second domain of the pair of affinity domains. Also provided herein are compositions that include any of the multi-chain chimeric polypeptides described herein, nucleic acids that encode any of the multi-chain chimeric polypeptides described herein, and cells that include any of the nucleic acids that encode any of the multi-chain chimeric polypeptides described herein. Also provided herein are methods of stimulating an immune cell and methods of treating a subject in need thereof that include the use of any of the multi-chain chimeric polypeptides described herein. Also provided herein are methods of producing any of the multi-chain chimeric polypeptides described herein.

Accordingly, ~~in one aspect,~~ provided herein is a multi-chain chimeric polypeptide comprising:

(a) a first chimeric polypeptide comprising:

(i) a first target-binding domain;

(ii) a soluble tissue factor domain; and

(iii) a first domain of a pair of affinity domains;

(b) a second chimeric polypeptide comprising:

(i) a second domain of a pair of affinity domains; and

(ii) a second target-binding domain,

wherein the first chimeric polypeptide and the second chimeric polypeptide associate through the binding of the first domain and the second domain of the pair of affinity domains.

In one aspect, the present disclosure refers to a multi-chain chimeric polypeptide comprising:

(a) a first chimeric polypeptide comprising:

(i) a first target-binding domain;

(ii) a soluble tissue factor domain; and

(iii) a first domain of a pair of affinity domains;

(b) a second chimeric polypeptide comprising:

(i) a second domain of a pair of affinity domains; and

(ii) a second target-binding domain,

wherein:

the first chimeric polypeptide and the second chimeric polypeptide associate through the binding of the first domain and the second domain of the pair of affinity domains;

the first target-binding domain, the second target-binding domain, the first domain of the pair of affinity domains, and the second domain of the pair of affinity domains are protein domains; and

the soluble tissue factor domain directly abuts or is connected to the first domain of the pair of affinity domains in the first chimeric polypeptide through a linker sequence. In some examples, the first target-binding domain and the soluble tissue factor domain directly abut each other in the first chimeric polypeptide. In some examples, the first chimeric polypeptide further comprises a linker sequence between the first target-binding domain and the soluble tissue factor domain in the first chimeric polypeptide. In some examples, the soluble tissue factor domain and the first domain of the pair of affinity domains directly abut each other in the first chimeric polypeptide. In some examples, the first chimeric polypeptide further comprises a linker sequence between the soluble tissue factor domain and the first domain of the pair of affinity domains in the first chimeric polypeptide. In some examples, the second domain of the pair of affinity domains and the second target-binding domain directly abut each other in the second chimeric polypeptide. In some examples, the second chimeric polypeptide further comprises a linker sequence between the second domain of the pair of affinity domains and the second target-binding domain in the second chimeric

examples, the soluble IL15 has a D8N or D8A amino acid substitution. In some examples, the human IL15Rα is a mature full-length IL15Rα. In some examples, the pair of affinity domains is selected from the group consisting of: barnase and barnstar, a PKA and an AKAP, adapter/docking tag modules based on mutated RNase I fragments, and SNARE modules based on interactions of the proteins syntaxin, synaptotagmin, synaptobrevin, and SNAP25. In some examples, the first chimeric polypeptide and/or the second chimeric polypeptide further comprises a signal sequence at its N-terminal end.

In one aspect, the present disclosure refers to a multi-chain chimeric polypeptide comprising:

(a) a first chimeric polypeptide comprising:

(i) a first target-binding domain;

(ii) a soluble tissue factor domain; and

(iii) a first domain of a pair of affinity domains;

(b) a second chimeric polypeptide comprising:

(i) a second domain of a pair of affinity domains; and

(ii) a second target-binding domain,

wherein:

the first chimeric polypeptide and the second chimeric polypeptide associate through the binding of the first domain and the second domain of the pair of affinity domains; ~~and~~

the first target-binding domain binds specifically to a ligand of TGF-β receptor II (TGF-βRII) and the second target-binding domain binds specifically to a ligand of TGF-βRII;

the first target-binding domain, the second target-binding domain, the first domain of the pair of affinity domains, and the second domain of the pair of affinity domains are protein domains; and

the soluble tissue factor domain directly abuts or is connected to the first domain of the pair of affinity domains in the first chimeric polypeptide through a linker sequence.

In one aspect, the present disclosure refers to a multi-chain chimeric polypeptide comprising:

(a) a first chimeric polypeptide comprising:

(i) a first target-binding domain;

(ii) a soluble tissue factor domain; and

(iii) a first domain of a pair of affinity domains;

(b) a second chimeric polypeptide comprising:

(i) a second domain of a pair of affinity domains; and

(ii) a second target-binding domain,

wherein:

the first chimeric polypeptide and the second chimeric polypeptide associate through the binding of the first domain and the second domain of the pair of affinity domains; ~~and~~

the first target-binding domain binds specifically to a receptor for IL-18 and the second target-binding domain binds specifically to a receptor for IL-12, or the first target-binding domain binds specifically to a receptor for IL-12 and the second target-binding domain binds specifically to a receptor for IL-18;

the first target-binding domain, the second target-binding domain, the first domain of the pair of affinity domains, and the second domain of the pair of affinity domains are protein domains; and

the soluble tissue factor domain directly abuts or is connected to the first domain of the pair of affinity domains in the first chimeric polypeptide through a linker sequence.

In one aspect, the present disclosure refers to a multi-chain chimeric polypeptide comprising:

(a) a first chimeric polypeptide comprising:

(i) a first target-binding domain;

(ii) a soluble tissue factor domain; and

(iii) a first domain of a pair of affinity domains;

(b) a second chimeric polypeptide comprising:

(i) a second domain of a pair of affinity domains; and

(ii) a second target-binding domain,

wherein:

the first chimeric polypeptide and the second chimeric polypeptide associate through the binding of the first domain and the second domain of the pair of affinity domains; ~~and~~

the first target-binding domain binds specifically to a receptor for IL-7 and the second target-binding domain binds specifically to a receptor for IL-21, or the first target-binding domain binds specifically to a receptor for IL-21 and the second target-binding domain binds specifically to a receptor for IL-7;

the first target-binding domain, the second target-binding domain, the first domain of the pair of affinity domains, and the second domain of the pair of affinity domains are protein domains; and

the soluble tissue factor domain directly abuts or is connected to the first domain of the pair of affinity domains in the first chimeric polypeptide through a linker sequence.

In some examples, the multi-chain chimeric polypeptide comprises a composition. In one aspect, the present disclosure refers to a composition comprising any of the multi-chain chimeric polypeptides as disclosed herein. In some examples, the composition is a pharmaceutical composition. In some examples, the composition comprises at least one dose of the multi-chain chimeric polypeptide. In one aspect, the present disclosure refers to a kit comprising at least one dose of the composition disclosed herein.

~~In one aspect, p~~Provided herein is a method of stimulating an immune cell, the method comprising: contacting an immune cell with an effective amount of any of the multi-chain chimeric polypeptides or compositions described above. In one aspect, the present disclosure refers to an in vitro method of stimulating an immune cell, the method comprising: contacting an immune cell with an effective amount of any of the multi-chain chimeric polypeptides or compositions described above. In some examples, the method comprises contacting the immune cell in vitro. In some examples, the method comprises obtaining the immune cell from a subject. In some examples, the method comprises obtaining the immune cell from the subject prior to the contacting step. In some examples, the method comprises contacting the immune cell in vivo. In some examples, the method comprises selecting the immune cell from the group consisting of: an immature thymocyte, a peripheral blood lymphocyte, a naïve T cell, a pluripotent Th cell precursor, a lymphoid progenitor cell, a Treg cell, a memory T cell, a Th17 cell, a Th22 cell, a Th9 cell, a Th2 cell, a Th1 cell, a Th3 cell, γδ T cell, an αβ T cell, a tumor-infiltrating T cell, a $CD8^+$ T cell, a $CD4^+$ T cell, a natural killer T cell, a mast cell, a macrophage, a neutrophil, a dendritic cell, a basophil, an eosinophil, and a natural killer cell. In some examples, the method comprises genetically modifying the immune cell to express a chimeric antigen receptor or a recombinant T-cell receptor. In some examples, the method comprises introducing into the immune cell a nucleic acid encoding a chimeric antigen-receptor or a recombinant T-cell receptor after the contacting step. In some examples, the method

