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(54) Title: MULTI-CHAIN CHIMERIC POLYPEPTIDES AND USES THEREOF

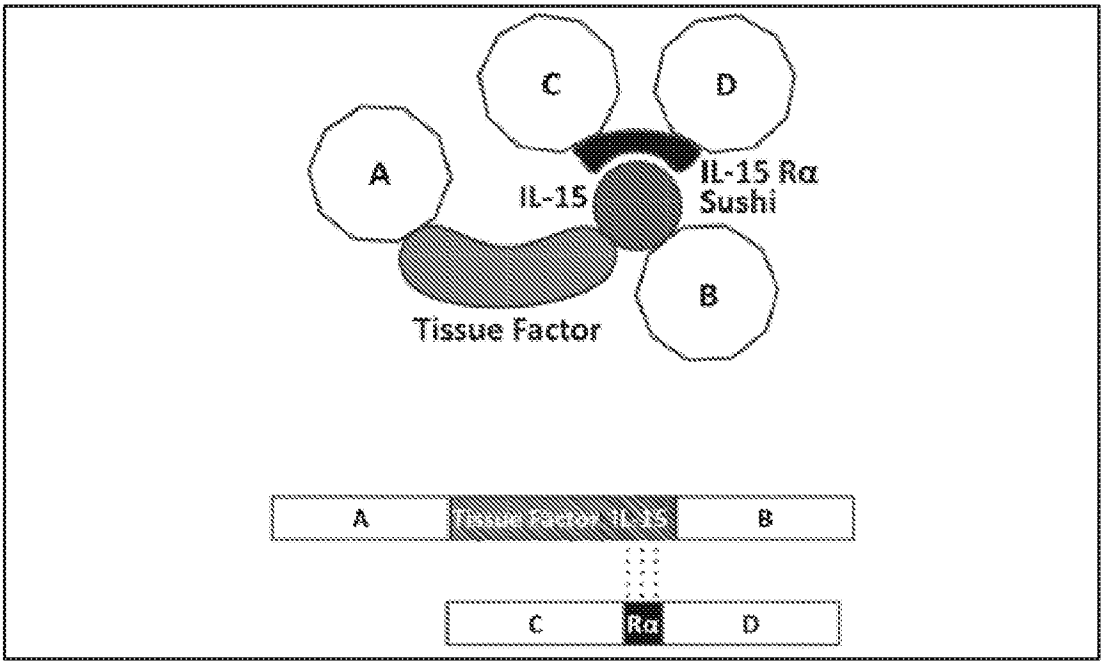

Figure 1

(57) Abrégé/Abstract:
Provided herein are multi-chain chimeric polypeptides that include: (a) a first chimeric polypeptide including a first target-binding domain, a soluble tissue factor domain, and a first domain of a pair of affinity domains; and (b) a second chimeric polypeptide including a second domain of a pair of affinity domains and a second target-binding domain, where 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. Also provided here are methods of using these multi-chain chimeric polypeptides and nucleic acids encoding these multi-chain chimeric polypeptides.

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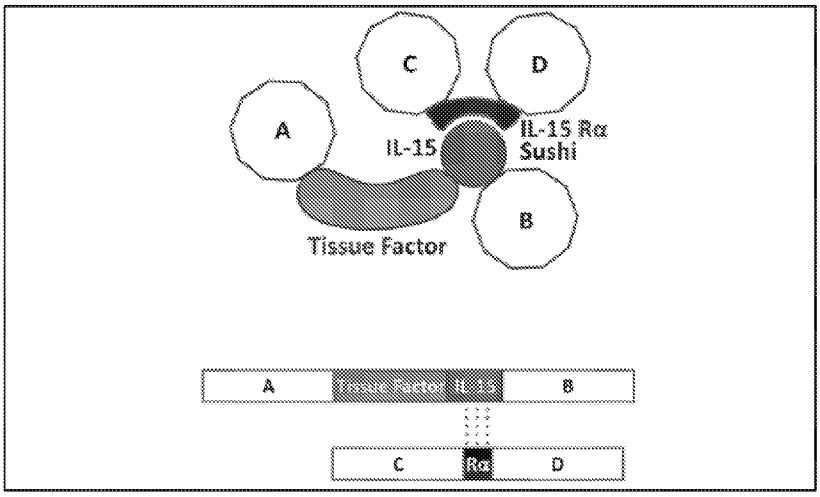

Figure 1

(57) Abstract: Provided herein are multi-chain chimeric polypeptides that include: (a) a first chimeric polypeptide including a first target-binding domain, a soluble tissue factor domain, and a first domain of a pair of affinity domains; and (b) a second chimeric polypeptide including a second domain of a pair of affinity domains and a second target-binding domain, where 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. Also provided here are methods of using these multi-chain chimeric polypeptides and nucleic acids encoding these multi-chain chimeric polypeptides.

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MULTI-CHAIN CHIMERIC POLYPEPTIDES AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to: U.S. Patent Application No. 62/724,969, filed August 30, 2018; U.S. Patent Application No. 62/817,230, filed March 12, 2019; U.S. Patent Application Serial No. 62/725,043, filed August 30, 2018; U.S. Patent Application Serial No. 62/725,010, filed August 30, 2018; U.S. Patent Application Serial No. 62/749,007, filed October 22, 2018; U.S. Patent Application Serial No. 62/746,832, filed October 17, 2018; U.S. Patent Application Serial No. 62/749,506, filed October 23, 2018; U.S. Patent Application Serial No. 62/817,241, filed March 12, 2019; U.S. Patent Application Serial No. 62/816,683, filed March 11, 2019; and U.S. Patent Application Serial No. 62/881,088, filed July 31, 2019, each of which is herein incorporated by reference in its entirety.

TECHNICAL FIELD

The present disclosure relates to the field of biotechnology, and more specifically, to antigen-binding molecules.

BACKGROUND

Tissue factor (TF), a 263 amino acid integral membrane glycoprotein with a molecular weight of ~46 kDa and the trigger protein of the extrinsic blood coagulation pathway, is the primary initiator of coagulation *in vivo*. Tissue factor, normally not in contact with circulating blood, initiates the coagulation cascade upon exposure to the circulating coagulation serine protease factors. Vascular damage exposes sub-endothelial cells expressing tissue factor, resulting in the formation of a calcium-dependent, high-affinity complex with pre-existing plasma factor VIIa (FVIIa). Binding of the serine protease FVIIa to tissue factor promotes rapid cleavage of FX to FXa and FIX to FIXa. The proteolytic activity of the resulting FXa and an active membrane surface then inefficiently converts a small amount of prothrombin to thrombin. The thrombin generated by FXa initiates platelet activation and activates minute amounts of the pro-cofactors factor V (FV) and factor VIII (FVIII) to become active cofactors, factor Va

(FVa) and factor VIIIa (FVIIIa). FIXa complexes with FVIIIa on the platelet surface forming the intrinsic tenase complex, which results in rapid generation of FXa. FXa complexes with FVa to form the pro-thrombinase complex on the activated platelet surface which results in rapid cleavage of prothrombin to thrombin.

In addition to the tissue factor-FVIIa complex, a recent study showed that the tissue factor-FVIIa-FXa complex can activate FVIII, which would provide additional levels of FVIIIa during the initiation phase. The extrinsic pathway is paramount in initiating coagulation via the activation of limited amounts of thrombin, whereas the intrinsic pathway maintains coagulation by dramatic amplification of the initial signal.

Much of the tissue factor expressed on a cell surface is "encrypted," which must be "decrypted" for full participation in coagulation. The mechanism of "decryption" of cell-surface tissue factor is still unclear at this time, however, exposure of anionic phospholipids plays a major role in this process. Healthy cells actively sequester anionic phospholipids such as phosphatidyl serine (PS) to the inner leaflet of the plasma membrane. Following cellular damage, activation, or increased levels of cytosolic Ca^{2+}, this bilayer asymmetry is lost, resulting in increased PS exposure on the outer leaflet, which increases the specific activity of cell-surface tissue factor-FVIIa complexes. PS exposure is known to decrease the apparent Km for activation of FIX and FX by tissue factor-FVIIa complexes, but additional mechanisms could include conformational rearrangement of tissue factor or tissue factor-FVIIa and subsequent exposure of substrate binding sites.

SUMMARY

The present invention is based on the discovery that soluble tissue factor can be used as a scaffold for chimeric polypeptides including an antigen-binding domain. Based on this discovery provided herein are multi-chain chimeric polypeptides that include: (a) a first chimeric polypeptide including: (i) a first target-binding domain; (ii) a soluble tissue factor domain; and (iii) a first domain of a pair of affinity domains; and (b) a second chimeric polypeptide including: (i) a second domain of a pair of affinity domains; and (ii) a second target-binding domain, where 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. 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, 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 some embodiments, the first target-binding domain and the soluble tissue factor domain directly abut each other in the first chimeric polypeptide. In some embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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

polypeptide. In some embodiments, the first target-binding domain and the second target-binding domain bind specifically to the same antigen. In some embodiments, the first target-binding domain and the second target-binding domain bind specifically to the same epitope. In some embodiments, the first target-binding domain and the second target-binding domain comprise the same amino acid sequence. In some embodiments, the first target-binding domain and the second target-binding domain bind specifically to different antigens. In some embodiments, one or both of the first target-binding domain and the second target-binding domain is an antigen-binding domain. In some embodiments, the first target-binding domain and the second target-binding domain are each antigen-binding domains. In some embodiments, the antigen-binding domain comprises a scFv or a single domain antibody. In some embodiments, 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. In some embodiments, one or both of the first target-binding domain and the second target-binding domain is a soluble interleukin, a soluble cytokine protein, or a ligand protein. In some embodiments, the soluble interleukin, soluble 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. In some embodiments, one

or both of the first target-binding domain and the second target-binding domain is a soluble interleukin, a cytokine receptor, or a soluble cell surface receptor. In some embodiments, the soluble receptor is a soluble TGF-β receptor II (TGF-β RII), 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. In some embodiments, the first chimeric polypeptide further comprises one or more additional target-binding domain(s), where at least one of the one or more additional antigen-binding domain(s) is positioned between the soluble tissue factor domain and the first domain of the pair of affinity domains. In some embodiments, the first chimeric polypeptide further comprises a linker sequence between the soluble tissue factor domain and the at least one of the one or more additional antigen-binding domain(s), and/or a linker sequence between the at least one of the one or more additional antigen-binding domain(s) and the first domain of the pair of affinity domains. In some embodiments, the first chimeric polypeptide further comprises one or more additional target-binding domains at the N-terminal and/or C-terminal end of the first chimeric polypeptide. In some embodiments, at least one of the one or more additional target-binding domains directly abuts the first domain of the pair of affinity domains in the first chimeric polypeptide. In some embodiments, the first chimeric polypeptide further comprises a linker sequence between the at least one of the one or more additional target-binding domains and the first domain of the pair of affinity domains. In some embodiments, the at least one of the one or more additional target-binding domains directly abuts the first target-binding domain in the first chimeric polypeptide. In some embodiments, the first chimeric polypeptide further comprises a linker sequence between the at least one of the one or more additional target-binding domains and the first target-binding domain. In some embodiments, at least one of the one or more additional target-binding domains is disposed at the N- and/or C-terminus of the first chimeric polypeptide, and at least one of the one or more additional target-binding domains is positioned between the soluble tissue factor domain and the first domain of the pair of affinity domains in the first chimeric polypeptide. In some embodiments, the at least one additional target-binding domain of the one or more additional target-binding domains disposed at the N-terminus directly abuts the first target-binding domain or the first domain of the pair of affinity

domains in the first chimeric polypeptide. In some embodiments, the first chimeric polypeptide further comprises a linker sequence disposed between the at least one additional target-binding domain and the first target-binding domain or the first domain of the pair of affinity domains in the first chimeric polypeptide. In some embodiments, the at least one additional target-binding domain of the one or more additional target-binding domains disposed at the C-terminus directly abuts the first target-binding domain or the first domain of the pair of affinity domains in the first chimeric polypeptide. In some embodiments, the first chimeric polypeptide further comprises a linker sequence disposed between the at least one additional target-binding domain and the first target-binding domain or the first domain of the pair of affinity domains in the first chimeric polypeptide. In some embodiments, the at least one of the one or more additional target-binding domains positioned between the soluble tissue factor domain and the first domain of the pair of affinity domains, directly abuts the soluble tissue factor domain and/or the first domain of the pair of affinity domains. In some embodiments, the first chimeric polypeptide further comprises a linker sequence disposed (i) between the soluble tissue factor domain and the at least one of the one or more additional target-binding domains positioned between the soluble tissue factor domain and the first domain of the pair of affinity domains, and/or (ii) between the first domain of the pair of affinity domains and the at least one of the one or more additional target-binding domains positioned between the soluble tissue factor domain and the first domain of the pair of affinity domains. In some embodiments, the second chimeric polypeptide further comprises one or more additional target-binding domains at the N-terminal end or the C-terminal end of the second chimeric polypeptide. In some embodiments, at least one of the one or more additional target-binding domains directly abuts the second domain of the pair of affinity domains in the second chimeric polypeptide. In some embodiments, the second chimeric polypeptide further comprises a linker sequence between at least one of the one or more additional target-binding domains and the second domain of the pair of affinity domains in the second chimeric polypeptide. In some embodiments, at least one of the one or more additional target-binding domains directly abuts the second target-binding domain in the second chimeric polypeptide. In some embodiments, the second chimeric polypeptide further comprises a linker sequence between at least one of the one or more

additional target-binding domains and the second target-binding domain in the second chimeric polypeptide. In some embodiments, two or more of the first target-binding domain, the second target-binding domain, and the one or more additional target-binding domains bind specifically to the same antigen. In some embodiments, two or more of the first target-binding domain, the second target-binding domain, and the one or more additional target-binding domains bind specifically to the same epitope. In some embodiments, two or more of the first target-binding domain, the second target-binding domain, and the one or more additional target-binding domains comprise the same amino acid sequence. In some embodiments, the first target-binding domain, the second target-binding domain, and the one or more additional target-binding domains each bind specifically to the same antigen. In some embodiments, the first target-binding domain, the second target-binding domain, and the one or more additional target-binding domains each bind specifically to the same epitope. In some embodiments, the first target-binding domain, the second target-binding domain, and the one or more additional target-binding domains each comprise the same amino acid sequence. In some embodiments, the first target-binding domain, the second target-binding domain, and the one or more additional target-binding domains bind specifically to different antigens. In some embodiments, one or more of the first target-binding domain, the second target-binding domain, and the one or more target-binding domains is an antigen-binding domain. In some embodiments, the first target-binding domain, the second target-binding domain, and the one or more additional target-binding domains are each an antigen-binding domain. In some embodiments, antigen-binding domain comprises a scFv. In some embodiments, one or more of the first target-binding domain, the second target-binding domain, and the one or more target-binding domains 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 CD3, and a receptor for CD28. In some embodiments, one or more of the first target-binding domain, the second target-binding domain, and the one or more additional target-binding domains is a soluble interleukin, a soluble cytokine protein, or a ligand protein. In some embodiments, the soluble interleukin, soluble 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. In some embodiments, one or more of the first target-binding domain, the second target-binding domain, and the one or more additional target-binding domains is a soluble interleukin or cytokine receptor. In some embodiments, the soluble receptor is a soluble TGF-β receptor II (TGF-β RII), 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, a soluble CD122, a soluble CD3, or a soluble CD28. In some embodiments, the first chimeric polypeptide further comprises a peptide tag at the N-terminal end or the C-terminal end of the first chimeric polypeptide. In some embodiments, the second chimeric polypeptide further comprises a peptide tag at the N-terminal end or the C-terminal end of the second chimeric polypeptide. In some embodiments, the soluble tissue factor domain is a soluble human tissue factor domain. In some embodiments, the soluble human tissue factor domain comprises a sequence that is at least 80% identical to SEQ ID NO: 1. In some embodiments, the soluble human tissue factor domain comprises a sequence that is at least 90% identical to SEQ ID NO: 1. In some embodiments, the soluble human tissue factor domain comprises a sequence that is at least 95% identical to SEQ ID NO: 1. In some embodiments, the soluble human tissue factor domain does not comprise one or more of: a lysine at an amino acid position that corresponds to amino acid position 20 of mature wildtype human tissue factor protein; an isoleucine at an amino acid position that

