signaling domain is a mutant CD2 signaling domain, optionally wherein the mutant CD2 signaling domain is a truncated CD2 signaling domain, optionally wherein the CD2 signaling domain comprises an amino acid sequence according to SEQ ID NO: 49; or
- c) the IL-2RB protein signaling domain comprises an amino acid sequence according to SEQ ID NO: 50.

22. The CIP of any one of claims 17-21, wherein the CIP is for expression in a T cell, wherein the T cell co-expresses at least one of the endogenous co-stimulatory molecules selected from CD28, CD2, OX-40, ICOS, CD28, CD3, CD4, CD8, CD40L, and a combination thereof.

23. The cell of claim 12, the modified T cell of claim 13, the composition of claim 14, or the plurality of modified T cells produced by the method of claim 15 for use in therapy.