~~In one aspect, a~~Also provided herein is a method of inducing or increasing proliferation of an immune cell, the method comprising: contacting an immune cell with an effective amount of any of the multi-chain chimeric polypeptides or compositions described above. In one aspect, the present disclosure refers to an in vitro method of inducing or increasing proliferation of an immune cell, the method comprising: contacting an immune cell with an effective amount of any of the multi-chain chimeric polypeptides or compositions described above. In some examples, the method comprises contacting the immune cell in vitro. In some examples, the method comprises obtaining the immune cell from a subject. In some examples, the method comprises obtaining the immune cell from the subject prior to the contacting step. In some examples, the method comprises contacting the immune cell in vivo. In some examples, the method comprises selecting the immune cell from the group consisting of: an immature thymocyte, a peripheral blood lymphocyte, a naïve T cell, a pluripotent Th cell precursor, a lymphoid progenitor cell, a Treg cell, a memory T cell, a Th17 cell, a Th22 cell, a Th9 cell, a Th2 cell, a Th1 cell, a Th3 cell, γδ T cell, an αβ T cell, a tumor-infiltrating T cell, a $CD8^+$ T cell, a $CD4^+$ T cell, a natural killer T cell, a mast cell, a macrophage, a neutrophil, a dendritic cell, a basophil, an eosinophil, and a natural killer cell. In some examples, the method comprises modifying the immune cell to express a chimeric antigen receptor or a recombinant T-cell receptor. In some examples, the method further comprises introducing into the immune cell a nucleic acid encoding a chimeric antigen-receptor or a recombinant T-cell receptor after the contacting step. In some examples, the method further comprises administering the immune cell to a subject in need thereof. In some examples, the method comprises identifying or diagnosing the subject as having an age-related disease or condition. In some examples, the age-related disease or condition is selected from the group consisting of: Alzheimer's disease, aneurysm, cystic fibrosis, fibrosis in pancreatitis, glaucoma, hypertension, idiopathic pulmonary fibrosis, inflammatory bowel disease, intervertebral disc degeneration, macular degeneration, osteoarthritis, type 2 diabetes mellitus, adipose atrophy, lipodystrophy, atherosclerosis, cataracts, COPD, idiopathic pulmonary fibrosis, kidney transplant failure, liver fibrosis, loss of bone mass, myocardial infarction, sarcopenia, wound healing, alopecia, cardiomyocyte hypertrophy, osteoarthritis, Parkinson's disease, age-associated loss of lung tissue elasticity, macular degeneration, cachexia, glomerulosclerosis, liver cirrhosis, NAFLD, osteoporosis, amyotrophic lateral sclerosis, Huntington's disease, spinocerebellar ataxia, multiple sclerosis, and renal dysfunction. In some examples, the method comprises

identifying or diagnosing the subject as having a cancer. In some examples, the cancer is selected from the group consisting of: solid tumor, hematological tumor, sarcoma, osteosarcoma, glioblastoma, neuroblastoma, melanoma, rhabdomyosarcoma, Ewing sarcoma, osteosarcoma, B-cell neoplasms, multiple myeloma, B-cell lymphoma, B-cell non-Hodgkin's lymphoma, Hodgkin's lymphoma, chronic lymphocytic leukemia (CLL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphocytic leukemia (ALL), myelodysplastic syndromes (MDS), cutaneous T-cell lymphoma, retinoblastoma, stomach cancer, urothelial carcinoma, lung cancer, renal cell carcinoma, gastric and esophageal cancer, pancreatic cancer, prostate cancer, breast cancer, colorectal cancer, ovarian cancer, non-small cell lung carcinoma, squamous cell head and neck carcinoma, endometrial cancer, cervical cancer, liver cancer, and hepatocellular carcinoma. In some examples, the method comprises diagnosing or identifying the subject as having an infectious disease. In some examples, the infectious disease is infection with human immunodeficiency virus, cytomegalovirus, adenovirus, coronavirus, rhinovirus, rotavirus, smallpox, herpes simplex virus, hepatitis B virus, hepatitis A virus, and hepatitis C virus, papillomavirus, and influenza virus.

~~In one aspect, a~~Also provided herein is a method of inducing differentiation of an immune cell into a memory or memory-like immune cell, the method comprising: contacting an immune cell with an effective amount of any of the multi-chain chimeric polypeptides or compositions discussed above. In one aspect, the present disclosure refers to an in vitro method of inducing differentiation of an immune cell into a memory or memory-like immune cell, the method comprising: contacting an immune cell with an effective amount of any of the multi-chain chimeric polypeptides or the compositions described above. In some examples, the method comprises contacting the immune cell in vitro. In some examples, the method comprises obtaining the immune cell from a subject. In some examples, the method further comprises obtaining the immune cell from the subject prior to the contacting step. In some examples, the method comprises contacting the immune cell in vivo. In some examples, the immune cell is selected from the group consisting of: an immature thymocyte, a peripheral blood lymphocyte, a naïve T cell, a pluripotent Th cell precursor, a lymphoid progenitor cell, a Treg cell, a Th17 cell, a Th22 cell, a Th9 cell, a Th2 cell, a Th1 cell, a Th3 cell, γδ T cell, an αβ T cell, a tumor-infiltrating T cell, a CD8+ T cell, a CD4+ T cell, a natural killer T cell, a mast cell, a macrophage, a neutrophil, a dendritic cell, a basophil, an eosinophil, and a natural killer cell. In some examples, the immune cell has previously been genetically modified to express a chimeric antigen

simplex virus, hepatitis B virus, hepatitis A virus, and hepatitis C virus, papillomavirus, and influenza virus.

~~In one aspect, a~~Also provided herein is a method of killing a cancer cell, an infected cell, or a senescent cell in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of any of the multi-chain chimeric polypeptides or compositions discussed above. In one aspect, the present disclosure refers to use of any of the multi-chain chimeric polypeptides described above in the manufacture of a medicament for killing a cancer cell, an infected cell, or a senescent cell in a subject having a cancer, an aging-related disease or condition, or an infectious disease. In some examples, the method comprises identifying or diagnosing the subject as having a cancer. In some examples, the cancer is selected from the group consisting of: solid tumor, hematological tumor, sarcoma, osteosarcoma, glioblastoma, neuroblastoma, melanoma, rhabdomyosarcoma, Ewing sarcoma, osteosarcoma, B-cell neoplasms, multiple myeloma, B-cell lymphoma, B-cell non-Hodgkin's lymphoma, Hodgkin's lymphoma, chronic lymphocytic leukemia (CLL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphocytic leukemia (ALL), myelodysplastic syndromes (MDS), cutaneous T-cell lymphoma, retinoblastoma, stomach cancer, urothelial carcinoma, lung cancer, renal cell carcinoma, gastric and esophageal cancer, pancreatic cancer, prostate cancer, breast cancer, colorectal cancer, ovarian cancer, non-small cell lung carcinoma, squamous cell head and neck carcinoma, endometrial cancer, cervical cancer, liver cancer, and hepatocellular carcinoma. In some examples, the method comprises identifying or diagnosing the subject as having an aging-related disease or condition. In some examples, the aging-related disease or condition is selected from the group consisting of: Alzheimer's disease, aneurysm, cystic fibrosis, fibrosis in pancreatitis, glaucoma, hypertension, idiopathic pulmonary fibrosis, inflammatory bowel disease, intervertebral disc degeneration, macular degeneration, osteoarthritis, type 2 diabetes mellitus, adipose atrophy, lipodystrophy, atherosclerosis, cataracts, COPD, idiopathic pulmonary fibrosis, kidney transplant failure, liver fibrosis, loss of bone mass, myocardial infarction, sarcopenia, wound healing, alopecia, cardiomyocyte hypertrophy, osteoarthritis, Parkinson's disease, age-associated loss of lung tissue elasticity, macular degeneration, cachexia, glomerulosclerosis, liver cirrhosis, NAFLD, osteoporosis, amyotrophic lateral sclerosis, Huntington's disease, spinocerebellar ataxia, multiple sclerosis, and renal dysfunction. In some examples, the method comprises administering to the subject a therapeutically effective amount of any of the multi-chain

In one aspect, the present disclosure refers to ~~a method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of any of the multi-chain chimeric polypeptides or compositions discussed above~~use of any of the multi-chain chimeric polypeptides described above in the manufacture of a medicament for treating a cancer, an aging-related disease or condition, or an infectious disease.