corresponds to amino acid position 22 of mature wildtype human tissue factor protein; a tryptophan at an amino acid position that corresponds to amino acid position 45 of mature wildtype human tissue factor protein; an aspartic acid at an amino acid position that corresponds to amino acid position 58 of mature wildtype human tissue factor protein; a tyrosine at an amino acid position that corresponds to amino acid position 94 of mature wildtype human tissue factor protein; an arginine at an amino acid position that corresponds to amino acid position 135 of mature wildtype human tissue factor protein; and a phenylalanine at an amino acid position that corresponds to amino acid position 140 of mature wildtype human tissue factor protein. In some embodiments, the soluble human tissue factor domain does not comprise any of: a lysine at an amino acid position that corresponds to amino acid position 20 of mature wildtype human tissue factor protein; an isoleucine at an amino acid position that corresponds to amino acid position 22 of mature wildtype human tissue factor protein; a tryptophan at an amino acid position that corresponds to amino acid position 45 of mature wildtype human tissue factor protein; an aspartic acid at an amino acid position that corresponds to amino acid position 58 of mature wildtype human tissue factor protein; a tyrosine at an amino acid position that corresponds to amino acid position 94 of mature wildtype human tissue factor protein; an arginine at an amino acid position that corresponds to amino acid position 135 of mature wildtype human tissue factor protein; and a phenylalanine at an amino acid position that corresponds to amino acid position 140 of mature wildtype human tissue factor protein. In some embodiments, the soluble tissue factor domain is not capable of binding to Factor VIIa. In some embodiments, the soluble tissue factor domain does not convert inactive Factor X into Factor Xa. In some embodiments, the multi-chain chimeric polypeptide does not stimulate blood coagulation in a mammal. In some embodiments of any of the single-chain chimeric polypeptides provided herein, the human soluble tissue factor domain does not initiate blood coagulation. In some embodiments of any of the single-chain chimeric polypeptides provided herein, the soluble tissue factor domain comprises or consists of a soluble wildtype human tissue factor.

In some embodiments, the pair of affinity domains is a sushi domain from an alpha chain of human IL-15 receptor (IL15Rα) and a soluble IL-15. In some

embodiments, the soluble IL15 has a D8N or D8A amino acid substitution. In some embodiments, the human IL15Rα is a mature full-length IL15Rα. In some embodiments, 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 embodiments, the first chimeric polypeptide and/or the second chimeric polypeptide further comprises a signal sequence at its N-terminal end.

In some embodiments, the multi-chain chimeric polypeptide comprises a composition. In some embodiments, the composition is a pharmaceutical composition. In some embodiments, the composition comprises at least one dose of the multi-chain chimeric polypeptide. In some embodiments, a kit comprises at least one dose of the composition.

In some embodiments, 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 some embodiments, the method comprises contacting the immune cell in vitro. In some embodiments, the method comprises obtaining the immune cell from a subject. In some embodiments, the method comprises obtaining the immune cell from the subject prior to the contacting step. In some embodiments, the method comprises contacting the immune cell in vivo. In some embodiments, 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 embodiments, the method comprises genetically modifying the immune cell to express a chimeric antigen receptor or a recombinant T-cell receptor. In some embodiments, 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 embodiments, the method

comprises administering the immune cell to a subject in need thereof. In some embodiments, the method comprises identifying or diagnosing the subject as having an age-related disease or condition. In some embodiments, 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 embodiments, the method comprises identifying or diagnosing the subject as having a cancer. In some embodiments, 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 embodiments, the method comprises diagnosing or identifying the subject as having an infectious disease. In some embodiments, 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.

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 some embodiments, the method comprises contacting the immune cell in vitro. In some embodiments, the method comprises obtaining the immune cell from a subject. In some embodiments, the method comprises obtaining the immune cell from the subject prior to the contacting step. In some embodiments, the method comprises contacting the immune cell in vivo. In some embodiments, 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 embodiments, the method comprises modifying the immune cell to express a chimeric antigen receptor or a recombinant T-cell receptor. In some embodiments, 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 embodiments, the method further comprises administering the immune cell to a subject in need thereof. In some embodiments, the method comprises identifying or diagnosing the subject as having an age-related disease or condition. In some embodiments, 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 embodiments, the method comprises

identifying or diagnosing the subject as having a cancer. In some embodiments, 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 embodiments, the method comprises diagnosing or identifying the subject as having an infectious disease. In some embodiments, 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.

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 some embodiments, the method comprises contacting the immune cell in vitro. In some embodiments, the method comprises obtaining the immune cell from a subject. In some embodiments, the method further comprises obtaining the immune cell from the subject prior to the contacting step. In some embodiments, the method comprises contacting the immune cell in vivo. In some embodiments, 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 embodiments, the immune cell has previously been genetically modified to express a chimeric antigen

receptor or a recombinant T-cell receptor. In some embodiments, 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 embodiments, the method further comprises administering the immune cell to a subject in need thereof. In some embodiments, the method comprises identifying or diagnosing the subject as having an age-related disease or condition. In some embodiments, 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 embodiments, the method comprises identifying or diagnosing the subject as having a cancer. In some embodiments, 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 embodiments, the method comprises diagnosing or identifying the subject as having an infectious disease. In some embodiments, 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.

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 some embodiments, the method comprises identifying or diagnosing the subject as having a cancer. In some embodiments, 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 embodiments, the method comprises identifying or diagnosing the subject as having an aging-related disease or condition. In some embodiments, 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 embodiments, the method comprises administering to the subject a therapeutically effective amount of any of the multi-chain

chimeric polypeptides or compositions discussed above. In some embodiments, the method comprises identifying or diagnosing the subject as having a cancer. In some embodiments, 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 embodiments, the method comprises identifying or diagnosing the subject as having an aging-related disease or condition. In some embodiments, 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 embodiments, the method comprises diagnosing or identifying the subject as having an infectious disease. In some embodiments, 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.

Also provided herein is a nucleic acid encoding any of the multi-chain chimeric polypeptides discussed above. Some embodiments comprise vector containing any of the nucleic acids discussed above. In some embodiments, the vector is an expression vector. Some embodiments comprise a cell containing any of the nucleic acids discussed above.

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 embodiments, the method comprises producing a multi-chain chimeric polypeptide by the methods discussed above.

In some embodiments, the mutant soluble human tissue factor domain comprises a sequence that is at least 80% identical to SEQ ID NO: 3. In some embodiments, the soluble human tissue factor domain comprises a sequence that is at least 90% identical to SEQ ID NO: 3. In some embodiments, the soluble human tissue factor domain comprises a sequence that is at least 95% identical to SEQ ID NO: 3. In some embodiments, 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 embodiments, the soluble human tissue factor domain comprises a sequence that is at least 80% identical to SEQ ID NO: 4. In some embodiments, the soluble human tissue factor domain comprises a sequence that is at least 90% identical to SEQ ID NO: 4. In some embodiments, the soluble human tissue factor domain comprises a sequence that is at least 95% identical to SEQ ID NO:4. In some embodiments, 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

embodiments, a chimeric polypeptide can include at least two different domains that are synthetic sequences (e.g., two different scFvs).

An "antigen-binding domain" is one or more protein domain(s) (e.g., formed from amino acids from a single polypeptide or formed from amino acids from two or more polypeptides (e.g., the same or different polypeptides) that is capable of specifically binding to one or more different antigen(s). In some examples, an antigen-binding domain can bind to an antigen or epitope with specificity and affinity similar to that of naturally-occurring antibodies. In some embodiments, the antigen-binding domain can be an antibody or a fragment thereof. In some embodiments, an antigen-binding domain can include an alternative scaffold. Non-limiting examples of antigen-binding domains are described herein. Additional examples of antigen-binding domains are known in the art.

A "soluble tissue factor domain" refers to a polypeptide having at least 70% identity (e.g., at least 75% identity, at least 80% identity, at least 85% identity, at least 90% identity, at least 95% identity, at least 99% identity, or 100% identical) to a segment of a wildtype mammalian tissue factor protein (e.g., a wildtype human tissue factor protein) that lacks the transmembrane domain and the intracellular domain. Non-limiting examples of soluble tissue factor domains are described herein.

The term "soluble interleukin protein" is used herein to refer to a mature and secreted interleukin protein or a biologically active fragment thereof. In some examples, a soluble interleukin protein can include a sequence that is at least 70% identical, at least 75% identical, at least 80% identical, at least 85% identical, at least 90% identical, at least 95% identical, at least 99% identical, or 100% identical to a wildtype mature and secreted mammalian interleukin protein (e.g., a wildtype human interleukin protein) and retains its biological activity. Non-limiting examples of soluble interleukin proteins are described herein.

The term "soluble cytokine protein" is used herein to refer to a mature and secreted cytokine protein or a biologically active fragment thereof. In some examples, a soluble cytokine protein can include a sequence that is at least 70% identical, at least 75% identical, at least 80% identical, at least 85% identical, at least 90% identical, at least 95% identical, at least 99% identical, or 100% identical to a wildtype mature and secreted

mammalian interleukin protein (e.g., a wildtype human interleukin protein) and retains its biological activity. Non-limiting examples of soluble cytokine proteins are described herein.

The term "soluble interleukin receptor" is used herein in the broadest sense to refer to a polypeptide that lacks a transmembrane domain (and optionally an intracellular domain) that is capable of binding one or more of its natural ligands (e.g., under physiological conditions, e.g., in phosphate buffered saline at room temperature). For example, a soluble interleukin receptor can include a sequence that is at least 70% identical (e.g., at least 75% identical, at least 80% identical, at least 85% identical, at least 90% identical, at least 95% identical, at least 99% identical, or 100% identical) to an extracellular domain of wildtype interleukin receptor and retains its ability to specifically bind to one or more of its natural ligands, but lacks its transmembrane domain (and optionally, further lacks its intracellular domain). Non-limiting examples of soluble interleukin receptors are described herein.

The term "soluble cytokine receptor" is used herein in the broadest sense to refer to a polypeptide that lacks a transmembrane domain (and optionally an intracellular domain) that is capable of binding one or more of its natural ligands (e.g., under physiological conditions, e.g., in phosphate buffered saline at room temperature). For example, a soluble cytokine receptor can include a sequence that is at least 70% identical (e.g., at least 75% identical, at least 80% identical, at least 85% identical, at least 90% identical, at least 95% identical, at least 99% identical, or 100% identical) to an extracellular domain of wildtype cytokine receptor and retains its ability to specifically bind to one or more of its natural ligands, but lacks its transmembrane domain (and optionally, further lacks its intracellular domain). Non-limiting examples of soluble cytokine receptors are described herein.

The term "antibody" is used herein in its broadest sense and includes certain types of immunoglobulin molecules that include one or more antigen-binding domains that specifically bind to an antigen or epitope. An antibody specifically includes, e.g., intact antibodies (e.g., intact immunoglobulins), antibody fragments, and multi-specific antibodies. One example of an antigen-binding domain is an antigen-binding domain

formed by a VH -VL dimer. Additional examples of an antibody are described herein. Additional examples of an antibody are known in the art.

"Affinity" refers to the strength of the sum total of non-covalent interactions between an antigen-binding site and its binding partner (e.g., an antigen or epitope). Unless indicated otherwise, as used herein, "affinity" refers to intrinsic binding affinity, which reflects a 1:1 interaction between members of an antigen-binding domain and an antigen or epitope. The affinity of a molecule X for its partner Y can be represented by the dissociation equilibrium constant (K_D). The kinetic components that contribute to the dissociation equilibrium constant are described in more detail below. Affinity can be measured by common methods known in the art, including those described herein. Affinity can be determined, for example, using surface plasmon resonance (SPR) technology (e.g., BIACORE®) or biolayer interferometry (e.g., FORTEBIO®). Additional methods for determining the affinity for an antigen-binding domain and its corresponding antigen or epitope are known in the art.

A "multi-chain polypeptide" as used herein to refers to a polypeptide comprising two or more (e.g., three, four, five, six, seven, eight, nine, or ten) protein chains (e.g., at least a first chimeric polypeptide and a second polypeptide), where the two or more proteins chains associate through non-covalent bonds to form a quaternary structure.

The term "pair of affinity domains" is two different protein domain(s) that bind specifically to each other with a K_D of less than of less than 1×10^{-7} M (e.g., less than 1×10^{-8} M, less than 1×10^{-9} M, less than 1×10^{-10} M, or less than 1×10^{-11} M). In some examples, a pair of affinity domains can be a pair of naturally-occurring proteins. In some embodiments, a pair of affinity domains can be a pair of synthetic proteins. Non-limiting examples of pairs of affinity domains are described herein.

The term "epitope" means a portion of an antigen that specifically binds to an antigen-binding domain. Epitopes can, e.g., consist of surface-accessible amino acid residues and/or sugar side chains and may have specific three-dimensional structural characteristics, as well as specific charge characteristics. Conformational and non-conformational epitopes are distinguished in that the binding to the former but not the latter may be lost in the presence of denaturing solvents. An epitope may comprise amino acid residues that are directly involved in the binding, and other amino acid

residues, which are not directly involved in the binding. Methods for identifying an epitope to which an antigen-binding domain binds are known in the art.

An "immune effector cell" refers to a cell of the immune system of a mammal that is capable, directly or indirectly, of recognizing and/or causing cytostasis or cell death of a pathogenic cell (e.g., a cancer cell) in the mammal. Non-limiting examples of immune effector cells include macrophages, T-lymphocytes (e.g., cytotoxic T-lymphocytes and T-helper cells), natural killer cells, neutrophils, monocytes, and eosinophils. Additional examples of immune effector cells are known in the art.

The term "treatment" means to ameliorate at least one symptom of a disorder. In some examples, the disorder being treated is cancer and to ameliorate at least one symptom of cancer includes reducing aberrant proliferation, gene expression, signaling, translation, and/or secretion of factors. Generally, the methods of treatment include administering a therapeutically effective amount of composition that reduces at least one symptom of a disorder to a subject who is in need of, or who has been determined to be in need of such treatment.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Methods and materials are described herein for use in the present invention; other, suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

Other features and advantages of the invention will be apparent from the following detailed description and figures, and from the claims.