In one aspect, also provided herein is a nucleic acid encoding any of the multi-chain chimeric polypeptides discussed above. Some examples comprise vector containing any of the nucleic acids discussed above. In one aspect, the present disclosure refers to a vector comprising the nucleic acid discussed above. In some examples, the vector is an expression vector. Some examples comprise a cell containing any of the nucleic acids discussed above. In one aspect, the present disclosure refers to a cell comprising the nucleic acid or the vector discussed above. In one aspect, the present disclosure refers to a cell comprising the nucleic acid discussed above.

In one aspect, also provided herein is a method of producing a multi-chain chimeric polypeptide, the method comprising: culturing the cell discussed above in a culture medium under conditions sufficient to result in the production of the multi-chain chimeric polypeptide; and recovering the multi-chain chimeric polypeptide from the cell and/or the culture medium. In some examples, the method comprises producing a multi-chain chimeric polypeptide by the methods discussed above. ~~In one aspect, the present disclosure refers to a multi-chain chimeric polypeptide produced by the method discussed above.~~

In some examples, the mutant soluble human tissue factor domain comprises a sequence that is at least 80% identical to SEQ ID NO: 3. In some examples, the soluble human tissue factor domain comprises a sequence that is at least 90% identical to SEQ ID NO: 3. In some examples, the soluble human tissue factor domain comprises a sequence that is at least 95% identical to SEQ ID NO: 3. In some examples, the multi-chain chimeric polypeptide of claim 140, wherein the soluble human tissue factor domain comprises a sequence that is 100% identical to SEQ ID NO: 3. In some examples, the soluble human tissue factor domain comprises a sequence that is at least 80% identical to SEQ ID NO: 4. In some examples, the soluble human tissue factor domain comprises a sequence that is at least 90% identical to SEQ ID NO: 4. In some examples, the soluble human tissue factor domain comprises a sequence that is at least 95% identical to SEQ ID NO:4. In some examples, the soluble human tissue factor domain comprises a sequence that is 100% identical to SEQ ID NO: 4.

As used herein, the term “chimeric” refers to a polypeptide that includes amino acid sequences (e.g., domains) originally derived from two different sources (e.g., two different naturally-occurring proteins, e.g., from the same or different species). For example, a chimeric polypeptide can include domains from at least two different naturally occurring human proteins. In some examples, a chimeric polypeptide can include a domain that is a synthetic sequence (e.g., an scFv) and a domain that is derived from a naturally-occurring protein (e.g., a naturally-occurring human protein). In some

WHAT IS CLAIMED IS:

1. A multi-chain chimeric polypeptide comprising:

(a) a first chimeric polypeptide comprising:

(i) a first target-binding domain;

(ii) a soluble tissue factor domain; and

(iii) a first domain of a pair of affinity domains;

(b) a second chimeric polypeptide comprising:

(i) a second domain of a pair of affinity domains; and

(ii) a second target-binding domain,

wherein:

the first chimeric polypeptide and the second chimeric polypeptide associate through the binding of the first domain and the second domain of the pair of affinity domains;

the first target-binding domain, the second target-binding domain, the first domain of the pair of affinity domains, and the second domain of the pair of affinity domains are protein domains; and

the soluble tissue factor domain directly abuts or is connected to the first domain of the pair of affinity domains in the first chimeric polypeptide through a linker sequence.

2. The multi-chain chimeric polypeptide of claim 1, wherein the first target-binding domain and the soluble tissue factor domain directly abut each other in the first chimeric polypeptide.

3. The multi-chain chimeric polypeptide of claim 1, wherein the first chimeric polypeptide further comprises a linker sequence between the first target-binding domain and the soluble tissue factor domain in the first chimeric polypeptide.

4. The multi-chain chimeric polypeptide of any one of claims 1-3, wherein the soluble tissue factor domain and the first domain of the pair of affinity domains directly abut each other in the first chimeric polypeptide.

5. The multi-chain chimeric polypeptide of any one of claims 1-3, wherein the ~~first chimeric polypeptide further comprises a linker sequence between the~~ soluble tissue factor domain and the first domain of the pair of affinity domains in the first chimeric polypeptide are connected through the linker sequence.

6. The multi-chain chimeric polypeptide of any one of claims 1-5, wherein the second domain of the pair of affinity domains and the second target-binding domain directly abut each other in the second chimeric polypeptide.

7. The multi-chain chimeric polypeptide of any one of claims 1-5, wherein second chimeric polypeptide further comprises a linker sequence between the second domain of the pair of affinity domains and the second target-binding domain in the second chimeric polypeptide.

8. The multi-chain chimeric polypeptide of any one of claims 1-7, wherein the first target-binding domain and the second target-binding domain bind specifically to the same antigen.

9. The multi-chain chimeric polypeptide of any one of claims 1-7, wherein the first target-binding domain and the second target-binding domain bind specifically to different antigens.

10. The multi-chain chimeric polypeptide of any one of claims 1-9, wherein one or both of the first target-binding domain and the second target-binding domain is an antigen-binding domain.

11. The multi-chain chimeric polypeptide of any one of claims 1-10, wherein one or both of the first target-binding domain and the second target-binding domain bind specifically to a target selected from the group consisting of: CD16a, CD28, CD3, CD33, CD20, CD19, CD22, CD123, IL-1R, IL-1, VEGF, IL-6R, IL-4, IL-10, PDL-1, TIGIT, PD-1, TIM3, CTLA4, MICA, MICB, IL-6, IL-8, TNFα, CD26a, CD36, ULBP2, CD30,

CD200, IGF-1R, MUC4AC, MUC5AC, Trop-2, CMET, EGFR, HER1, HER2, HER3, PSMA, CEA, B7H3, EPCAM, BCMA, P-cadherin, CEACAM5, a UL16-binding protein, HLA-DR, DLL4, TYRO3, AXL, MER, CD122, CD155, PDGF-DD, a ligand of TGF-β receptor II (TGF-βRII), a ligand of TGF-βRIII, a ligand of DNAM-1, a ligand of NKp46, a ligand of NKp44, a ligand of NKG2D, a ligand of NKp30, a ligand for a scMHCI, a ligand for a scMHCII, a ligand for a scTCR, a receptor for IL-1, a receptor for IL-2, a receptor for IL-3, a receptor for IL-7, a receptor for IL-8, a receptor for IL-10, a receptor for IL-12, a receptor for IL-15, a receptor for IL-17, a receptor for IL-18, a receptor for IL-21, a receptor for PDGF-DD, a receptor for stem cell factor (SCF), a receptor for stem cell-like tyrosine kinase 3 ligand (FLT3L), a receptor for MICA, a receptor for MICB, a receptor for a ULP16-binding protein, a receptor for CD155, a receptor for CD122, and a receptor for CD28.

12. The multi-chain chimeric polypeptide of any one of claims 1-10, wherein one or both of the first target-binding domain and the second target-binding domain is a soluble interleukin or cytokine protein.

13. The multi-chain chimeric polypeptide of claim 12, wherein the soluble interleukin, cytokine, or ligand protein is selected from the group consisting of: IL-1, IL-2, IL-3, IL-7, IL-8, IL-10, IL-12, IL-15, IL-17, IL-18, IL-21, PDGF-DD, SCF, and FLT3L.

14. The multi-chain chimeric polypeptide of any one of claims 1-10, wherein one or both of the first target-binding domain and the second target-binding domain is a soluble interleukin or cytokine receptor.

15. The multi-chain chimeric polypeptide of claim 14, wherein the soluble receptor is a soluble TGF-β receptor II (TGF-βRII), a soluble TGF-βRIII, a soluble NKG2D, a soluble NKp30, a soluble NKp44, a soluble NKp46, a soluble DNAM-1, a scMHCI, a scMHCII, a scTCR, a soluble CD155, or a soluble CD28.

16. The multi-chain chimeric polypeptide of any one of claims 1-15, wherein the first chimeric polypeptide further comprises one or more additional target-binding domain(s).

17. The multi-chain chimeric polypeptide of any one of claims 1-16, wherein the second chimeric polypeptide further comprises one or more additional target-binding domains.

18. The multi-chain chimeric polypeptide of any one of claims 1-17, wherein the soluble tissue factor domain is a soluble human tissue factor domain.

19. The multi-chain chimeric polypeptide of claim 18, wherein the soluble human tissue factor domain comprises a sequence that is at least 80% identical to SEQ ID NO: 1.

20. The multi-chain chimeric polypeptide of any one of claims 1-19, wherein the pair of affinity domains is a sushi domain from an alpha chain of human IL-15 receptor (IL15Rα) and a soluble IL-15.

21. The multi-chain chimeric polypeptide of any one of claims 1-19, wherein the pair of affinity domains is selected from the group consisting of: barnase and barnstar, a PKA and an AKAP, adapter/docking tag modules based on mutated RNase I fragments, and SNARE modules based on interactions of the proteins syntaxin, synaptotagmin, synaptobrevin, and SNAP25.

22. The multi-chain chimeric polypeptide of any one of claims 1-21, wherein the first chimeric polypeptide and/or the second chimeric polypeptide further comprises a signal sequence at its N-terminal end.

23. A composition comprising any of the multi-chain chimeric polypeptides of claims 1-22.

24. The composition of claim 23, wherein the composition is a pharmaceutical composition.

25. A kit comprising at least one dose of the composition of claim 23 or 24.

26. An in vitro method of stimulating an immune cell, the method comprising:

contacting an immune cell with an effective amount of any of the multi-chain chimeric polypeptides of claims 1-22 or the composition of claim 23 or 24.

27. An in vitro method of inducing or increasing proliferation of an immune cell, the method comprising:

contacting an immune cell with an effective amount of any of the multi-chain chimeric polypeptides of claims 1-22 or the composition of claim 23 or 24.

28. An in vitro method of inducing differentiation of an immune cell into a memory or memory-like immune cell, the method comprising:

contacting an immune cell with an effective amount of any of the multi-chain chimeric polypeptides of claims 1-22 or the composition of claim 23 or 24.

~~29. The method of any one of claims 26-28, wherein the immune cell is contacted in vitro.~~

~~30. The method of any one of claims 26-28, wherein the immune cell is contacted in vivo.~~

~~31~~29. The method of any one of claims 26-~~30~~28, wherein the immune cell is selected from the group consisting of: an immature thymocyte, a peripheral blood lymphocyte, a naïve T cell, a pluripotent Th cell precursor, a lymphoid progenitor cell, a Treg cell, a Th17 cell, a Th22 cell, a Th9 cell, a Th2 cell, a Th1 cell, a Th3 cell, γδ T cell, an αβ T cell, a tumor-infiltrating T cell, a CD8+ T cell, a CD4+ T cell, a natural killer T

cell, a mast cell, a macrophage, a neutrophil, a dendritic cell, a basophil, an eosinophil, and a natural killer cell.

~~32~~30. The method of any one of claims 26-~~31~~29, wherein the immune cell has previously been genetically modified to express a chimeric antigen receptor or a recombinant T-cell receptor.

~~33~~31. Use of the multi-chain chimeric polypeptide of any one of claims 1-22 in the manufacture of a medicament for ~~A method of~~ killing a cancer cell, an infected cell, or a senescent cell in a subject having a cancer, an aging-related disease or condition, or an infectious disease~~in need thereof, the method comprising administering to the subject a therapeutically effective amount of any of the multi-chain chimeric polypeptides of claims 1-22 or the composition of claim 23 or 24~~.

~~34~~32. Use of the multi-chain chimeric polypeptide of any one of claims 1-22 in the manufacture of a medicament for~~A method of~~ treating a cancer, an aging-related disease or condition, or an infectious disease ~~a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of any of the multi-chain chimeric polypeptides of claims 1-22 or the composition of claim 23 or 24~~.

~~35. The method of claim 33 or 34, wherein the subject has been identified or diagnosed as having a cancer, an aging-related disease or condition, or an infectious disease.~~

~~36~~33. The use~~method~~ of claim ~~35~~31 or 32, wherein the cancer is selected from the group consisting of: solid tumor, hematological tumor, sarcoma, osteosarcoma, glioblastoma, neuroblastoma, melanoma, rhabdomyosarcoma, Ewing sarcoma, osteosarcoma, B-cell neoplasms, multiple myeloma, B-cell lymphoma, B-cell non-Hodgkin's lymphoma, Hodgkin's lymphoma, chronic lymphocytic leukemia (CLL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphocytic leukemia (ALL), myelodysplastic syndromes (MDS), cutaneous T-cell lymphoma,

retinoblastoma, stomach cancer, urothelial carcinoma, lung cancer, renal cell carcinoma, gastric and esophageal cancer, pancreatic cancer, prostate cancer, breast cancer, colorectal cancer, ovarian cancer, non-small cell lung carcinoma, squamous cell head and neck carcinoma, endometrial cancer, cervical cancer, liver cancer, and hepatocellular carcinoma.

~~37~~34. The use~~method~~ of claim ~~35~~31 or 32, wherein the aging-related disease or condition is selected from the group consisting of: Alzheimer's disease, aneurysm, cystic fibrosis, fibrosis in pancreatitis, glaucoma, hypertension, idiopathic pulmonary fibrosis, inflammatory bowel disease, intervertebral disc degeneration, macular degeneration, osteoarthritis, type 2 diabetes mellitus, adipose atrophy, lipodystrophy, atherosclerosis, cataracts, COPD, idiopathic pulmonary fibrosis, kidney transplant failure, liver fibrosis, loss of bone mass, myocardial infarction, sarcopenia, wound healing, alopecia, cardiomyocyte hypertrophy, osteoarthritis, Parkinson's disease, age-associated loss of lung tissue elasticity, macular degeneration, cachexia, glomerulosclerosis, liver cirrhosis, NAFLD, osteoporosis, amyotrophic lateral sclerosis, Huntington's disease, spinocerebellar ataxia, multiple sclerosis, and renal dysfunction.

~~38~~35. The use~~method~~ of claim ~~35~~31 or 32, wherein the infectious disease is infection with human immunodeficiency virus, cytomegalovirus, adenovirus, coronavirus, rhinovirus, rotavirus, smallpox, herpes simplex virus, hepatitis B virus, hepatitis A virus, and hepatitis C virus, papillomavirus, and influenza virus.

~~39~~36. Nucleic acid encoding any of the multi-chain chimeric polypeptides of any one of claims 1-22.

~~40~~37. A vector comprising the nucleic acid of claim ~~39~~36.

~~41~~38. A cell comprising the nucleic acid of claim ~~39~~ 36 or the vector of claim ~~40~~37.

~~42~~39. A method of producing a multi-chain chimeric polypeptide, the method comprising:

culturing the cell of claim ~~41~~ 38 in a culture medium under conditions sufficient to result in the production of the multi-chain chimeric polypeptide; and

recovering the multi-chain chimeric polypeptide from the cell and/or the culture medium.

~~43. A multi-chain chimeric polypeptide produced by the method of claim 42.~~

~~44~~40. The multi-chain chimeric polypeptide of claim 18, wherein the human soluble tissue factor domain does not initiate blood coagulation.

~~45~~41. The multi-chain chimeric polypeptide of any one of claims 1-22, wherein the soluble tissue factor domain comprises or consists of a sequence from a wildtype soluble human tissue factor.