BRIEF DESCRIPTION OF DRAWINGS

Figure 1 shows exemplary diagrams for a multi-chain chimeric polypeptide: (i) a first chimeric polypeptide including a first target-binding domain (A), a soluble tissue factor domain, a first domain of an affinity pair of domains (soluble interleukin IL-15), and an additional target-binding domain (B); and (ii) second chimeric polypeptide

including a second domain of an affinity pair of domains (IL-15 receptor alpha sushi domain), a second target-binding domain (C), and an additional antigen-binding domain (D). The top cartoon diagram depicts the association of the first and the second chimeric polypeptides through the pair of affinity domains. The bottom schematic diagrams show the order of the domains in the first and second chimeric polypeptides.

Figure 2 shows exemplary diagrams for a multi-chain chimeric polypeptide: (i) a first chimeric polypeptide including a first target-binding domain (A), a soluble tissue factor domain including five amino acid substitutions in order to remove binding of the soluble tissue factor domain to FVIIa, a first domain of an affinity pair of domains (soluble interleukin IL-15 including a D8N or D8A amino acid substitution), and an additional target-binding domain (B); and (ii) second chimeric polypeptide including a second domain of an affinity pair of domains (IL-15 receptor alpha sushi domain), a second target-binding domain (C), and an additional antigen-binding domain (D). The top cartoon diagram depicts the association of the first and the second chimeric polypeptides through the pair of affinity domains. The bottom schematic diagrams show the order of the domains in the first and second chimeric polypeptides. In other embodiments of any of the multi-chain chimeric polypeptides described herein the soluble tissue factor domain can comprise or consists of a soluble wildtype human tissue factor domain (comprising or consisting of a contiguous sequence within wildtype human tissue factor).

Figure 3 shows a schematic diagram of an exemplary IL-12/IL-15RαSu DNA construct.

Figure 4 shows a schematic diagram of an exemplary IL-18/TF/IL-15 DNA construct.

Figure 5 shows a schematic diagram of the interaction between the exemplary IL-12/IL-15RαSu and IL-18/TF/IL-15 DNA constructs.

Figure 6 shows a schematic diagram of the interaction between the exemplary IL-12/IL-15RαSu and IL-18/TF/IL-15 fusion proteins resulting in IL-18/TF/IL-15:IL-12/IL-15RαSu complex (18t15-12s).

Figure 7 shows a chromatograph of 18t15-12s purification elution from an anti-TF antibody affinity column.

Figure 8 shows an exemplary chromatographic profile of anti-TF Ab / SEC-purified 18t15-12s protein following elution on an analytical size exclusion column, demonstrating separation of monomeric multiprotein 18t15-12s complexes from protein aggregates.

Figure 9 shows an example of a 4-12% SDS-PAGE of the 18t15-12s complex following disulfide bond reduction. Lane 1: SeeBlue Plus2 marker; Lane 2: an anti-tissue factor antibody affinity column-purified 18t15-12s (0.5 μg); Lane 3: an anti-tissue factor antibody affinity column-purified 18t15-12s (1 μg).

Figure 10 shows SDS PAGE analysis of deglycosylated and non-deglycosylated 18t15-12s. Lane 1: an anti-tissue factor antibody affinity column-purified 18t15-12s (0.5 μg), non-deglycosylated; Lane 2: anti-TF Ab-purified 18t15-12s (1 μg), non-deglycosylated; Lane 3: 18t15-12s (1 μg), deglycosylated, Lane 4: Mark12 unstained maker.

Figure 11 shows a sandwich ELISA for the 18t15-12s complex, comprising an anti-human tissue factor capture antibody and a biotinylated anti-human IL-12 detection antibody (BAF 219).

Figure 12 shows a sandwich ELISA for the 18t15-12s complex, comprising an anti-human tissue factor capture antibody and a biotinylated anti-human IL-15 detection antibody (BAM 247).

Figure 13 shows a sandwich ELISA for the 18t15-12s complex, comprising an anti-human tissue factor capture antibody and a biotinylated anti-human IL-18 detection antibody (D045-6).

Figure 14 shows a sandwich ELISA for the 18t15-12s complex, comprising an anti-human tissue factor (I43) capture antibody and an anti-human tissue factor detection antibody.

Figure 15 shows proliferation of IL-15-dependent 32Dβ cells mediated by the 18t15-12s complex (open squares) and recombinant IL-15 (black squares).

Figure 16 shows biological activity of IL-18 within the 18t15-12s complex (open squares), where recombinant IL-18 (black squares) and recombinant IL-12 (black circles) serve as positive and negative controls, respectively.

Figure 17 shows biological activity of IL-12 within the 18t15-12s complex (open squares), where recombinant IL-12 (black circles) and recombinant IL-18 (open squares) serve as positive and negative controls, respectively.

Figures 18A and 18B show cell-surface expression of CD25 on NK cells induced by the 18t15-12s complex and cell-surface CD69 expression of NK cells induced by the 18t15-12s complex.

Figure 19 shows a flow cytometry graph of intracellular interferon gamma expression of NK cells induced by the 18t15-12s complex.

Figure 20 shows cytotoxicity of 18t15-12s induced human NK cells against K562 cells.

Figure 21 shows a schematic diagram of an exemplary IL-12/IL-15RαSu/αCD16 DNA construct.

Figure 22 shows a schematic diagram of an exemplary IL-18/TF/IL-15 DNA construct.

Figure 23 shows a schematic diagram of the interaction between the exemplary IL-12/IL-15RαSu/αCD16scFv and IL-18/TF/IL-15 DNA constructs.

Figure 24 shows a schematic diagram of an exemplary 18t15-12s/αCD16 protein complex.

Figure 25 shows a sandwich ELISA for the 18t15-12s16 complex, comprising an anti-human tissue factor capture antibody and a biotinylated anti-human IL-12 or IL-18 detection antibody.

Figure 26 shows a schematic diagram of an exemplary TGFβRII/IL-15RαSu DNA construct.

Figure 27 shows a schematic diagram of an exemplary IL-21/TF/IL-15 construct.

Figure 28 shows a schematic diagram of the interaction between the exemplary IL- IL-21/TF/IL-15 and TGFβRII/IL-15RαSu constructs.

Figure 29 shows a schematic diagram of the interaction between the exemplary TGFβRII/IL-15RαSu and IL-21/TF/IL-15 fusion proteins, resulting in an IL-21/TF/IL-15/TGFβRII/IL-15RαSu complex (21t15-TGFRs).

Figure 30 shows a chromatograph of 21t15-TGFRs purification elution from an anti-TF antibody affinity column.

Figure 31 shows an exemplary 21t15-TGFRs size exclusion chromatograph showing a main protein peak and a high molecular weight peak

Figure 32 shows an example of a 4-12% SDS-PAGE of the 21t15-TGFRs complex following disulfide bond reduction. Lane 1: Mark12 unstained marker (numbers on the left side indicate molecular weights in kDa); Lane 2: 21t15-TGFRs (0.5 μg); Lane 3: 21t15-TGFRs (1 μg); Lane 4: 21t15-TGFRs, deglycosylated (1 μg), wherein the MW was the expected size of 53kDa and 39.08 kDa.

Figure 33 shows a sandwich ELISA for the 21t15-TGFRs complex, comprising an anti-human tissue factor capture antibody and a biotinylated anti-human IL-21 detection antibody (13-7218-81, BioLegend).

Figure 34 shows a sandwich ELISA for the 21t15-TGFRs complex, comprising an anti-human tissue factor capture antibody and a biotinylated anti-human IL-15 detection antibody (BAM 247, R&D Systems).

Figure 35 shows a sandwich ELISA for the 21t15-TGFRs complex, comprising an anti-human tissue factor capture antibody and a biotinylated anti-human TGFβRII detection antibody (BAF241, R&D Systems).

Figure 36 shows a sandwich ELISA for the 21t15-TGFRs complex, comprising an anti-human tissue factor (I43) capture antibody and an anti-human tissue factor detection antibody.

Figure 37 shows IL-15-dependent proliferation of 32Dβ cells mediated by the 21t15-TGFRs complex (open squares) compared to IL-15 (black squares).

Figure 38 shows biological activity of the TGFβRII domain within the 21t15-TGFRs complex (open squares). TGFβRII/Fc (black squares) served as a positive control.

Figure 39 A shows a flow cytometry graph of cell-surface CD25 expression of NK cells induced by the 21t15-TGFRs complex.

Figure 40 shows a flow cytometry graph of cell-surface CD69 expression of NK cells induced by the 21t15-TGFRs complex.

Figure 41 shows a flow cytometry graph of intracellular interferon gamma expression of NK cells induced by the 21t15-TGFRs complex.

Figure 42 shows cytotoxicity of 21t15-TGFRs-induced human NK cells against K562 cells.

Figure 43 shows a schematic diagram of an exemplary IL-7/IL-15RαSu DNA construct.

Figure 44 shows a schematic diagram of an exemplary IL-21/TF/IL-15 DNA construct.

Figure 45 shows a schematic diagram of the interaction between the exemplary IL-7/IL-15RαSu and IL-21/TF/IL-15 DNA constructs.

Figure 46 shows a schematic diagram of the interaction between the exemplary IL-7/IL-15RαSu and IL-21/TF/IL-15 fusion proteins resulting in an IL-21/TF/IL-15:IL-7/IL-15RαSu complex (21t15-7s).

Figure 47 shows the expansion of primary natural killer (NK) cells by stimulation with 21t15-7s + anti-TF IgG1 antibody.

Figure 48 shows activation of expanded primary NK cells, using CD25 MFI and CD69 MFI as markers of NK cell activation.

Figure 49 shows cytotoxic activity of expanded NK cells against K562 human tumor cells, wherein NK cells stimulated with 21t15-7s + anti-TF IgG1 antibody demonstrate greater specific lysis of K562 cells than NK cells not stimulated with 21t15-7s + anti-TF IgG1 antibody.

Figure 50 shows a schematic diagram of an exemplary IL-21/IL-15RαSu DNA construct.

Figure 51 shows a schematic diagram of an exemplary IL-7/TF/IL-15 DNA construct.

Figure 52 shows a schematic diagram of the interaction between the exemplary IL-21/IL-15RαSu and IL-7/TF/IL-15 DNA constructs.

Figure 53 shows a schematic diagram of the interaction between the exemplary IL-21/IL-15RαSu and IL-7/TF/IL-15 fusion proteins resulting in an IL-7/TF/IL-15:IL-21/IL-15RαSU complex (7t15-21s).

Figure 54 shows in diagrammatic form the activation and expansion of primary natural killer (NK) cells by stimulation with 21t15-TGFRs + anti-TF IgG1 antibody.

Figure 55 shows size exclusion chromatography (SEC) profiles of anti-TF IgG1 antibody, 7t15-21s and the complex containing equal amounts of anti-TF IgG1 antibody and 7t15-21s.

Figure 56 shows the oxygen consumption rate (OCR) in pmoles/min for human NK cells isolated from blood (2 x 10^6 cells/mL) of two different donors.

Figure 57 shows the extracellular acidification rate (ECAR) in mpH/minute for human NK cells isolated from blood (2 x 10^6 cells/mL) of two different donors.

Figure 58 shows a schematic of the 7t15-16s21 construct.

Figure 59 shows an additional schematic of the 7t15-16s21 construct.

Figures 60A and 60B show binding of 7t15-16s21 to CHO cells expressing human CD16b as compared to a control protein.

Figures 61A-61C are results from ELISA experiments using antibodies against IL-15, IL-21, and IL-7 in detecting 7t15-16s21.

Figure 62 shows results of the 32Dβ cell proliferation assay with 7t15-16s21 or recombinant IL-15.

Figure 63 shows the chromatographic profile of 7t15-16s21 protein containing cell culture supernatant following binding and elution on anti-TF antibody resin.

Figure 64 shows the analytical SEC Profile of 7t15-16s21.

Figure 65 shows a schematic of the TGFRt15-16s21 construct.

Figure 66 shows an additional schematic of the TGFRt15-16s21 construct.

Figures 67A and 67B show binding affinity of TGFRt15-16S21 and 7t15-21s with CHO cells expressing human CD16b. Figure 67A shows binding affinity of TGFRt15-16S21 with CHO cells expressing human CD16b. Figure 67B shows binding affinity of 7t15-21s with CHO cells expressing human CD16b.

Figure 68 shows results of TGFβ1 inhibition by TGFRt15-16s21 and TGFR-Fc.

Figure 69 shows results of 32Dβ cell proliferation assay with TGFRt15-16s21 or recombinant IL-15.

Figures 70A-70C show results of detecting IL-15, IL-21, and TGFβRII in TGFRt15-16s21 with corresponding antibodies using ELISA.

Figure 71 shows the chromatographic profile of TGFRt15-16s21 protein containing cell culture supernatant following binding and elution on anti-TF antibody resin.

Figure 72 shows results of a reduced SDS-PAGE analysis of TGFRt15-16s21.

Figure 73 shows a schematic of the 7t15-7s construct.

Figure 74 shows an additional schematic of the 7t15-7s construct.

Figure 75 shows the chromatographic profile of 7t15-7s protein containing cell culture supernatant following binding and elution on anti-TF antibody resin.

Figure 76 shows detection of TF, IL-15 and IL-7 in 7t15-7s using ELISA.

Figure 77 shows a schematic of the TGFRt15-TGFRs construct.

Figure 78 shows an additional schematic of the TGFRt15-TGFRs construct.

Figure 79 shows results of TGFβ1 inhibition by TGFRt15-TGFRs and TGFR-Fc.

Figure 80 shows results of 32Dβ cell proliferation assay with TGFRt15-TGFRs or recombinant IL-15

Figures 81A and 81B show results of detecting IL-15 and TGFβRII in TGFRt15-TGFRs with corresponding antibodies using ELISA.

Figure 82 is a line graph showing the chromatographic profile of TGFRt15-TGFRs protein containing cell culture supernatant following binding and elution on anti-TF antibody resin.

Figure 83 shows the analytical SEC profile of TGFRt15-TGFRs.

Figure 84 shows TGFRt15-TGFRs before and after deglycosylation as analyzed by reduced SDS-PAGE.

Figures 85A and 85B show spleen weight and the percentages of immune cell types in TGFRt15-TGFRs-treated and control-treated mice. Figure 85A shows spleen weight in mice treated with TGFRt15-TGFRs as compared to PBS control. Figure 85B shows the percentage of $CD4^+$ T cells, $CD8^+$ T cells, and NK cells in mice treated with TGFRt15-TGFRs as compared to PBS control.

Figure 86A and 86B show the spleen weight and immunostimulation over 92 hours in mice treated with TGFRt15-TGFRs. Figure 86A shows spleen weight of mice treated with TGFRt15-TGFRs at 16, 24, 48, 72, and 92 hours after treatment. Figure 86B

shows the percentages of immune cells in mice treated with TGFRt15-TGFRs at 16, 24, 48, 72, and 92 hours after treatment.

Figure 87A and 87B show Ki67 and Granzyme B expression in mice treated with TGFRt15-TGFRs over time.