~~46~~42. A multi-chain chimeric polypeptide comprising:

(a) a first chimeric polypeptide comprising:

(i) a first target-binding domain;

(ii) a soluble tissue factor domain; and

(iii) a first domain of a pair of affinity domains;

(b) a second chimeric polypeptide comprising:

(i) a second domain of a pair of affinity domains; and

(ii) a second target-binding domain,

wherein:

the first chimeric polypeptide and the second chimeric polypeptide associate through the binding of the first domain and the second domain of the pair of affinity domains; ~~and~~

the first target-binding domain binds specifically to a ligand of TGF-β receptor II (TGF-βRII) and the second target-binding domain binds specifically to a ligand of TGF-βRII;

the first target-binding domain, the second target-binding domain, the first domain of the pair of affinity domains, and the second domain of the pair of affinity domains are protein domains; and

the soluble tissue factor domain directly abuts or is connected to the first domain of the pair of affinity domains in the first chimeric polypeptide through a linker sequence.

~~47~~43. The multi-chain chimeric polypeptide of claim ~~46~~42, wherein the first target-binding domain and the soluble tissue factor domain directly abut each other in the first chimeric polypeptide.

~~48~~44. The multi-chain chimeric polypeptide of claim ~~46~~42, wherein the first chimeric polypeptide further comprises a linker sequence between the first target-binding domain and the soluble tissue factor domain in the first chimeric polypeptide.

~~49~~45. The multi-chain chimeric polypeptide of any one of claims ~~46~~42-~~48~~44, wherein the soluble tissue factor domain and the first domain of the pair of affinity domains directly abut each other in the first chimeric polypeptide.

~~50~~46. The multi-chain chimeric polypeptide of any one of claims ~~46~~42-~~48~~44, wherein the ~~first chimeric polypeptide further comprises a linker sequence between the~~ soluble tissue factor domain and the first domain of the pair of affinity domains in the first chimeric polypeptide are connected through the linker sequence.

~~51~~47. The multi-chain chimeric polypeptide of any one of claims ~~46~~42-~~50~~46, wherein the second domain of the pair of affinity domains and the second target-binding domain directly abut each other in the second chimeric polypeptide.

~~52~~48. The multi-chain chimeric polypeptide of any one of claims ~~46~~42-~~50~~46, wherein second chimeric polypeptide further comprises a linker sequence between the second domain of the pair of affinity domains and the second target-binding domain in the second chimeric polypeptide.

~~53~~49. The multi-chain chimeric polypeptide of any one of claims ~~46~~42-~~52~~48, wherein one or both of the first target-binding domain and the second target-binding domain is an antigen-binding domain.

~~54~~50. The multi-chain chimeric polypeptide of any one of claims ~~46~~42-~~53~~49, wherein one or both of the first target-binding domain and the second target-binding domain is a soluble interleukin or cytokine receptor.

~~55~~51. The multi-chain chimeric polypeptide of any one of claims ~~46~~42-~~54~~50, wherein the first chimeric polypeptide further comprises one or more additional target-binding domain(s).

~~56~~52. The multi-chain chimeric polypeptide of any one of claims ~~46~~42-~~55~~51, wherein the second chimeric polypeptide further comprises one or more additional target-binding domain(s).

~~57~~53. The multi-chain chimeric polypeptide of any one of claims ~~46~~42-~~56~~52, wherein the soluble tissue factor domain is a soluble human tissue factor domain.

~~58~~54. The multi-chain chimeric polypeptide of claim ~~57~~53, wherein the soluble human tissue factor domain comprises a sequence that is at least 80% identical to SEQ ID NO: 1.

~~59~~55. The multi-chain chimeric polypeptide of any one of claims ~~46~~42-~~58~~54, wherein the pair of affinity domains is a sushi domain from an alpha chain of human IL-15 receptor (IL-15Rα) and a soluble IL-15.

~~60~~56. The multi-chain chimeric polypeptide of claim ~~46~~42, wherein the first target-binding domain comprises a soluble TGF-βRII.

~~61~~57. The multi-chain chimeric polypeptide of claim ~~46~~42, wherein the first target-binding domain comprises a first sequence that is at least 80% identical to SEQ ID NO: 81 and a second sequence that is at least 80% identical to SEQ ID NO: 81, wherein the first and second sequence are separated by a linker.

~~62~~58. The multi-chain chimeric polypeptide of claim ~~61~~57, wherein the first target-binding domain comprises a first sequence that is at least 90% identical to SEQ ID NO: 81 and a second sequence that is at least 90% identical to SEQ ID NO: 81

~~63~~59. The multi-chain chimeric polypeptide of claim ~~62~~58, wherein the first target-binding domain comprises a first sequence of SEQ ID NO: 81 and a second sequence of SEQ ID NO: 81.

~~64~~60. The multi-chain chimeric polypeptide of claim ~~61~~57, wherein the linker comprises a sequence of SEQ ID NO: 7.

~~65~~61. The multi-chain chimeric polypeptide of claim ~~60~~56, wherein the first target-binding domain comprises a sequence that is at least 80% identical to SEQ ID NO: 85.

~~66~~62. The multi-chain chimeric polypeptide of claim ~~65~~61, wherein the first target-binding domain comprises a sequence that is at least 90% identical to SEQ ID NO: 85.

~~67~~63. The multi-chain chimeric polypeptide of claim ~~66~~62, wherein the first target-binding domain comprises a sequence of SEQ ID NO: 85.

~~68~~64. The multi-chain chimeric polypeptide of claim ~~46~~42, wherein the first chimeric polypeptide comprises a sequence that is at least 80% identical to SEQ ID NO: 133.

6965. The multi-chain chimeric polypeptide of claim 6864, wherein the first chimeric polypeptide comprises a sequence that is at least 90% identical to SEQ ID NO: 133.

7066. The multi-chain chimeric polypeptide of claim 6965, wherein the first chimeric polypeptide comprises a sequence of SEQ ID NO: 133.

7167. The multi-chain chimeric polypeptide of claim 7066, wherein the first chimeric polypeptide comprises a sequence of SEQ ID NO: 135.

7268. The multi-chain chimeric polypeptide of claim 4642, wherein the second target-binding domain comprises a soluble TGF-βRII.

7369. The multi-chain chimeric polypeptide of claim 7268, wherein the second target-binding domain comprises a first sequence that is at least 80% identical to SEQ ID NO: 81 and a second sequence that is at least 80% identical to SEQ ID NO: 81, wherein the first and second sequence are separated by a linker.

7470. The multi-chain chimeric polypeptide of claim 7369, wherein the second target-binding domain comprises a first sequence that is at least 90% identical to SEQ ID NO: 81 and a second sequence that is at least 90% identical to SEQ ID NO: 81.

7571. The multi-chain chimeric polypeptide of claim 7470, wherein the second target-binding domain comprises a first sequence of SEQ ID NO: 81 and a second sequence of SEQ ID NO: 81.

7672. The multi-chain chimeric polypeptide of claim 7369, wherein the linker comprises a sequence of SEQ ID NO: 7.

~~77~~73. The multi-chain chimeric polypeptide of claim ~~72~~68, wherein the second target-binding domain comprises a sequence that is at least 80% identical to SEQ ID NO: 85.

~~78~~74. The multi-chain chimeric polypeptide of claim ~~73~~69, wherein the second target-binding domain comprises a sequence that is at least 90% identical to SEQ ID NO: 85.

~~79~~75. The multi-chain chimeric polypeptide of claim ~~74~~70, wherein the second target-binding domain comprises a sequence of SEQ ID NO: 85.

~~80~~76. The multi-chain chimeric polypeptide of claim ~~46~~42, wherein the second chimeric polypeptide comprises a sequence that is at least 80% identical to SEQ ID NO: 177.

~~81~~77. The multi-chain chimeric polypeptide of claim ~~80~~76, wherein the first chimeric polypeptide comprises a sequence that is at least 80% identical to SEQ ID NO: 133.

~~82~~78. The multi-chain chimeric polypeptide of claim ~~80~~76, wherein the second chimeric polypeptide comprises a sequence that is at least 90% identical to SEQ ID NO: 177.

~~83~~79. The multi-chain chimeric polypeptide of claim ~~82~~78, wherein the second chimeric polypeptide comprises a sequence of SEQ ID NO: 177.

~~84~~80. The multi-chain chimeric polypeptide of claim ~~83~~79, wherein the first chimeric polypeptide comprises a sequence of SEQ ID NO: 133.

~~85~~81. The multi-chain chimeric polypeptide of claim ~~83~~79, wherein the second chimeric polypeptide comprises a sequence of SEQ ID NO: 92.

~~86~~82. A nucleic acid encoding the multi-chain chimeric polypeptide of any one of claims ~~46~~42-~~85~~81.

~~87~~83. A cell comprising the nucleic acid of claim ~~86~~82.

~~88~~84. A method of producing the multi-chain chimeric polypeptide comprising:

culturing a cell of claim ~~87~~ 83 in a culture medium under conditions sufficient to result in the production of the multi-chain chimeric polypeptide; and

recovering the multi-chain chimeric polypeptide from the cell and/or the culture medium.

~~89~~85. The multi-chain chimeric polypeptide of claim ~~57~~53, wherein the human soluble tissue factor domain does not initiate blood coagulation.

~~90~~86. A composition comprising the multi-chain chimeric polypeptide of any one of claims ~~46~~42-~~85~~ 81 and ~~89~~85.

~~91~~87. An in vitro method of stimulating an immune cell, the method comprising:

contacting an immune cell with an effective amount of the multi-chain chimeric polypeptide of any one of claims ~~46~~42-~~85~~ 81 and ~~89~~85, or the composition of claim ~~90~~86.

~~92~~88. An in vitro method of inducing or increasing proliferation of an immune cell, the method comprising:

contacting an immune cell with an effective amount of the multi-chain chimeric polypeptide of any one of claims ~~46~~42-~~85~~ 81 and ~~89~~85, or the composition of claim ~~90~~86.

~~93~~89. Use of the multi-chain chimeric polypeptide of any one of claims 42-81 and 85 in the manufacture of a medicament for ~~A method of~~ killing a cancer cell, an infected cell, or a senescent cell in a subject having a cancer, an aging-related disease or condition, or an infectious disease~~in need thereof, the method comprising administering~~

~~to the subject a therapeutically effective amount of the multi-chain chimeric polypeptide of any one of claims 46-85 and 89, or the composition of claim 90~~.

~~94~~90. Use of the multi-chain chimeric polypeptide of any one of claims 42-81 and 85 in the manufacture of a medicament for ~~A method of~~ treating a cancer, an aging-related disease or condition, or an infectious disease~~a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the multi-chain chimeric polypeptide of any one of claims 46-85 and 89, or the composition of claim 90~~.

~~95. The method of claim 94, wherein the subject has been identified or diagnosed as having a cancer, an aging-related disease or condition, or an infectious disease.~~

~~96~~91. A multi-chain chimeric polypeptide comprising:

(a) a first chimeric polypeptide comprising:

(i) a first target-binding domain;

(ii) a soluble tissue factor domain; and

(iii) a first domain of a pair of affinity domains;

(b) a second chimeric polypeptide comprising:

(i) a second domain of a pair of affinity domains; and

(ii) a second target-binding domain,

wherein:

the first chimeric polypeptide and the second chimeric polypeptide associate through the binding of the first domain and the second domain of the pair of affinity domains; ~~and~~

the first target-binding domain binds specifically to a receptor for IL-18 and the second target-binding domain binds specifically to a receptor for IL-12, or the first target-binding domain binds specifically to a receptor for IL-12 and the second target-binding domain binds specifically to a receptor for IL-18;

the first target-binding domain, the second target-binding domain, the first domain of the pair of affinity domains, and the second domain of the pair of affinity domains are protein domains; and

the soluble tissue factor domain directly abuts or is connected to the first domain of the pair of affinity domains in the first chimeric polypeptide through a linker sequence.

9792. The multi-chain chimeric polypeptide of claim 9691, wherein the first target-binding domain and the soluble tissue factor domain directly abut each other in the first chimeric polypeptide.

9893. The multi-chain chimeric polypeptide of claim 9691, wherein the first chimeric polypeptide further comprises a linker sequence between the first target-binding domain and the soluble tissue factor domain in the first chimeric polypeptide.

9994. The multi-chain chimeric polypeptide of any one of claims 9691-9893, wherein the soluble tissue factor domain and the first domain of the pair of affinity domains directly abut each other in the first chimeric polypeptide.

10095. The multi-chain chimeric polypeptide of any one of claims 9691-9893, wherein the ~~first chimeric polypeptide further comprises a linker sequence between the~~ soluble tissue factor domain and the first domain of the pair of affinity domains in the first chimeric polypeptide are connected through the linker sequence.

10196. The multi-chain chimeric polypeptide of any one of claims 9691-10095, wherein the second domain of the pair of affinity domains and the second target-binding domain directly abut each other in the second chimeric polypeptide.

10297. The multi-chain chimeric polypeptide of any one of claims 9691-10095, wherein second chimeric polypeptide further comprises a linker sequence between the second domain of the pair of affinity domains and the second target-binding domain in the second chimeric polypeptide.

~~103~~98. The multi-chain chimeric polypeptide of any one of claims ~~96~~91-~~102~~97, wherein one or both of the first target-binding domain and the second target-binding domain is an antigen-binding domain.

~~104~~99. The multi-chain chimeric polypeptide of any one of claims ~~96~~91-~~102~~97, wherein one or both of the first target-binding domain and the second target-binding domain is a soluble interleukin or cytokine protein.

~~105~~100. The multi-chain chimeric polypeptide of any one of claims ~~96~~91-~~104~~99, wherein the first chimeric polypeptide further comprises one or more additional target-binding domain(s).

~~106~~101. The multi-chain chimeric polypeptide of any one of claims ~~96~~91-~~105~~100, wherein the second chimeric polypeptide further comprises one or more additional target-binding domain(s).

~~107~~102. The multi-chain chimeric polypeptide of any one of claims ~~96~~91-~~106~~101, wherein the soluble tissue factor domain is a soluble human tissue factor domain.

~~108~~103. The multi-chain chimeric polypeptide of claim ~~107~~102, wherein the soluble human tissue factor domain comprises a sequence that is at least 80% identical to SEQ ID NO: 1.

~~109~~104. The multi-chain chimeric polypeptide of claim ~~107~~102, wherein the human soluble tissue factor domain does not initiate blood coagulation.

~~110~~105. The multi-chain chimeric polypeptide of any one of claims ~~96~~91-~~109~~104, wherein the pair of affinity domains is a sushi domain from an alpha chain of human IL-15 receptor (IL-15Rα) and a soluble IL-15.

~~111~~106. The multi-chain chimeric polypeptide of any one of claims ~~96~~91-~~110~~105, wherein the first target-binding domain specifically binds to a receptor for IL-18 and the second target-binding domain specifically binds to a receptor for IL-12.

~~112~~107. The multi-chain chimeric polypeptide of claim ~~111~~106, wherein the first target-binding domain comprises a soluble IL-18.

~~113~~108. The multi-chain chimeric polypeptide of claim ~~112~~107, wherein the first target-binding domain comprises a sequence that is at least 80% identical to SEQ ID NO: 16.

~~114~~109. The multi-chain chimeric polypeptide of claim ~~113~~108, wherein the first target-binding domain comprises a sequence that is at least 90% identical to SEQ ID NO: 16.

~~115~~110. The multi-chain chimeric polypeptide of claim ~~114~~109, wherein the first target-binding domain comprises a sequence of SEQ ID NO: 16.

~~116~~111. The multi-chain chimeric polypeptide of claim ~~96~~91, wherein the first chimeric polypeptide comprises a sequence that is at least 80% identical to SEQ ID NO: 70.