Figure 88 shows enhancement of cytotoxicity of splenocytes by TGFRt15-TGFRs in C57BL/6 Mice.

Figure 89 shows changes in tumor size in response to PBS treatment, chemotherapy alone, TGFRt15-TGFRs alone, or chemotherapy and TGFRt15-TGFRs combination, in a pancreatic cancer mouse model.

Figure 90 shows the cytotoxicity of NK cells isolated from mice treated with TGFRt15-TGFRs.

Figure 91 shows a schematic of the 7t15-21s137L (long version) construct.

Figure 92 shows an additional schematic of the 7t15-21s137L (long version) construct.

Figure 93 is a line graph showing the chromatographic profile of 7t15-21s137L (long version) protein containing cell culture supernatant following binding and elution on anti-TF antibody resin.

Figure 94 shows the analytical SEC profile of 7t15-21s137L (long version).

Figure 95 shows binding of 7t15-21s137L (short version) to CD137L (4.1BBL)

Figures 96A-96C show detection of IL15, IL21, and IL7 in 7t15-21s137L (short version) with ELISA. Figure 96A shows detection of IL15 in 7t15-21s137L (short version) with ELISA. Figure 96B shows detection of IL21 in 7t15-21s137L (short version) with ELISA. Figure 96C shows detection of IL7 in 7t15-21s137L (short version) with ELISA.

Figure 97 shows results from a CTLL-2 cell proliferation assay.

Figure 98 shows the activity of 7t15-1s137L (short version) in promoting IL21R containing B9 cell proliferation.

Figure 99 shows a schematic of the 7t15-TGFRs construct.

Figure 100 shows an additional schematic of the 7t15-TGFRs construct.

Figure 101 shows results of TGFβ1 inhibition by 7t15-TGFRs and TGFR-Fc.

Figures 102A-102C show detection of IL-15, TGFβRII, and IL-7 in 7t15-TGFRs with ELISA.

Figure 103 shows results of a 32Dβ cell proliferation assay with 7t15-TGFRs or recombinant IL-15.

Figure 104 is a line graph showing the chromatographic profile of 7t15-TGFRs protein containing cell culture supernatant following binding and elution on anti-TF antibody affinity column.

Figure 105 shows 7t15-TGFRs before and after deglycosylation as analyzed using reduced SDS-PAGE.

Figure 106 shows ELISA detection of IL-7, IL-15 and TGFβRII in the 7t15-TGFRs protein.

Figures 107A and 107B show spleen weight and the percentages of immune cell types in 7t15-TGFRs-treated and control-treated mice. Figure 107A shows spleen weight in mice treated with 7t15-TGFRs at various dosages, as compared to PBS control. Figure 107B shows the percentage of $CD4^+$ T cells, $CD8^+$ T cells, and NK cells in mice treated with 7t15-TGFRs at various dosages, as compared to PBS control.

Figures 108A and 108B show upregulation of CD44 expression of $CD4^+$ and $CD8^+$ T cells by 7t15-TGFRs in C57BL/6 mice.

Figures 109A and 109B show upregulation of Ki67 expression and Granzyme B expression of $CD8^+$ T cells and NK Cells by 7t15-TGFRs in C57BL/6 mice.

Figure 110 shows enhancement of cytotoxicity of splenocytes by 7t15-TGFRs in C57BL/6 mice.

Figure 111 shows a schematic of the TGFRt15-21s137L construct.

Figure 112 shows an additional schematic of the TGFRt15-21s137L construct.

Figure 113 is a line graph showing the chromatographic profile of TGFRt15-21s137L protein containing cell culture supernatant following binding and elution on anti-TF antibody affinity column.

Figure 114 shows a schematic of the TGFRt15-TGFRs21 construct.

Figure 115 shows an additional schematic of the TGFRt15-TGFRs21 construct.

Figure 116 is a line graph showing the chromatographic profile of TGFRt15-TGFRs21 protein containing cell culture supernatant following binding and elution on anti-TF antibody affinity column.

Figure 117 shows TGFRt15-TGFRs21 before and after deglycosylation as analyzed by reduced SDS-PAGE.

Figures 118A and 118B show detection of components of TGFRt15-TGFRs21 using ELISA.

Figures 119A and 119B show the percentages and proliferation of $CD4^+$ T cells, $CD8^+$ T cells, and natural killer (NK) cells present in the spleen of control-treated and TGFRt15-TGFRs21-treated mice.

Figure 120 shows upregulation of Granzyme B expression of splenocytes in mice treated with TGFRt15-TGFRs21.

Figure 121 shows enhancement of cytotoxicity of splenocytes by TGFRt15-TGFRs21 in C57BL/6 Mice.

Figure 122 shows a schematic of the TGFRt15-TGFRs16 construct.

Figure 123 shows an additional schematic of the TGFRt15-TGFRs16 construct.

Figure 124 shows a schematic of the TGFRt15-TGFRs137L construct.

Figure 125 shows an additional schematic of the TGFRt15-TGFRs137L construct.

Figure 126 shows changes in the surface phenotype of lymphocyte populations after stimulation with 18t15-12s, 18t15-12s16, and 7t15-21s.

Figure 127 shows an increase in phospho-STAT4 and phospho-STAT5 levels in NK cells after stimulation with 18t15-12s.

Figures 128A-128C show *in vivo* stimulation of Tregs, NK cells, and $CD8^+$ T cells in $ApoE^{-/-}$ mice fed with a Western diet and treated with TGFRt15-TGFRs.

Figures 129A-129C show immunostimulation in C57BL/6 mice following treatment with TGFRt15-TGFRs.

Figures 130A and 130B show *in vivo* induction of proliferation of NK cells and $CD8^+$ T cells in $ApoE^{-/-}$ mice fed with a Western diet and treated with TGFRt15-TGFRs.

Figures 131A and 131B show enhancement of cytotoxicity of NK cells following treatment of NK cells with TGFRt15-TGFRs.

Figures 132A and 132B show enhancement of ADCC activity of NK cells following treatment of NK cells with TGFRt15-TGFRs.

Figures 133A-133H show antitumor activity of TGFRt15-TGFRs plus anti-TRP1 antibody (TA99) in combination with chemotherapy in a melanoma mouse model.

Figures 134A-134C show amelioration of the Western diet-induced hyperglycemia in $ApoE^{-/-}$ mice by TGFRt15-TGFRs.

Figure 135 shows cell surface staining summarizing the differentiation of NK cells into cytokine-induced memory like NK Cells (CIML-NK Cells) after stimulation with 18t15-12s and cultured in rhIL15.

Figure 136 shows upregulation shows upregulation of CD44hi memory T cells upon treatment with TGFRt15-TGFRs.

Figure 137 shows a graph of Factor X (FX) activation following treatment with single-chain or multi-chain chimeric polypeptides.

Figure 138 shows clotting time for a buffer with varying concentrations of Innovin in a prothrombin time (PT) test.

Figure 139 shows clotting time for multi-chain chimeric polypeptides in a PT Assay.

Figure 140 shows clotting time of the multi-chain chimeric polypeptides in a PT assay when mixed with 32DB cells.

Figure 141 shows clotting time of multi-chain chimeric polypeptides in a PT assay when mixed with human PBMC.

Figure 142 shows binding of 7t15-21s137L (long version) and 7t15-21s137L (short version) to CD137 (4.1BB).

Figure 143A-143D show detection of IL7, IL21, IL15, and 4.1BBL in 7t15-21s137L (long version) by the respective antibodies using ELISA.

Figure 144 shows IL-15 activity of 7t15-21s137L (long version) and 7t15-21s137L (short version) as evaluated by a IL2Rαβγ-containing CTLL2 cell proliferation assay.

DETAILED DESCRIPTION

Provided herein are multi-chain chimeric polypeptides that include: (a) a first chimeric polypeptide including: (i) a first target-binding domain; (ii) a soluble tissue factor domain; and (iii) a first domain of a pair of affinity domains; and (b) a second chimeric polypeptide including: (i) a second domain of a pair of affinity domains; and (ii) a second target-binding domain, where 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. 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.

In some examples of any of the multi-chain chimeric polypeptides described herein the total length of first chimeric polypeptide and/or the second chimeric polypeptide can each independently be about 50 amino acids to about 3000 amino acids, about 50 amino acids to about 2500 amino acids, about 50 amino acids to about 2000 amino acids, about 50 amino acids to about 1500 amino acids, about 50 amino acids to about 1000 amino acids, about 50 amino acids to about 950 amino acids, about 50 amino acids to about 900 amino acids, about 50 amino acids to about 850 amino acids, about 50 amino acids to about 800 amino acids, about 50 amino acids to about 750 amino acids, about 50 amino acids to about 700 amino acids, about 50 amino acids to about 650 amino acids, about 50 amino acids to about 600 amino acids, about 50 amino acids to about 550 amino acids, about 50 amino acids to about 500 amino acids, about 50 amino acids to about 480 amino acids, about 50 amino acids to about 460 amino acids, about 50 amino acids to about 440 amino acids, about 50 amino acids to about 420 amino acids, about 50 amino acids to about 400 amino acids, about 50 amino acids to about 380 amino acids, about 50 amino acids to about 360 amino acids, about 50 amino acids to about 340 amino acids, about 50 amino acids to about 320 amino acids, about 50 amino acids to about 300

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In some embodiments of any of the multi-chain chimeric polypeptides described herein, the first target-binding domain (e.g., any of the first target-binding domains described herein) and the soluble tissue factor domain (e.g., any of the exemplary soluble tissue factor domains described herein) directly abut each other in the first chimeric polypeptide. In some embodiments of any of the multi-chain chimeric polypeptides described herein, the first chimeric polypeptide further comprises a linker sequence (e.g., any of the exemplary linker sequences described herein or known in the art) between the first target-binding domain (e.g., any of the exemplary first target-binding domains described herein) and the soluble tissue factor domain (e.g., any of the exemplary soluble tissue factor domains described herein) in the first chimeric polypeptide.

In some embodiments of any of the multi-chain chimeric polypeptides described herein, the soluble tissue factor domain (e.g., any of the exemplary soluble tissue factor domains described herein) and the first domain of the pair of affinity domains (e.g., any of the exemplary first domains of any of the exemplary pairs of affinity domains described herein) directly abut each other in the first chimeric polypeptide. In some embodiments of any of the multi-chain chimeric polypeptides described herein, the first chimeric polypeptide further comprises a linker sequence (e.g., any of the exemplary linker sequences described herein or known in the art) between the soluble tissue factor domain (e.g., any of the exemplary soluble tissue factor domains described herein) and the first domain of the pair of affinity domains (e.g., any of the exemplary first domains

of any of the exemplary pairs of affinity domains described herein) in the first chimeric polypeptide.

In some embodiments of any of the multi-chain chimeric polypeptides described herein, the second domain of the pair of affinity domains (e.g., any of the exemplary second domains of any of the exemplary pairs of affinity domains described herein) and the second target-binding domain (e.g., any of the exemplary second target-binding domains described herein) directly abut each other in the second chimeric polypeptide. In some embodiments of any of the multi-chain chimeric polypeptides described herein, the second chimeric polypeptide further comprises a linker sequence (e.g., any of the exemplary linker sequences described herein or known in the art) between the second domain of the pair of affinity domains (e.g., any of the exemplary second domains of any of the exemplary pairs of affinity domains described herein) and the second target-binding domain (e.g., any of the exemplary second target-binding domains described herein) in the second chimeric polypeptide.

Non-limiting aspects of these chimeric polypeptides, nucleic acids, vectors, cells, and methods are described below, and can be used in any combination without limitation. Additional aspects of these chimeric polypeptides, nucleic acids, vectors, cells, and methods are known in the art.

Tissue Factor

Human tissue factor is a 263 amino-acid transmembrane protein containing three domains: (1) a 219-amino acid N-terminal extracellular domain (residues 1-219); (2) a 22-amino acid transmembrane domain (residues 220-242); and (3) a 21-amino acid cytoplasmic C-terminal tail (residues 242-263) ((UniProtKB Identifier Number: P13726). The cytoplasmic tail contains two phosphorylation sites at Ser253 and Ser258, and one S-palmitoylation site at Cys245. Deletion or mutation of the cytoplasmic domain was not found to affect tissue factor coagulation activity. Tissue factor has one S-palmitoylation site in the intracellular domain of the protein at Cys245. The Cys245 is located at the amino acid terminus of the intracellular domain and close to the membrane surface. The tissue factor transmembrane domain is composed of a single-spanning α-helix.

The extracellular domain of tissue factor, composed of two fibronectin type III domains, is connected to the transmembrane domain through a six-amino acid linker. This linker provides conformational flexibility to decouple the tissue factor extracellular domain from its transmembrane and cytoplasmic domains. Each tissue factor fibronectin type III module is composed of two overlapping β sheets with the top sheet domain containing three antiparallel β-strands and the bottom sheet containing four β-strands. The β-strands are connected by β-loops between strand βA and βB, βC and βD, and βE and βF, all of which are conserved in conformation in the two modules. There are three short α-helix segments connecting the β-strands. A unique feature of tissue factor is a 17-amino acid β-hairpin between strand β10 and strand β11, which is not a common element of the fibronectin superfamily. The N-terminal domain also contains a 12 amino acid loop between β6F and β7G that is not present in the C-terminal domain and is unique to tissue factor. Such a fibronectin type III domain structure is a feature of the immunoglobulin-like family of protein folds and is conserved among a wide variety of extracellular proteins.

The zymogen FVII is rapidly converted to FVIIa by limited proteolysis once it binds to tissue to form the active tissue factor-FVIIa complex. The FVIIa, which circulates as an enzyme at a concentration of approximately 0.1 nM (1% of plasma FVII), can also bind directly to tissue factor. The allosteric interaction between tissue factor and FVIIa on the tissue factor-FVIIa complex greatly increases the enzymatic activity of FVIIa: an approximate 20- to 100-fold increase in the rate of hydrolysis of small, chromogenic peptidyl substrates, and nearly a million-fold increase in the rate of activation of the natural macromolecular substrates FIX and FX. In concert with allosteric activation of the active site of FVIIa upon binding to tissue factor, the formation of tissue factor-FVIIa complex on phospholipid bilayer (i.e., upon exposure of phosphatidyl-L-serine on membrane surfaces) increases the rate of FIX or FX activation, in a Ca^{2+}-dependent manner, an additional 1,000-fold. The roughly million-fold overall increase in FX activation by tissue factor-FVIIa-phospholipid complex relative to free FVIIa is a critical regulatory point for the coagulation cascade.