~~117~~112. The multi-chain chimeric polypeptide of claim ~~116~~111, wherein the first chimeric polypeptide comprises a sequence that is at least 90% identical to SEQ ID NO: 70.

~~118~~113. The multi-chain chimeric polypeptide of claim ~~117~~112, wherein the first chimeric polypeptide comprises a sequence of SEQ ID NO: 70.

~~119~~114. The multi-chain chimeric polypeptide of claim ~~118~~113, wherein the first chimeric polypeptide comprises a sequence of SEQ ID NO: 72.

~~120~~115. The multi-chain chimeric polypeptide of claim ~~111~~106, wherein the second target-binding domain comprises a soluble IL-12.

~~121~~116. The multi-chain chimeric polypeptide of claim ~~120~~115, wherein the second target-binding domain comprises a first sequence that is at least 80% identical to SEQ ID NO: 66 and a second sequence that is at least 80% identical to SEQ ID NO: 68, wherein the first and second sequence are separated by a linker.

~~122~~117. The multi-chain chimeric polypeptide of claim ~~121~~116, wherein the second target-binding domain comprises a first sequence that is at least 90% identical to SEQ ID NO: 66 and a second sequence that is at least 90% identical to SEQ ID NO: 68.

~~123~~118. The multi-chain chimeric polypeptide of claim ~~122~~117, wherein the second target-binding domain comprises a first sequence of SEQ ID NO: 66 and a second sequence of SEQ ID NO: 68.

~~124~~119. The multi-chain chimeric polypeptide of claim ~~121~~116, wherein the linker comprises a sequence of SEQ ID NO: 7.

~~125~~120. The multi-chain chimeric polypeptide of claim ~~96~~91, wherein the second chimeric polypeptide comprises a sequence that is at least 80% identical to SEQ ID NO: 74.

~~126~~121. The multi-chain chimeric polypeptide of claim ~~116~~111, wherein the second chimeric polypeptide comprises a sequence that is at least 80% identical to SEQ ID NO: 74.

~~127~~122. The multi-chain chimeric polypeptide of claim ~~125~~120, wherein the second chimeric polypeptide comprises a sequence that is at least 90% identical to SEQ ID NO: 74.

~~128~~123. The multi-chain chimeric polypeptide of claim ~~127~~122, wherein the second chimeric polypeptide comprises a sequence of SEQ ID NO: 74.

~~129~~124. The multi-chain chimeric polypeptide of claim ~~128~~123, wherein the first chimeric polypeptide comprises a sequence of SEQ ID NO: 70.

~~130~~125. The multi-chain chimeric polypeptide of claim ~~128~~123, wherein the second chimeric polypeptide comprises a sequence of SEQ ID NO: 76.

~~131~~126. A composition comprising the multi-chain chimeric polypeptide of any one of claims ~~96~~91-~~130~~ 125 and ~~136~~131.

~~132~~127. The composition of claim ~~131~~126, wherein the composition is a pharmaceutical composition.

~~133~~128. A nucleic acid encoding the multi-chain chimeric polypeptide of any one of claims ~~96~~91-~~130~~ 125 and ~~136~~131.

~~134~~129. A cell comprising the nucleic acid of claim ~~133~~128.

~~135~~130. A method of producing the multi-chain chimeric polypeptide comprising:

culturing a cell of claim ~~134~~ 129 in a culture medium under conditions sufficient to result in the production of the multi-chain chimeric polypeptide; and

recovering the multi-chain chimeric polypeptide from the cell and/or the culture medium.

~~136~~131. The multi-chain chimeric polypeptide of any one of claims ~~96~~91-~~110~~105, wherein the first target-binding domain binds specifically to a receptor for IL-12 and the second target-binding domain binds specifically to a receptor for IL-18.

~~137~~132. An in vitro method of stimulating an immune cell, the method comprising:

contacting an immune cell with an effective amount of the multi-chain chimeric polypeptide of any one of claims ~~96~~91-~~130~~ 125 and ~~136~~131, or the composition of claim ~~131~~ 126 or ~~132~~127.

~~138~~133. An in vitro method of inducing or increasing proliferation of an immune cell, the method comprising:

contacting an immune cell with an effective amount of the multi-chain chimeric polypeptide of any one of claims ~~96~~91-~~130~~ 125 and ~~136~~131, or the composition of claim ~~131~~ 126 or ~~132~~127.

~~139~~134. An in vitro method of inducing differentiation of an immune cell into a memory or memory-like immune cell, the method comprising:

contacting an immune cell with an effective amount of the multi-chain chimeric polypeptide of any one of claims ~~96~~91-~~130~~ 125 and ~~136~~131, or the composition of claim ~~131~~ 126 or ~~132~~127.

~~140~~135. Use of the multi-chain chimeric polypeptide of any one of claims 91-125 and 131 in the manufacture of a medicament for ~~A method of~~ killing a cancer cell, an infected cell, or a senescent cell in a subject having a cancer, an aging-related disease or condition, or an infectious disease~~in need thereof, the method comprising administering to the subject a therapeutically effective amount of the multi-chain chimeric polypeptide of any one of claims 96-130 and 136, or the composition of claim 131 or 132~~.

~~141~~136. Use of the multi-chain chimeric polypeptide of any one of claims 91-125 and 131 in the manufacture of a medicament for ~~A method of~~ treating a cancer, an aging-related disease or condition, or an infectious disease~~a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the multi-chain chimeric polypeptide of any one of claims 96-130 and 136, or the composition of claim 131 or 132~~.

~~142. The method of claim 141, wherein the subject has been identified or diagnosed as having a cancer, an aging-related disease or condition, or an infectious disease.~~

~~143~~137. A multi-chain chimeric polypeptide comprising:

(a) a first chimeric polypeptide comprising:

(i) a first target-binding domain;

(ii) a soluble tissue factor domain; and

(iii) a first domain of a pair of affinity domains;

(b) a second chimeric polypeptide comprising:

(i) a second domain of a pair of affinity domains; and

(ii) a second target-binding domain,

wherein:

the first chimeric polypeptide and the second chimeric polypeptide associate through the binding of the first domain and the second domain of the pair of affinity domains; ~~and~~

the first target-binding domain binds specifically to a receptor for IL-7 and the second target-binding domain binds specifically to a receptor for IL-21, or the first target-binding domain binds specifically to a receptor for IL-21 and the second target-binding domain binds specifically to a receptor for IL-7;

the first target-binding domain, the second target-binding domain, the first domain of the pair of affinity domains, and the second domain of the pair of affinity domains are protein domains; and

the soluble tissue factor domain directly abuts or is connected to the first domain of the pair of affinity domains in the first chimeric polypeptide through a linker sequence.

~~144~~138. The multi-chain chimeric polypeptide of claim ~~143~~137, wherein the first target-binding domain and the soluble tissue factor domain directly abut each other in the first chimeric polypeptide.

~~145~~139. The multi-chain chimeric polypeptide of claim ~~143~~137, wherein the first chimeric polypeptide further comprises a linker sequence between the first target-binding domain and the soluble tissue factor domain in the first chimeric polypeptide.

~~146~~140. The multi-chain chimeric polypeptide of any one of claims ~~143~~137-~~145~~139, wherein the soluble tissue factor domain and the first domain of the pair of affinity domains directly abut each other in the first chimeric polypeptide.

~~147~~141. The multi-chain chimeric polypeptide of any one of claims ~~143~~137-~~145~~139, wherein the ~~first chimeric polypeptide further comprises a linker sequence between the~~ soluble tissue factor domain and the first domain of the pair of affinity domains in the first chimeric polypeptide are connected through the linker sequence.

~~148~~142. The multi-chain chimeric polypeptide of any one of claims ~~143~~137-~~147~~141, wherein the second domain of the pair of affinity domains and the second target-binding domain directly abut each other in the second chimeric polypeptide.

~~149~~143. The multi-chain chimeric polypeptide of any one of claims ~~143~~137-~~147~~141, wherein second chimeric polypeptide further comprises a linker sequence between the second domain of the pair of affinity domains and the second target-binding domain in the second chimeric polypeptide.

~~150~~144. The multi-chain chimeric polypeptide of any one of claims ~~143~~137-~~149~~143, wherein one or both of the first target-binding domain and the second target-binding domain is an antigen-binding domain.

~~151~~145. The multi-chain chimeric polypeptide of any one of claims ~~143~~137-~~150~~144, wherein one or both of the first target-binding domain and the second target-binding domain is a soluble interleukin or cytokine protein.

~~152~~146. The multi-chain chimeric polypeptide of any one of claims ~~143~~137-~~151~~145, wherein the first chimeric polypeptide further comprises one or more additional target-binding domain(s).

~~153~~147. The multi-chain chimeric polypeptide of any one of claims ~~143~~137-~~152~~146, wherein the second chimeric polypeptide further comprises one or more additional target-binding domain(s).

~~154~~148. The multi-chain chimeric polypeptide of any one of claims ~~143~~137-~~153~~147, wherein the soluble tissue factor domain is a soluble human tissue factor domain.

~~155~~149. The multi-chain chimeric polypeptide of claim ~~154~~148, wherein the soluble human tissue factor domain comprises a sequence that is at least 80% identical to SEQ ID NO: 1.

~~156~~150. The multi-chain chimeric polypeptide of claim ~~154~~149, wherein the soluble human tissue factor domain comprises a sequence that is at least 90% identical to SEQ ID NO: 1~~is a soluble human tissue factor domain~~.

~~157~~151. The multi-chain chimeric polypeptide of any one of claims ~~143~~137-~~156~~150, wherein the pair of affinity domains is a sushi domain from an alpha chain of human IL-15 receptor (IL-15Rα) and a soluble IL-15.

~~158~~152. The multi-chain chimeric polypeptide of any one of claims ~~143~~137-~~157~~151, wherein the first target-binding domain specifically binds to a receptor for IL-7 and the second target-binding domain specifically binds to a receptor for IL-21.

~~159~~153. The multi-chain chimeric polypeptide of claim ~~158~~152, wherein the first target-binding domain comprises a soluble IL-7.

~~160~~154. The multi-chain chimeric polypeptide of claim ~~159~~153, wherein the first target-binding domain comprises a sequence that is at least 80% identical to SEQ ID NO: 11.

~~161~~155. The multi-chain chimeric polypeptide of claim ~~160~~154, wherein the first target-binding domain comprises a sequence that is at least 90% identical to SEQ ID NO: 11.

~~162~~156. The multi-chain chimeric polypeptide of claim ~~161~~155, wherein the first target-binding domain comprises a sequence of SEQ ID NO: 11.

~~163~~157. The multi-chain chimeric polypeptide of claim ~~143~~137, wherein the first chimeric polypeptide comprises a sequence that is at least 80% identical to SEQ ID NO: 104.

~~164~~158. The multi-chain chimeric polypeptide of claim ~~163~~157, wherein the first chimeric polypeptide comprises a sequence that is at least 90% identical to SEQ ID NO: 104.

~~165~~159. The multi-chain chimeric polypeptide of claim ~~164~~158, wherein the first chimeric polypeptide comprises a sequence of SEQ ID NO: 104.

~~166~~160. The multi-chain chimeric polypeptide of claim ~~165~~159, wherein the first chimeric polypeptide comprises a sequence of SEQ ID NO: 106.

~~167~~161. The multi-chain chimeric polypeptide of claim ~~158~~152, wherein the second target-binding domain comprises a soluble IL-21.

~~168~~162. The multi-chain chimeric polypeptide of claim ~~167~~161, wherein the second target-binding domain comprises a sequence that is at least 80% identical to SEQ ID NO: 78.

~~169~~163. The multi-chain chimeric polypeptide of claim ~~168~~162, wherein the second target-binding domain comprises a sequence that is at least 90% identical to SEQ ID NO: 78.

~~170~~164. The multi-chain chimeric polypeptide of claim ~~169~~163, wherein the second target-binding domain comprises a sequence of SEQ ID NO: 78.

~~171~~165. The multi-chain chimeric polypeptide of claim ~~143~~137, wherein the second chimeric polypeptide comprises a sequence that is at least 80% identical to SEQ ID NO: 108.

~~172~~166. The multi-chain chimeric polypeptide of claim ~~163~~157, wherein the second chimeric polypeptide comprises a sequence that is at least 80% identical to SEQ ID NO: 108.

~~173~~167. The multi-chain chimeric polypeptide of claim ~~171~~165, wherein the second chimeric polypeptide comprises a sequence that is at least 90% identical to SEQ ID NO: 108.

~~174~~168. The multi-chain chimeric polypeptide of claim ~~173~~167, wherein the second chimeric polypeptide comprises a sequence of SEQ ID NO: 108.

~~175~~169. The multi-chain chimeric polypeptide of claim ~~174~~168, wherein the first chimeric polypeptide comprises a sequence of SEQ ID NO: 104.

~~176~~170. The multi-chain chimeric polypeptide of claim ~~174~~168, wherein the second chimeric polypeptide comprises a sequence of SEQ ID NO: 110.

~~177~~171. A composition comprising the multi-chain chimeric polypeptide of any one of claims ~~143~~137-~~176~~ 170 and ~~182~~176.

~~178~~172. The composition of claim ~~177~~171, wherein the composition is a pharmaceutical composition.

~~179~~173. A nucleic acid encoding the multi-chain chimeric polypeptide of any one of claims ~~143~~137-~~176~~ 170 and ~~182~~176.

~~180~~174. A cell comprising the nucleic acid of claim ~~179~~173.

~~181~~175. A method of producing the multi-chain chimeric polypeptide comprising:

culturing a cell of claim ~~180~~ 174 in a culture medium under conditions sufficient to result in the production of the multi-chain chimeric polypeptide; and

recovering the multi-chain chimeric polypeptide from the cell and/or the culture medium.

~~182~~176. The multi-chain chimeric polypeptide of any one of claims ~~143~~137-~~157~~151, wherein the first target-binding domain binds specifically to a receptor for IL-21 and the second target-binding domain binds specifically to a receptor for IL-7.

~~183~~177. An in vitro method of stimulating an immune cell, the method comprising:

contacting an immune cell with an effective amount of the multi-chain chimeric polypeptide of any one of claims ~~143~~137-~~176~~ 170 and ~~182~~176, or the composition of claim ~~177~~ 171 or ~~178~~172.

~~184~~178. An in vitro method of inducing or increasing proliferation of an immune cell, the method comprising:

contacting an immune cell with an effective amount of the multi-chain chimeric polypeptide of any one of claims ~~143~~137-~~176~~ 170 and ~~182~~176, or the composition of claim ~~177~~ 171 or ~~178~~172.

~~185~~179. An in vitro method of inducing differentiation of an immune cell into a memory or memory-like immune cell, the method comprising:

contacting an immune cell with an effective amount of the multi-chain chimeric polypeptide of any one of claims ~~143~~137-~~176~~ 170 and ~~182~~176, or the composition of claim ~~177~~ 171 or ~~178~~172.

~~186~~180. Use of the multi-chain chimeric polypeptide of any one of claims 137-170 and 176 in the manufacture of a medicament for ~~A method of~~ killing a cancer cell, an infected cell, or a senescent cell in a subject having a cancer, an aging-related disease or condition, or an infectious disease~~in need thereof, the method comprising administering to the subject a therapeutically effective amount of the multi-chain chimeric polypeptide of any one of claims 143-176 and 182, or the composition of claim 177 or 178~~.

~~187~~181. Use of the multi-chain chimeric polypeptide of any one of claims 137-170 and 176 in the manufacture of a medicament for~~A method of~~ treating a subject having a cancer, an aging-related disease or condition, or an infectious disease~~in need thereof, the method comprising administering to the subject a therapeutically effective amount of the multi-chain chimeric polypeptide of any one of claims 143-176 and 182, or the composition of claim 177 or 178~~.

~~188. The method of claim 187, wherein the subject has been identified or diagnosed as having a cancer, an aging-related disease or condition, or an infectious disease.~~