FVII is a ~50 kDa, single-chain polypeptide consisting of 406 amino acid residues, with an N-terminal γ-carboxyglutamate-rich (GLA) domain, two epidermal

growth factor-like domains (EGF1 and EFG2), and a C-terminal serine protease domain. FVII is activated to FVIIa by a specific proteolytic cleavage of the Ile-^{154}-Arg^{152} bond in the short linker region between the EGF2 and the protease domain. This cleavage results in the light and heavy chains being held together by a single disulfide bond of Cys^{135} and Cys^{262}. FVIIa binds phospholipid membrane in a Ca^{2+}-dependent manner through its N-terminal GLA-domain. Immediately C-terminal to the GLA domain is an aromatic stack and two EGF domains. The aromatic stack connects the GLA to EGF1 domain which binds a single Ca^{2+} ion. Occupancy of this Ca^{2+}-binding site increases FVIIa amidolytic activity and tissue factor association. The catalytic triad consist of His^{193}, Asp^{242}, and Ser^{344}, and binding of a single Ca^{2+} ion within the FVIIa protease domain is critical for its catalytic activity. Proteolytic activation of FVII to FVIIa frees the newly formed amino terminus at Ile^{153} to fold back and be inserted into the activation pocket forming a salt bridge with the carboxylate of Asp^{343} to generate the oxyanion hole. Formation of this salt bridge is critical for FVIIa activity. However, oxyanion hole formation does not occur in free FVIIa upon proteolytic activation. As a result, FVIIa circulates in a zymogen-like state that is poorly recognized by plasma protease inhibitors, allowing it to circulate with a half-life of approximately 90 minutes.

Tissue factor-mediated positioning of the FVIIa active site above the membrane surface is important for FVIIa towards cognate substrates. Free FVIIa adopts a stable, extended structure when bound to the membrane with its active site positioned ~80Å above the membrane surface. Upon FVIIa binding to tissue factor, the FVa active site is repositioned ~6Å closer to the membrane. This modulation may aid in a proper alignment of the FVIIa catalytic triad with the target substrate cleavage site. Using GLA-domainless FVIIa, it has been shown that the active site was still positioned a similar distance above the membrane, demonstrating that tissue factor is able to fully support FVIIa active site positioning even in the absence of FVIIa-membrane interaction. Additional data showed that tissue factor supported full FVIIa proteolytic activity as long as the tissue factor extracellular domain was tethered in some way to the membrane surface. However, raising the active site of FVIIa greater than 80Å above the membrane surface greatly reduced the ability of the tissue factor-FVIIa complex to activate FX but did not diminish tissue factor-FVIIa amidolytic activity.

Alanine scanning mutagenesis has been used to assess the role of specific amino acid side chains in the tissue factor extracellular domain for interaction with FVIIa (Gibbs et al., *Biochemistry* 33(47): 14003-14010, 1994; Schullek et al., *J Biol Chem* 269(30): 19399-19403, 1994). Alanine substitution identified a limited number of residue positions at which alanine replacements cause 5- to 10-fold lower affinity for FVIIa binding. Most of these residue side chains were found to be well-exposed to solvent in the crystal structure, concordant with macromolecular ligand interaction. The FVIIa ligand-binding site is located over an extensive region at the boundary between the two modules. In the C-module, residues Arg^{135} and Phe^{140} located on the protruding B-C loop provide an independent contact with FVIIa. Leu^{133} is located at the base of the fingerlike structure and packed into the cleft between the two modules. This provides continuity to a major cluster of important binding residues consisting of Lys^{20}, Thr^{60}, Asp^{58}, and Ile^{22}. Thr^{60} is only partially solvent-exposed and may play a local structural role rather than making a significant contact with ligand. The binding site extends onto the concave side of the intermodule angle involving Glu^{24} and Gln^{110}, and potentially the more distant residue Val^{207}. The binding region extends from Asp58 onto a convex surface area formed by Lys^{48}, Lys^{46}, Gln^{37}, Asp^{44}, and Trp^{45}. Trp^{45} and Asp^{44} do not interact independently with FVIIa, indicating that the mutational effect at the Trp^{45} position may reflect a structural importance of this side chain for the local packing of the adjacent Asp^{44} and Gln^{37} side chain. The interactive area further includes two surface-exposed aromatic residues, Phe^{76} and Tyr^{78}, which form part of the hydrophobic cluster in the N-module.

The known physiologic substrates of tissue factor-FVIIa are FVII, FIX, and FX and certain proteinase-activated receptors. Mutational analysis has identified a number of residues that, when mutated, support full FVIIa amidolytic activity towards small peptidyl substrates but are deficient in their ability to support macromolecular substrate (i.e., FVII, FIX, and FX) activation (Ruf et al., *J Biol Chem* 267(31): 22206-22210, 1992; Ruf et al., *J Biol Chem* 267(9): 6375-6381, 1992; Huang et al., *J Biol Chem* 271(36): 21752-21757, 1996; Kirchhofer et al., *Biochemistry* 39(25): 7380-7387, 2000). The tissue factor loop region at residues 159-165, and residues in or adjacent to this flexible loop have been shown to be critical for the proteolytic activity of the tissue factor-FVIIa

complex. This defines the proposed substrate-binding exosite region of tissue factor that is quite distant from the FVIIa active site. A substitution of the glycine residue by a marginally bulkier residue alanine, significantly impairs tissue factor-FVIIa proteolytic activity. This suggests that the flexibility afforded by glycine is critical for the loop of residues 159-165 for tissue factor macromolecular substrate recognition.

The residues Lys^{165} and Lys^{166} have also been demonstrated to be important for substrate recognition and binding. Mutation of either of these residues to alanine results in a significant decrease in the tissue factor co-factor function. Lys^{165} and Lys^{166} face away from each other, with Lys^{165} pointing towards FVIIa in most tissue factor-FVIIa structures, and Lys^{166} pointing into the substrate binding exosite region in the crystal structure. Putative salt bridge formation between Lys^{165} of and Gla^{35} of FVIIa would support the notion that tissue factor interaction with the GLA domain of FVIIa modulates substrate recognition. These results suggest that the C-terminal portion of the tissue factor ectodomain directly interacts with the GLA-domain, the possible adjacent EGF1 domains, of FIX and FX, and that the presence of the FVIIa GLA-domain may modulate these interactions either directly or indirectly.

Soluble Tissue Factor Domain

In some embodiments of any of the polypeptides, compositions, or methods described herein, the soluble tissue factor domain can be a wildtype tissue factor polypeptide lacking the signal sequence, the transmembrane domain, and the intracellular domain. In some examples, the soluble tissue factor domain can be a tissue factor mutant, wherein a wildtype tissue factor polypeptide lacking the signal sequence, the transmembrane domain, and the intracellular domain, and has been further modified at selected amino acids. In some examples, the soluble tissue factor domain can be a soluble human tissue factor domain. In some examples, the soluble tissue factor domain can be a soluble mouse tissue factor domain. In some examples, the soluble tissue factor domain can be a soluble rat tissue factor domain. Non-limiting examples of soluble human tissue factor domains, a mouse soluble tissue factor domain, a rat soluble tissue factor domain, and mutant soluble tissue factor domains are shown below.

Exemplary Soluble Human Tissue Factor Domain (SEQ ID NO: 1)

SGTTNTVAAYNLTWKSTNFKTILEWEPKPVNQVYTVQISTKSGDWKSKCFYTTD
TECDLTDEIVKDVKQTYLARVFSYPAGNVESTGSAGEPLYENSPEFTPYLETNLGQ
PTIQSFEQVGTKVNVTVEDERTLVRRNNTFLSLRDVFGKDLIYTLYYWKSSSSGK
KTAKTNTNEFLIDVDKGENYCFSVQAVIPSRTVNRKSTDSPVECMGQEKGEFRE

Exemplary Nucleic Acid Encoding Soluble Human Tissue Factor Domain (SEQ ID NO: 2)

AGCGGCACAACCAACACAGTCGCTGCCTATAACCTCACTTGGAAGAGCACCA
ACTTCAAAACCATCCTCGAATGGGAACCCAAACCCGTTAACCAAGTTTACACC
GTGCAGATCAGCACCAAGTCCGGCGACTGGAAGTCCAAATGTTTCTATACCAC
CGACACCGAGTGCGATCTCACCGATGAGATCGTGAAAGATGTGAAACAGACC
TACCTCGCCCGGGTGTTTAGCTACCCCGCCGGCAATGTGGAGAGCACTGGTTC
CGCTGGCGAGCCTTTATACGAGAACAGCCCCGAATTTACCCCTTACCTCGAGA
CCAATTTAGGACAGCCCACCATCCAAAGCTTTGAGCAAGTTGGCACAAAGGT
GAATGTGACAGTGGAGGACGAGCGGACTTTAGTGCGGCGGAACAACACCTTT
CTCAGCCTCCGGGATGTGTTCGGCAAAGATTTAATCTACACACTGTATTACTGG
AAGTCCTCTTCCTCCGGCAAGAAGACAGCTAAAACCAACACAAACGAGTTTT
TAATCGACGTGGATAAAGGCGAAAACTACTGTTTCAGCGTGCAAGCTGTGATC
CCCTCCCGGACCGTGAATAGGAAAAGCACCGATAGCCCCGTTGAGTGCATGG
GCCAAGAAAAGGGCGAGTTCCGGGAG

Exemplary Mutant Soluble Human Tissue Factor Domain (SEQ ID NO: 3)

SGTTNTVAAYNLTWKSTNFATALEWEPKPVNQVYTVQISTKSGDWKSKCFYTT
DTECALTDEIVKDVKQTYLARVFSYPAGNVESTGSAGEPLYENSPEFTPYLETNL
GQPTIQSFEQVGTKVNVTVEDERTLVARNNTALSLRDVFGKDLIYTLYYWKSSSS
GKKTAKTNTNEFLIDVDKGENYCFSVQAVIPSRTVNRKSTDSPVECMGQEKGEF
RE

Exemplary Mutant Soluble Human Tissue Factor Domain (SEQ ID NO: 4)

SGTTNTVAAYNLTWKSTNFATALEWEPKPVNQVYTVQISTKSGDAKSKCFYTTD
TECALTDEIVKDVKQTYLARVFSYPAGNVESTGSAGEPLAENSPEFTPYLETNLG

QPTIQSFEQVGTKVNVTVEDERTLVARNNTALSLRDVFGKDLIYTLYYWKSSSSG
KKTAKTNTNEFLIDVDKGENYCFSVQAVIPSRTVNRKSTDSPVECMGQEKGEFR
E

Exemplary Soluble Mouse Tissue Factor Domain (SEQ ID NO: 5)

agipekafnltwistdfktilewqpkptnytytvqisdrsrnwknkcfstt
dtecdltdeivkdvtwayeakvlsvprrnsvhgdgdqlvihgeeppftnap
kflpyrdtnlgqpviqqfeqdgrklnvvvkdsltlvrkngtfltlrqvfgk
dlgyiityrkgsstgkktnitntnefsidveegvsycffvqamifsrktnq
nspgsstvcteqwksflge

Exemplary Soluble Rat Tissue Factor Domain (SEQ ID NO: 6)

Agtppgkafnltwistdfktilewqpkptnytytvqisdrsrnwkykctgt
tdtecdltdeivkdvnwtyearvlsvpwrnsthgketlfgthgeeppftna
rkflpyrdtkigqpviqkyeqggtklkvtvkdsftlvrkngtfltlrqvfg
ndlgyiltyrkdsstgrktntthtneflidvekgvsycffaqavifsrktn
hkspesitkcteqwksvlge

In some embodiments, a soluble tissue factor domain can include a sequence that is at least 70% identical, at least 72% identical, at least 74% identical, at least 76% identical, at least 78% identical, at least 80% identical, at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical to SEQ ID NO: 1, 3, 4, 5, or 6. In some embodiments, a soluble tissue factor domain can include a sequence of SEQ ID NO: 1, 3, 4, 5, or 6, with one to twenty amino acids (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) amino acids removed from its N-terminus and/or one to twenty amino acids (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) amino acids removed from its C-terminus.

As can be appreciated in the art, one skilled in the art would understand that mutation of amino acids that are conserved between different mammalian species is more likely to decrease the activity and/or structural stability of the protein, while mutation of

amino acids that are not conserved between different mammalian species is less likely to decrease the activity and/or structural stability of the protein.

In some examples of any of the multi-chain chimeric polypeptides described herein, the soluble tissue factor domain is not capable of binding to Factor VIIa. In some examples of any of the multi-chain chimeric polypeptides described herein, the soluble tissue factor domain does not convert inactive Factor X into Factor Xa. In some embodiments of any of the multi-chain chimeric polypeptides described herein, the multi-chain chimeric polypeptide does not stimulate blood coagulation in a mammal.

In some examples, the soluble tissue factor domain can be a soluble human tissue factor domain. In some embodiments, the soluble tissue factor domain can be a soluble mouse tissue factor domain. In some embodiments, the soluble tissue factor domain can be a soluble rat tissue factor domain.

In some examples, the soluble tissue factor domain does not include one or more (e.g., two, three, four, five, six, or seven) of: a lysine at an amino acid position that corresponds to amino acid position 20 of mature wildtype human tissue factor protein; an isoleucine at an amino acid position that corresponds to amino acid position 22 of mature wildtype human tissue factor protein; a tryptophan at an amino acid position that corresponds to amino acid position 45 of mature wildtype human tissue factor protein; an aspartic acid at an amino acid position that corresponds to amino acid position 58 of mature wildtype human tissue factor protein; a tyrosine at an amino acid position that corresponds to amino acid position 94 of mature wildtype human tissue factor protein; an arginine at an amino acid position that corresponds to amino acid position 135 of mature wildtype human tissue factor protein; and a phenylalanine at an amino acid position that corresponds to amino acid position 140 of mature wildtype human tissue factor protein. In some embodiments, the mutant soluble tissue factor possesses the amino acid sequence of SEQ ID NO: 3 or SEQ ID NO: 4.

In some examples, the soluble tissue factor domain can be encoded by a nucleic acid including a sequence that is at least 70% identical, at least 72% identical, at least 74% identical, at least 76% identical, at least 78% identical, at least 80% identical, at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96%

identical, at least 98% identical, at least 99% identical, or 100% identical to SEQ ID NO: 2.

In some embodiments, the soluble tissue factor domain can have a total length of about 20 amino acids to about 220 amino acids, about 20 amino acids to about 215 amino acids, about 20 amino acids to about 210 amino acids, about 20 amino acids to about 205 amino acids, about 20 amino acids to about 200 amino acids, about 20 amino acids to about 195 amino acids, about 20 amino acids to about 190 amino acids, about 20 amino acids to about 185 amino acids, about 20 amino acids to about 180 amino acids, about 20 amino acids to about 175 amino acids, about 20 amino acids to about 170 amino acids, about 20 amino acids to about 165 amino acids, about 20 amino acids to about 160 amino acids, about 20 amino acids to about 155 amino acids, about 20 amino acids to about 150 amino acids, about 20 amino acids to about 145 amino acids, about 20 amino acids to about 140 amino acids, about 20 amino acids to about 135 amino acids, about 20 amino acids to about 130 amino acids, about 20 amino acids to about 125 amino acids, about 20 amino acids to about 120 amino acids, about 20 amino acids to about 115 amino acids, about 20 amino acids to about 110 amino acids, about 20 amino acids to about 105 amino acids, about 20 amino acids to about 100 amino acids, about 20 amino acids to about 95 amino acids, about 20 amino acids to about 90 amino acids, about 20 amino acids to about 85 amino acids, about 20 amino acids to about 80 amino acids, about 20 amino acids to about 75 amino acids, about 20 amino acids to about 70 amino acids, about 20 amino acids to about 60 amino acids, about 20 amino acids to about 50 amino acids, about 20 amino acids to about 40 amino acids, about 20 amino acids to about 30 amino acids, about 30 amino acids to about 220 amino acids, about 30 amino acids to about 215 amino acids, about 30 amino acids to about 210 amino acids, about 30 amino acids to about 205 amino acids, about 30 amino acids to about 200 amino acids, about 30 amino acids to about 195 amino acids, about 30 amino acids to about 190 amino acids, about 30 amino acids to about 185 amino acids, about 30 amino acids to about 180 amino acids, about 30 amino acids to about 175 amino acids, about 30 amino acids to about 170 amino acids, about 30 amino acids to about 165 amino acids, about 30 amino acids to about 160 amino acids, about 30 amino acids to about 155 amino acids, about 30 amino acids to about 150 amino acids, about 30 amino acids to about 145 amino acids, about 30 amino

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Linker Sequences

In some embodiments, the linker sequence can be a flexible linker sequence. Non-limiting examples of linker sequences that can be used are described in Klein et al., *Protein Engineering, Design & Selection* 27(10):325–330, 2014; Priyanka et al., *Protein Sci.* 22(2):153–167, 2013. In some examples, the linker sequence is a synthetic linker sequence.

In some embodiments of any of the multi-chain chimeric polypeptides described herein, the first chimeric polypeptide can include one, two, three, four, five, six, seven, eight, nine, or ten linker sequence(s) (e.g., the same or different linker sequences, e.g., any of the exemplary linker sequences described herein or known in the art). In some embodiments of any of the multi-chain chimeric polypeptides described herein, the second chimeric polypeptide can include one, two, three, four, five, six, seven, eight, nine, or ten linker sequence(s) (e.g., the same or different linker sequences, e.g., any of the exemplary linker sequences described herein or known in the art).

In some embodiments, a linker sequence can have a total length of 1 amino acid to about 100 amino acids, 1 amino acid to about 90 amino acids, 1 amino acid to about 80 amino acids, 1 amino acid to about 70 amino acids, 1 amino acid to about 60 amino acids, 1 amino acid to about 50 amino acids, 1 amino acid to about 45 amino acids, 1 amino acid to about 40 amino acids, 1 amino acid to about 35 amino acids, 1 amino acid to about 30 amino acids, 1 amino acid to about 25 amino acids, 1 amino acid to about 24 amino acids, 1 amino acid to about 22 amino acids, 1 amino acid to about 20 amino acids, 1 amino acid to about 18 amino acids, 1 amino acid to about 16 amino acids, 1 amino acid to about 14 amino acids, 1 amino acid to about 12 amino acids, 1 amino acid to about 10 amino acids, 1 amino acid to about 8 amino acids, 1 amino acid to about 6 amino acids, 1 amino acid to about 4 amino acids, about 2 amino acids to about 100 amino acids, about 2 amino acids to about 90 amino acids, about 2 amino acids to about 80 amino acids, about 2 amino acids to about 70 amino acids, about 2 amino acids to about 60 amino acids, about 2 amino acids to about 50 amino acids, about 2 amino acids to about 45 amino acids, about 2 amino acids to about 40 amino acids, about 2 amino acids to about 35 amino acids, about 2 amino acids to about 30 amino acids, about 2 amino acids to about 25 amino acids, about 2 amino acids to about 24 amino acids, about 2 amino acids to about 22 amino acids, about 2 amino acids to about 20 amino acids, about 2 amino acids to about 18 amino acids, about 2 amino acids to about 16 amino acids, about 2 amino acids to about 14 amino acids, about 2 amino acids to about 12 amino acids, about 2 amino acids to about 10 amino acids, about 2 amino acids to about 8 amino acids, about 2 amino acids to about 6 amino acids, about 2 amino acids to about 4 amino acids, about 4 amino acids to about 100 amino acids, about 4 amino acids to about 90 amino acids, about 4 amino acids to about 80 amino acids, about 4 amino acids to about 70 amino acids, about 4 amino acids to about 60 amino acids, about 4 amino acids to about 50 amino acids, about 4 amino acids to about 45 amino acids, about 4 amino acids to about 40 amino acids, about 4 amino acids to about 35 amino acids, about 4 amino acids to about 30 amino acids, about 4 amino acids to about 25 amino acids, about 4 amino acids to about 24 amino acids, about 4 amino acids to about 22 amino acids, about 4 amino acids to about 20 amino acids, about 4 amino acids to about 18 amino acids, about 4 amino acids to about 16 amino acids, about 4 amino acids to about 14

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In some embodiments, the linker is rich in glycine (Gly or G) residues. In some embodiments, the linker is rich in serine (Ser or S) residues. In some embodiments, the linker is rich in glycine and serine residues. In some embodiments, the linker has one or more glycine-serine residue pairs (GS), e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more GS pairs. In some embodiments, the linker has one or more Gly-Gly-Gly-Ser (GGGS) sequences, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more GGGS sequences. In some embodiments, the linker has one or more Gly-Gly-Gly-Gly-Ser (GGGGS) sequences, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more GGGGS sequences. In some embodiments, the linker has one or more Gly-Gly-Ser-Gly (GGSG) sequences, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more GGSG sequences.

In some embodiments, the linker sequence can comprise or consist of GGGGSGGGGSGGGGS (SEQ ID NO: 7). In some embodiments, the linker sequence can be encoded by a nucleic acid comprising or consisting of: GGCGGTGGAGGATCCGGAGGAGGTGGCTCCGGCGGCGGAGGATCT (SEQ ID

NO: 8). In some embodiments, the linker sequence can comprise or consist of: GGGSGGGS (SEQ ID NO: 9).

Target-Binding Domains

In some embodiments of any of the multi-chain chimeric polypeptides described herein, the first target-binding domain, the second target-binding domain, and/or the additional one or more target-binding domains can be an antigen-binding domain (e.g., any of the exemplary antigen-binding domains described herein or known in the art), a soluble interleukin or cytokine protein (e.g., any of the exemplary soluble interleukin proteins or soluble cytokine proteins described herein), and a soluble interleukin or cytokine receptor (e.g., any of the exemplary soluble interleukin receptors or soluble cytokine receptors described herein).

In some embodiments of any of the multi-chain chimeric polypeptides described herein, one or more of the first target-binding domain (e.g., any of the exemplary first target binding domains described herein or known in the art), the second target-binding domain (e.g., any of the exemplary second target binding domains described herein or known in the art), and the one or more additional target binding domains can each, independently, bind specifically to a target selected from the group of: bind specifically to a target selected from the group consisting of: CD16a, CD28, CD3 (e.g., one or more of CD3α, CD3β, CD3δ, CD3ε, and CD3γ), 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 (e.g., ULBP1, ULBP2, ULBP3, ULBP4, ULBP5, and ULBP6), HLA-DR, DLL4, TYRO3, AXL, MER, CD122, CD155, PDGF-DD, a ligand of TGF- β receptor II (TGF- β RII), a ligand of TGF- β RIII, 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.

In some embodiments of any of the multi-chain chimeric polypeptides described herein, the first target-binding domain, the second target-binding domain, and/or the one or more additional target-binding domains can each independent have a total number of amino acids of about 5 amino acids to about 1000 amino acids, about 5 amino acids to about 950 amino acids, about 5 amino acids to about 900 amino acids, about 5 amino acids to about 850 amino acids, about 5 amino acids to about 800 amino acids, about 5 amino acids to about 750 amino acids, about 5 amino acids to about 700 amino acids, about 5 amino acids to about 650 amino acids, about 5 amino acids to about 600 amino acids, about 5 amino acids to about 550 amino acids, about 5 amino acids to about 500 amino acids, about 5 amino acids to about 450 amino acids, about 5 amino acids to about 400 amino acids, about 5 amino acids to about 350 amino acids, about 5 amino acids to about 300 amino acids, about 5 amino acids to about 280 amino acids, about 5 amino acids to about 260 amino acids, about 5 amino acids to about 240 amino acids, about 5 amino acids to about 220 amino acids, about 5 amino acids to about 200 amino acids, about 5 amino acids to about 195 amino acids, about 5 amino acids to about 190 amino acids, about 5 amino acids to about 185 amino acids, about 5 amino acids to about 180 amino acids, about 5 amino acids to about 175 amino acids, about 5 amino acids to about 170 amino acids, about 5 amino acids to about 165 amino acids, about 5 amino acids to about 160 amino acids, about 5 amino acids to about 155 amino acids, about 5 amino acids to about 150 amino acids, about 5 amino acids to about 145 amino acids, about 5 amino acids to about 140 amino acids, about 5 amino acids to about 135 amino acids, about 5 amino acids to about 130 amino acids, about 5 amino acids to about 125 amino acids, about 5 amino acids to about 120 amino acids, about 5 amino acids to about 115 amino acids, about 5 amino acids to about 110 amino acids, about 5 amino acids to about 105 amino acids, about 5 amino acids to about 100 amino acids, about 5 amino acids to about 95 amino acids, about 5 amino acids to about 90 amino acids, about 5 amino acids to about 85 amino acids, about 5 amino acids to about 80 amino acids, about 5 amino acids to about 75 amino acids, about 5 amino acids to about 70 amino acids, about 5

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Any of the target-binding domains described herein can bind to its target with a dissociation equilibrium constant (K_D) of less than 1 x 10^{-7} M, less than 1 x 10^{-8} M, less than 1 x 10^{-9} M, less than 1 x 10^{-10} M, less than 1 x 10^{-11} M, less than 1 x 10^{-12} M, or less than 1 x 10^{-13} M. In some embodiments, the antigen-binding protein construct provided herein can bind to an identifying antigen with a K_D of about 1 x 10^{-3} M to about 1 x 10^{-5} M, about 1 x 10^{-4} M to about 1 x 10^{-6} M, about 1 x 10^{-5} M to about 1 x 10^{-7} M, about 1 x 10^{-6} M to about 1 x 10^{-8} M, about 1 x 10^{-7} M to about 1 x 10^{-9} M, about 1 x 10^{-8} M to about 1 x 10^{-10} M, or about 1 x 10^{-9} M to about 1 x 10^{-11} M (inclusive).

Any of the target-binding domains described herein can bind to its target with a K_D of between about 1 pM to about 30 nM (e.g., about 1 pM to about 25 nM, about 1 pM to about 20 nM, about 1 pM to about 15 nM, about 1 pM to about 10 nM, about 1 pM to about 5 nM, about 1 pM to about 2 nM, about 1 pM to about 1 nM, about 1 pM to about 950 pM, about 1 pM to about 900 pM, about 1 pM to about 850 pM, about 1 pM to about 800 pM, about 1 pM to about 750 pM, about 1 pM to about 700 pM, about 1 pM to about 650 pM, about 1 pM to about 600 pM, about 1 pM to about 550 pM, about 1 pM to about 500 pM, about 1 pM to about 450 pM, about 1 pM to about 400 pM, about 1 pM to about 350 pM, about 1 pM to about 300 pM, about 1 pM to about 250 pM, about 1 pM to about 200 pM, about 1 pM to about 150 pM, about 1 pM to about 100 pM, about 1 pM to about 90 pM, about 1 pM to about 80 pM, about 1 pM to about 70 pM, about 1 pM to about 60 pM, about 1 pM to about 50 pM, about 1 pM to about 40 pM, about 1 pM to about 30 pM, about 1 pM to about 20 pM, about 1 pM to about 10 pM, about 1 pM to about 5 pM, about 1 pM to about 4 pM, about 1 pM to about 3 pM, about 1 pM to about 2 pM, about 2 pM to about 30 nM, about 2 pM to about 25 nM, about 2 pM to about 20 nM, about 2 pM to about 15 nM, about 2 pM to about 10 nM, about 2 pM to about 5 nM, about 2 pM to about 2 nM, about 2 pM to about 1 nM, about 2 pM to about 950 pM, about 2 pM to about 900 pM, about 2 pM to about 850 pM, about 2 pM to about 800 pM, about 2 pM to about 750 pM, about 2 pM to about 700 pM, about 2 pM to about 650 pM, about 2 pM to about 600 pM, about 2 pM to about 550 pM, about 2 pM to about 500 pM, about 2 pM to about 450 pM, about 2 pM to about 400 pM, about 2 pM to about 350 pM, about 2 pM to about 300 pM, about 2 pM to about 250 pM, about 2 pM to about 200 pM, about 2 pM to about 150 pM, about 2 pM to about 100 pM, about 2 pM to about 90 pM, about 2 pM to

about 80 pM, about 2 pM to about 70 pM, about 2 pM to about 60 pM, about 2 pM to about 50 pM, about 2 pM to about 40 pM, about 2 pM to about 30 pM, about 2 pM to about 20 pM, about 2 pM to about 10 pM, about 2 pM to about 5 pM, about 2 pM to about 4 pM, about 2 pM to about 3 pM, about 5 pM to about 30 nM, about 5 pM to about 25 nM, about 5 pM to about 20 nM, about 5 pM to about 15 nM, about 5 pM to about 10 nM, about 5 pM to about 5 nM, about 5 pM to about 2 nM, about 5 pM to about 1 nM, about 5 pM to about 950 pM, about 5 pM to about 900 pM, about 5 pM to about 850 pM, about 5 pM to about 800 pM, about 5 pM to about 750 pM, about 5 pM to about 700 pM, about 5 pM to about 650 pM, about 5 pM to about 600 pM, about 5 pM to about 550 pM, about 5 pM to about 500 pM, about 5 pM to about 450 pM, about 5 pM to about 400 pM, about 5 pM to about 350 pM, about 5 pM to about 300 pM, about 5 pM to about 250 pM, about 5 pM to about 200 pM, about 5 pM to about 150 pM, about 5 pM to about 100 pM, about 5 pM to about 90 pM, about 5 pM to about 80 pM, about 5 pM to about 70 pM, about 5 pM to about 60 pM, about 5 pM to about 50 pM, about 5 pM to about 40 pM, about 5 pM to about 30 pM, about 5 pM to about 20 pM, about 5 pM to about 10 pM, about 10 pM to about 30 nM, about 10 pM to about 25 nM, about 10 pM to about 20 nM, about 10 pM to about 15 nM, about 10 pM to about 10 nM, about 10 pM to about 5 nM, about 10 pM to about 2 nM, about 10 pM to about 1 nM, about 10 pM to about 950 pM, about 10 pM to about 900 pM, about 10 pM to about 850 pM, about 10 pM to about 800 pM, about 10 pM to about 750 pM, about 10 pM to about 700 pM, about 10 pM to about 650 pM, about 10 pM to about 600 pM, about 10 pM to about 550 pM, about 10 pM to about 500 pM, about 10 pM to about 450 pM, about 10 pM to about 400 pM, about 10 pM to about 350 pM, about 10 pM to about 300 pM, about 10 pM to about 250 pM, about 10 pM to about 200 pM, about 10 pM to about 150 pM, about 10 pM to about 100 pM, about 10 pM to about 90 pM, about 10 pM to about 80 pM, about 10 pM to about 70 pM, about 10 pM to about 60 pM, about 10 pM to about 50 pM, about 10 pM to about 40 pM, about 10 pM to about 30 pM, about 10 pM to about 20 pM, about 15 pM to about 30 nM, about 15 pM to about 25 nM, about 15 pM to about 20 nM, about 15 pM to about 15 nM, about 15 pM to about 10 nM, about 15 pM to about 5 nM, about 15 pM to about 2 nM, about 15 pM to about 1 nM, about 15 pM to about 950 pM, about 15 pM to about 900 pM, about 15 pM to about 850 pM, about 15 pM to about 800 pM, about 15 pM to about

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15 nM, about 400 pM to about 10 nM, about 400 pM to about 5 nM, about 400 pM to about 2 nM, about 400 pM to about 1 nM, about 400 pM to about 950 pM, about 400 pM to about 900 pM, about 400 pM to about 850 pM, about 400 pM to about 800 pM, about 400 pM to about 750 pM, about 400 pM to about 700 pM, about 400 pM to about 650 pM, about 400 pM to about 600 pM, about 400 pM to about 550 pM, about 400 pM to about 500 pM, about 500 pM to about 30 nM, about 500 pM to about 25 nM, about 500 pM to about 30 nM, about 500 pM to about 15 nM, about 500 pM to about 10 nM, about 500 pM to about 5 nM, about 500 pM to about 2 nM, about 500 pM to about 1 nM, about 500 pM to about 950 pM, about 500 pM to about 900 pM, about 500 pM to about 850 pM, about 500 pM to about 800 pM, about 500 pM to about 750 pM, about 500 pM to about 700 pM, about 500 pM to about 650 pM, about 500 pM to about 600 pM, about 500 pM to about 550 pM, about 600 pM to about 30 nM, about 600 pM to about 25 nM, about 600 pM to about 30 nM, about 600 pM to about 15 nM, about 600 pM to about 10 nM, about 600 pM to about 5 nM, about 600 pM to about 2 nM, about 600 pM to about 1 nM, about 600 pM to about 950 pM, about 600 pM to about 900 pM, about 600 pM to about 850 pM, about 600 pM to about 800 pM, about 600 pM to about 750 pM, about 600 pM to about 700 pM, about 600 pM to about 650 pM, about 700 pM to about 30 nM, about 700 pM to about 25 nM, about 700 pM to about 30 nM, about 700 pM to about 15 nM, about 700 pM to about 10 nM, about 700 pM to about 5 nM, about 700 pM to about 2 nM, about 700 pM to about 1 nM, about 700 pM to about 950 pM, about 700 pM to about 900 pM, about 700 pM to about 850 pM, about 700 pM to about 800 pM, about 700 pM to about 750 pM, about 800 pM to about 30 nM, about 800 pM to about 25 nM, about 800 pM to about 30 nM, about 800 pM to about 15 nM, about 800 pM to about 10 nM, about 800 pM to about 5 nM, about 800 pM to about 2 nM, about 800 pM to about 1 nM, about 800 pM to about 950 pM, about 800 pM to about 900 pM, about 800 pM to about 850 pM, about 900 pM to about 30 nM, about 900 pM to about 25 nM, about 900 pM to about 30 nM, about 900 pM to about 15 nM, about 900 pM to about 10 nM, about 900 pM to about 5 nM, about 900 pM to about 2 nM, about 900 pM to about 1 nM, about 900 pM to about 950 pM, about 1 nM to about 30 nM, about 1 nM to about 25 nM, about 1 nM to about 20 nM, about 1 nM to about 15 nM, about 1 nM to about 10 nM, about 1 nM to about 5 nM, about 2 nM to about 30 nM, about 2 nM to about 25 nM, about 2 nM

to about 20 nM, about 2 nM to about 15 nM, about 2 nM to about 10 nM, about 2 nM to about 5 nM, about 4 nM to about 30 nM, about 4 nM to about 25 nM, about 4 nM to about 20 nM, about 4 nM to about 15 nM, about 4 nM to about 10 nM, about 4 nM to about 5 nM, about 5 nM to about 30 nM, about 5 nM to about 25 nM, about 5 nM to about 20 nM, about 5 nM to about 15 nM, about 5 nM to about 10 nM, about 10 nM to about 30 nM, about 10 nM to about 25 nM, about 10 nM to about 20 nM, about 10 nM to about 15 nM, about 15 nM to about 30 nM, about 15 nM to about 25 nM, about 15 nM to about 20 nM, about 20 nM to about 30 nM, and about 20 nM to about 25 nM).

Any of the target-binding domains described herein can bind to its target with a K_D of between about 1 nM to about 10 nM (e.g., about 1 nM to about 9 nM, about 1 nM to about 8 nM, about 1 nM to about 7 nM, about 1 nM to about 6 nM, about 1 nM to about 5 nM, about 1 nM to about 4 nM, about 1 nM to about 3 nM, about 1 nM to about 2 nM, about 2 nM to about 10 nM, about 2 nM to about 9 nM, about 2 nM to about 8 nM, about 2 nM to about 7 nM, about 2 nM to about 6 nM, about 2 nM to about 5 nM, about 2 nM to about 4 nM, about 2 nM to about 3 nM, about 3 nM to about 10 nM, about 3 nM to about 9 nM, about 3 nM to about 8 nM, about 3 nM to about 7 nM, about 3 nM to about 6 nM, about 3 nM to about 5 nM, about 3 nM to about 4 nM, about 4 nM to about 10 nM, about 4 nM to about 9 nM, about 4 nM to about 8 nM, about 4 nM to about 7 nM, about 4 nM to about 6 nM, about 4 nM to about 5 nM, about 5 nM to about 10 nM, about 5 nM to about 9 nM, about 5 nM to about 8 nM, about 5 nM to about 7 nM, about 5 nM to about 6 nM, about 6 nM to about 10 nM, about 6 nM to about 9 nM, about 6 nM to about 8 nM, about 6 nM to about 7 nM, about 7 nM to about 10 nM, about 7 nM to about 9 nM, about 7 nM to about 8 nM, about 8 nM to about 10 nM, about 8 nM to about 9 nM, and about 9 nM to about 10 nM).

A variety of different methods known in the art can be used to determine the K_D values of any of the antigen-binding protein constructs described herein (e.g., an electrophoretic mobility shift assay, a filter binding assay, surface plasmon resonance, and a biomolecular binding kinetics assay, etc.).

Antigen-Binding Domains

In some embodiments of any of the multi-chain chimeric polypeptides described herein, the first target-binding domain and the second target-binding domain bind specifically to the same antigen. In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain and the second target-binding domain bind specifically to the same epitope. In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain and the second target-binding domain include the same amino acid sequence.

In some embodiments of any of the multi-chain chimeric polypeptides described herein, the first target-binding domain and the second target-binding domain bind specifically to different antigens.

In some embodiments of any of the multi-chain chimeric polypeptides described herein, one or both of the first target-binding domain and the second target-binding domain is an antigen-binding domain. In some embodiments of any of the multi-chain chimeric polypeptides described herein, the first target-binding domain and the second target-binding domain are each antigen-binding domains.

In some embodiments of any of the multi-chain chimeric polypeptides described herein, the antigen-binding domain includes or is a scFv or a single domain antibody (e.g., a VHH or a VNAR domain).

In some examples, an antigen-binding domain (e.g., any of the antigen-binding domains described herein) can bind specifically to any one of CD16a (see, e.g., those described in U.S. Patent No. 9,035,026), CD28 (see, e.g., those described in U.S. Patent No. 7,723,482), CD3 (see, e.g., those described in U.S. Patent No. 9,226,962), CD33 (see, e.g., those described in U.S. Patent No. 8,759,494), CD20 (see, e.g., those described in WO 2014/026054), CD19 (see, e.g., those described in U.S. Patent No. 9,701,758), CD22 (see, e.g., those described in WO 2003/104425), CD123 (see, e.g., those described in WO 2014/130635), IL-1R (see, e.g., those described in U.S. Patent No. 8,741,604), IL-1 (see, e.g., those described in WO 2014/095808), VEGF (see, e.g., those described in U.S. Patent No. 9,090,684), IL-6R (see, e.g., those described in U.S. Patent No. 7,482,436), IL-4 (see, e.g., those described in U.S. Patent Application Publication No. 2012/0171197), IL-10 (see, e.g., those described in U.S. Patent Application Publication

No. 2016/0340413), PDL-1 (see, e.g., those described in Drees et al., *Protein Express. Purif.* 94:60-66, 2014), TIGIT (see, e.g., those described in U.S. Patent Application Publication No. 2017/0198042), PD-1 (see, e.g., those described in U.S. Patent No. 7,488,802), TIM3 (see, e.g., those described in U.S. Patent No. 8,552,156), CTLA4 (see, e.g., those described in WO 2012/120125), MICA (see, e.g., those described in WO 2016/154585), MICB (see, e.g., those described in U.S. Patent No. 8,753,640), IL-6 (see, e.g., those described in Gejima et al., *Human Antibodies* 11(4):121-129, 2002), IL-8 (see, e.g., those described in U.S. Patent No. 6,117,980), TNFα (see, e.g., those described in Geng et al., *Immunol. Res.* 62(3):377-385, 2015), CD26a (see, e.g., those described in WO 2017/189526), CD36 (see, e.g., those described in U.S. Patent Application Publication No. 2015/0259429), ULBP2 (see, e.g., those described in U.S. Patent No. 9,273,136), CD30 (see, e.g., those described in Homach et al., *Scand. J. Immunol.* 48(5):497-501, 1998), CD200 (see, e.g., those described in U.S. Patent No. 9,085,623), IGF-1R (see, e.g., those described in U.S. Patent Application Publication No. 2017/0051063), MUC4AC (see, e.g., those described in WO 2012/170470), MUC5AC (see, e.g., those described in U.S. Patent No. 9,238,084), Trop-2 (see, e.g., those described in WO 2013/068946), CMET (see, e.g., those described in Edwardraja et al., *Biotechnol. Bioeng.* 106(3):367-375, 2010), EGFR (see, e.g., those described in Akbari et al., *Protein Expr. Purif.* 127:8-15, 2016), HER1 (see, e.g., those described in U.S. Patent Application Publication No. 2013/0274446), HER2 (see, e.g., those described in Cao et al., *Biotechnol. Lett.* 37(7):1347-1354, 2015), HER3 (see, e.g., those described in U.S. Patent No. 9,505,843), PSMA (see, e.g., those described in Parker et al., *Protein Expr. Purif.* 89(2):136-145, 2013), CEA (see, e.g., those described in WO 1995/015341), B7H3 (see, e.g., those described in U.S. Patent No. 9,371,395), EPCAM (see, e.g., those described in WO 2014/159531), BCMA (see, e.g., those described in Smith et al., *Mol. Ther.* 26(6):1447-1456, 2018), P-cadherin (see, e.g., those described in U.S. Patent No. 7,452,537), CEACAM5 (see, e.g., those described in U.S. Patent No. 9,617,345), a UL16-binding protein (see, e.g., those described in WO 2017/083612), HLA-DR (see, e.g., Pistillo et al., *Exp. Clin. Immunogenet.* 14(2):123-130, 1997), DLL4 (see, e.g., those described in WO 2014/007513), TYRO3 (see, e.g., those described in WO 2016/166348), AXL (see, e.g., those described in WO 2012/175692), MER (see, e.g., those described in

WO 2016/106221), CD122 (see, e.g., those described in U.S. Patent Application Publication No. 2016/0367664), CD155 (see, e.g., those described in WO 2017/149538), or PDGF-DD (see, e.g., those described in U.S. Patent No. 9,441,034).

The antigen-binding domains present in any of the multi-chain chimeric polypeptides described herein are each independently selected from the group consisting of: a VHH domain, a VNAR domain, and a scFv. In some embodiments, any of the antigen-binding domains described herein is a BiTe, a $(scFv)_2$, a nanobody, a nanobody-HSA, a DART, a TandAb, a scDiabody, a scDiabody-CH3, scFv-CH-CL-scFv, a HSAbody, scDiabody-HAS, or a tandem-scFv. Additional examples of antigen-binding domains that can be used in any of the multi-chain chimeric polypeptide are known in the art.

A VHH domain is a single monomeric variable antibody domain that can be found in camelids. A VNAR domain is a single monomeric variable antibody domain that can be found in cartilaginous fish. Non-limiting aspects of VHH domains and V_{NAR} domains are described in, e.g., Cromie et al., *Curr. Top. Med. Chem.* 15:2543-2557, 2016; De Genst et al., *Dev. Comp. Immunol.* 30:187-198, 2006; De Meyer et al., *Trends Biotechnol.* 32:263-270, 2014; Kijanka et al., *Nanomedicine* 10:161-174, 2015; Kovaleva et al., *Expert. Opin. Biol. Ther.* 14:1527-1539, 2014; Krah et al., *Immunopharmacol. Immunotoxicol.* 38:21-28, 2016; Mujic-Delic et al., *Trends Pharmacol. Sci.* 35:247-255, 2014; Muyldermans, *J. Biotechnol.* 74:277-302, 2001; Muyldermans et al., *Trends Biochem. Sci.* 26:230-235, 2001; Muyldermans, *Ann. Rev. Biochem.* 82:775-797, 2013; Rahbarizadeh et al., *Immunol. Invest.* 40:299-338, 2011; Van Audenhove et al., *EBioMedicine* 8:40-48, 2016; Van Bockstaele et al., *Curr. Opin. Investig. Drugs* 10:1212-1224, 2009; Vincke et al., *Methods Mol. Biol.* 911:15-26, 2012; and Wesolowski et al., *Med. Microbiol. Immunol.* 198:157-174, 2009.

In some embodiments, each of the antigen-binding domains in the multi-chain chimeric polypeptides described herein are both VHH domains, or at least one antigen-binding domain is a VHH domain. In some embodiments, each of the antigen-binding domains in the multi-chain chimeric polypeptides described herein are both VNAR domains, or at least one antigen-binding domain is a VNAR domain. In some embodiments, each of the antigen-binding domains in the multi-chain chimeric

polypeptides described herein are both scFv domains, or at least one antigen-binding domain is a scFv domain.

In some embodiments, two or more of polypeptides present in the multi-chain chimeric polypeptide can assemble (e.g., non-covalently assemble) to form any of the antigen-binding domains described herein, e.g., an antigen-binding fragment of an antibody (e.g., any of the antigen-binding fragments of an antibody described herein), a VHH-scAb, a VHH-Fab, a Dual scFab, a F(ab')2, a diabody, a crossMab, a DAF (two-in-one), a DAF (four-in-one), a DutaMab, a DT-IgG, a knobs-in-holes common light chain, a knobs-in-holes assembly, a charge pair, a Fab-arm exchange, a SEEDbody, a LUZ-Y, a Fcab, a κλ-body, an orthogonal Fab, a DVD-IgG, a IgG(H)-scFv, a scFv-(H)IgG, IgG(L)-scFv, scFv-(L)IgG, IgG(L,H)-Fv, IgG(H)-V, V(H)-IgG, IgG(L)-V, V(L)-IgG, KIH IgG-scFab, 2scFv-IgG, IgG-2scFv, scFv4-Ig, Zybody, DVI-IgG, Diabody-CH3, a triple body, a miniantibody, a minibody, a TriBi minibody, scFv-CH3 KIH, Fab-scFv, a F(ab')2-scFv2, a scFv-KIH, a Fab-scFv-Fc, a tetravalent HCAb, a scDiabody-Fc, a Diabody-Fc, a tandem scFv-Fc, an Intrabody, a dock and lock, a lmmTAC, an IgG-IgG conjugate, a Cov-X-Body, and a scFv1-PEG-scFv2. See, e.g., Spiess et al., *Mol. Immunol.* 67:95-106, 2015, incorporated in its entirety herewith, for a description of these elements. Non-limiting examples of an antigen-binding fragment of an antibody include an Fv fragment, a Fab fragment, a $F(ab')_2$ fragment, and a Fab' fragment. Additional examples of an antigen-binding fragment of an antibody is an antigen-binding fragment of an IgG (e.g., an antigen-binding fragment of IgG1, IgG2, IgG3, or IgG4) (e.g., an antigen-binding fragment of a human or humanized IgG, e.g., human or humanized IgG1, IgG2, IgG3, or IgG4); an antigen-binding fragment of an IgA (e.g., an antigen-binding fragment of IgA1 or IgA2) (e.g., an antigen-binding fragment of a human or humanized IgA, e.g., a human or humanized IgA1 or IgA2); an antigen-binding fragment of an IgD (e.g., an antigen-binding fragment of a human or humanized IgD); an antigen-binding fragment of an IgE (e.g., an antigen-binding fragment of a human or humanized IgE); or an antigen-binding fragment of an IgM (e.g., an antigen-binding fragment of a human or humanized IgM).

An "Fv" fragment includes a non-covalently-linked dimer of one heavy chain variable domain and one light chain variable domain.

A "Fab" fragment includes, the constant domain of the light chain and the first constant domain (C_{H1}) of the heavy chain, in addition to the heavy and light chain variable domains of the Fv fragment.

A "F(ab')$_2$" fragment includes two Fab fragments joined, near the hinge region, by disulfide bonds.

A "dual variable domain immunoglobulin" or "DVD-Ig" refers to multivalent and multispecific binding proteins as described, e.g., in DiGiammarino et al., *Methods Mol. Biol.* 899:145-156, 2012; Jakob et al., *MABs* 5:358-363, 2013; and U.S. Patent Nos. 7,612,181; 8,258,268; 8,586,714; 8,716,450; 8,722,855; 8,735,546; and 8,822,645, each of which is incorporated by reference in its entirety.

DARTs are described in, e.g., Garber, *Nature Reviews Drug Discovery* 13:799-801, 2014.

In some embodiments of any of the antigen-binding domains described herein can bind to an antigen selected from the group consisting of: a protein, a carbohydrate, a lipid, and a combination thereof.

Additional examples and aspects of antigen-binding domains are known in the art.

Soluble Interleukin or Cytokine Protein

In some embodiments of any of the multi-chain chimeric polypeptides described herein, one or both of the first target-binding domain and the second target-binding domain can be a soluble interleukin protein or soluble cytokine protein. In some embodiments, the soluble interleukin or soluble cytokine protein is selected from the group of: 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. Non-limiting examples of soluble IL-2, IL-3, IL-7, IL-8, IL-10, IL-15, IL-17, IL-18, IL-21, PDGF-DD, SCF, and FLT3Lare provided below.

Human Soluble IL-2 (SEQ ID NO: 9)

aptssstkkt qlqlehllld lqmilnginn yknpkltrml tfkfympkka
telkhlqcle eelkpleevl nlaqsknfhl rprdlisnin vivlelkgse
ttfmceyade tativeflnr witfcqsiis tlt

Human Soluble IL-3 (SEQ ID NO: 10)

apmtqttplkt swvncsnmid eiithlkqpp lplldfnnln gedqdilmen nlrrpnleaf nravkslqna saiesilknl lpclplataa ptrhpihikd gdwnefrrkl tfylktlena qaqqttlsla if

Human Soluble IL-7 (SEQ ID NO: 11)

dcdiegkdgkqyesv lmvsidqlld smkeigsncl nnefnffkrh icdankegmf lfraarklrq flkmnstgdf dlhllkvseg ttillnctgq vkgrkpaalg eaqptkslee nkslkeqkkl ndlcflkrll qeiktcwnki lmgtkeh

Human Soluble IL-8 (SEQ ID NO: 12)

egavlprsak elrcqcikty skpfhpkfik elrviesgph canteiivkl sdgrelcldp kenwvqrvve kflkraens

Human Soluble IL-10 (SEQ ID NO: 13)

spgqgtqsensc thfpgnlpnm lrdlrdafsr vktffqmkdq ldnlllkesl ledfkgylgc qalsemiqfy leevmpqaen qdpdikahvn slgenlktlr lrlrrchrfl pcenkskave qvknafnklq ekgiykamse fdifinyiea ymtmkirn

Human Soluble IL-15 (SEQ ID NO: 14)

Nwvnvisdlkki edliqsmhid atlytesdvh psckvtamkc fllelqvisl esgdasihdt venliilann slssngnvte sgckeceele eknikeflqs fvhivqmfin ts

Human Soluble IL-17 (SEQ ID NO: 15)

gitiprn pgcpnsedkn fprtvmvnln ihnrntntnp krssdyynrs tspwnlhrne dperypsviw eakcrhlgci nadgnvdyhm nsvpiqqeil vlrrepphcp nsfrlekilv svgctcvtpi vhhva

Human Soluble IL-18 (SEQ ID NO: 16)

yfgklesklsvirn lndqvlfidq gnrplfedmt dsdcrdnapr tifiismykd
sqprgmavti svkcekistl scenkiisfk emnppdnikd tksdiiffqr
svpghdnkmq fesssyegyf lacekerdlf klilkkedel gdrsimftvq ned

Human Soluble PDGF-DD (SEQ ID NO: 17)

rdtsatpqsasi kalrnanlrr desnhltdly rrdetiqvkg ngyvqsprfp
nsyprnlllt wrlhsqentr iqlvfdnqfg leeaendicr ydfvevedis
etstiirgrw cghkevppri ksrtnqikit fksddyfvak pgfkiyysll
edfqpaaase tnwesvtssi sgvsynspsv tdptliadal dkkiaefdtv
edllkyfnpe swqedlenmy ldtpryrgrs yhdrkskvdl drlnddakry
sctprnysvn ireelklanv vffprcllvq rcggncgcgt vnwrsctcns
gktvkkyhev lqfepghikr rgraktmalv diqldhherc dcicssrppr

Human Soluble SCF (SEQ ID NO: 18)

egicrnrvtnnvkdv tklvanlpkd ymitlkyvpg mdvlpshcwi semvvqlsds
ltdlldkfsn iseglsnysi idklvnivdd lvecvkenss kdlkksfksp
eprlftpeef frifnrsida fkdfvvaset sdcvvsstls pekdsrvsvt
kpfmlppvaa sslrndssss nrkaknppgd sslhwaamal palfsliigf
afgalywkkr qpsltraven iqineednei smlqekeref qev

Human Soluble FLT3L (SEQ ID NO: 19)

tqdcsfqhspissd favkirelsd yllqdypvtv asnlqdeelc gglwrlvlaq
rwmerlktva gskmqgller vnteihfvtk cafqpppscl rfvqtnisrl
lqetseqlva lkpwitrqnf srclelqcqp dsstlpppws prpleatapt
apqppllllll llpvglllla aawclhwqrt rrrtprpgeq vppvpspqdl
llveh

Non-limiting examples of soluble MICA, MICB, ULBP1, ULBP2, ULBP3, ULBP4, ULBP5, and ULBP6 are provided below.

Human Soluble MICA (SEQ ID NO: 20)

ephslry nltvlswdgs vqsgfltevh ldgqpflrcd rqkcrakpqg
qwaedvlgnk twdretrdlt gngkdlrmtl ahikdqkegl hslqeirvce
ihednstrss qhfyydgelf lsqnletkew tmpqssraqt lamnvrnflk
edamktkthy hamhadclqe lrrylksgvv lrrtvppmvn vtrseasegn
itvtcrasgf ypwnitlswr qdgvslshdt qqwgdvlpdg ngtyqtwvat
ricqgeeqrf tcymehsgnh sthpvpsgkv lvlqshwqtf hvsavaaaai
fviiifyvrc ckkktsaaeg pelvslqvld qhpvgtsdhr datqlgfqpl
msdlgstgst ega

Human Soluble MICB (SEQ ID NO: 21)

aephslry nlmvlsqdes vqsgflaegh ldgqpflryd rqkrrakpqg
qwaedvlgak twdtetedlt engqdlrrtl thikdqkggl hslqeirvce
ihedsstrgs rhfyydgelf lsqnletqes tvpqssraqt lamnvtnfwk
edamktkthy ramqadclqk lqrylksgva irrtvppmvn vtcsevsegn
itvtcrassf yprnitltwr qdgvslshnt qqwgdvlpdg ngtyqtwvat
rirqgeeqrf tcymehsgnh gthpvpsgkv lvlqsqrtdf pyvsaampcf
viiiilcvpc ckkktsaaeg pelvslqvld qhpvgtgdhr
daaqlgfqpl msatgstgst ega

Human Soluble ULBP1 (SEQ ID NO: 22)

wvdthclcydfiit pksrpepqwc evqglvderp flhydcvnhk akafaslgkk
vnvtktweeq tetlrdvvdf lkgqlldiqv enlipieplt lqarmscehe
ahghgrgswq flfngqkfll fdsnnrkwta lhpgakkmte kweknrdvtm
ffqkislgdc kmwleeflmy weqmldptkp pslapg

Human Soluble ULBP2 (SEQ ID NO: 23)

gradphslcyditvi pkfrpgprwc avqgqvdekt flhydcgnkt vtpvsplgkk
lnvttawkaq npvlrevvdi lteqlrdiql enytpkeplt lqarmsceqk
aeghssgswq fsfdgqifll fdsekrmwtt vhpgarkmke kwendkvvam
sfhyfsmgdc igwledflmg mdstlepsag aplams

Human Soluble ULBP3 (SEQ ID NO: 24)

dahslwynfti ihlprhgqqw cevqsqvdqk nflsydcgsd kvlsmghlee
qlyatdawgk qlemlrevgq rlrleladte ledftpsgpl tlqvrmscec
eadgyirgsw qfsfdgrkfl lfdsnnrkwt vvhagarrmk ekwekdsglt
tffkmvsmrd ckswlrdflm hrkkrlepta pptmapg

Human Soluble ULBP4 (SEQ ID NO: 25)

hslcfnftik slsrpgqpwc eaqvflnknl flqynsdnnm vkplglgkk
vyatstwgel tqtlgevgrd lrmllcdikp qiktsdpstl qvemfcqrea
erctgaswqf atngeksllf damnmtwtvi nheaskiket wkkdrgleky
frklskgdcd hwlreflghw eampeptvsp vnasdihwss sslpdrwiil
gafillvlmg ivlicvwwqn gewqaglwpl rts

Human Soluble ULBP5 (SEQ ID NO: 26)

gladp hslcyditvi pkfrpgprwc avqgqvdekt flhydcgskt
vtpvsplgkk lnvttawkaq npvlrevvdi lteqlldiql enyipkeplt
lqarmsceqk aeghgsgswq lsfdgqifll fdsenrmwtt vhpgarkmke
kwendkdmtm sfhyismgdc tgwledflmg mdstlepsag apptmssg

Human Soluble ULBP6 (SEQ ID NO: 27)

rrddp hslcyditvi pkfrpgprwc avqgqvdekt flhydcgnkt
vtpvsplgkk lnvtmawkaq npvlrevvdi lteqlldiql enytpkeplt
lqarmsceqk aeghssgswq fsidgqtfll fdsekrmwtt vhpgarkmke
kwendkdvam sfhyismgdc igwledflmg mdstlepsag aplamssg

Additional examples of soluble interleukin proteins and soluble cytokine proteins are known in the art.

Soluble Receptor

In some embodiments of any of the multi-chain chimeric polypeptides described herein, one or both of the first target-binding domain and the second target-binding

domain is a soluble interleukin receptor, a soluble cytokine receptor or a ligand receptor. In some embodiments, the soluble receptor is a soluble TGF-β receptor II (TGF-β RII) (see, e.g., those described in Yung et al., *Am. J. Resp. Crit. Care Med.* 194(9):1140-1151, 2016), a soluble TGF-βRIII (see, e.g., those described in Heng et al., *Placenta* 57:320, 2017), a soluble NKG2D (see, e.g., Cosman et al., *Immunity* 14(2):123-133, 2001; Costa et al., *Front. Immunol.*, Vol. 9, Article 1150, May 29, 2018; doi: 10.3389/fimmu.2018.01150), a soluble NKp30 (see, e.g., Costa et al., *Front. Immunol.*, Vol. 9, Article 1150, May 29, 2018; doi: 10.3389/fimmu.2018.01150), a soluble NKp44 (see, e.g., those described in Costa et al., *Front. Immunol.*, Vol. 9, Article 1150, May 29, 2018; doi: 10.3389/fimmu.2018.01150), a soluble NKp46 (see, e.g., Mandelboim et al., *Nature* 409:1055-1060, 2001; Costa et al., *Front. Immunol.*, Vol. 9, Article 1150, May 29, 2018; doi: 10.3389/fimmu.2018.01150), a soluble DNAM-1 (see, e.g., those described in Costa et al., *Front. Immunol.*, Vol. 9, Article 1150, May 29, 2018; doi: 10.3389/fimmu.2018.01150), a scMHCI (see, e.g., those described in Washburn et al., *PLoS One* 6(3):e18439, 2011), a scMHCII (see, e.g., those described in Bishwajit et al., *Cellular Immunol.* 170(1):25-33, 1996), a scTCR (see, e.g., those described in Weber et al., *Nature* 356(6372):793-796, 1992), a soluble CD155 (see, e.g., those described in Tahara-Hanaoka et al., *Int. Immunol.* 16(4):533-538, 2004), or a soluble CD28 (see, e.g., Hebbar et al., *Clin. Exp. Immunol.* 136:388-392, 2004).

Additional examples of soluble interleukin receptors and soluble cytokine receptors are known in the art.

Additional Antigen-Binding Domains

In some embodiments of any of the multi-chain chimeric polypeptides, the first chimeric polypeptide further includes one or more (e.g., two, three, four, five, six, seven, eight, nine, or ten) additional target-binding domain(s) (e.g., any of the exemplary target-binding domains described herein or known in the art), where at least one of the one or more additional antigen-binding domain(s) is positioned between the soluble tissue factor domain (e.g., any of the exemplary soluble tissue factor domains described herein or known in the art) and the first domain of the pair of affinity domains (e.g., any of the exemplary first domains of any of the exemplary pairs of affinity domains described

herein). In some embodiments, the first chimeric polypeptide can further include a linker sequence (e.g., any of the exemplary linker sequences described herein or known in the art) between the soluble tissue factor domain (e.g., any of the exemplary soluble tissue factor domains described herein) and the at least one of the one or more additional target-binding domain(s) (e.g., any of the exemplary target-binding domains described herein or known in the art), and/or a linker sequence (e.g., any of the exemplary linker sequences described herein or known in the art) between the at least one of the one or more additional target-binding domain(s) (e.g., any of the exemplary target-binding domains described herein or known in the art) and the first domain of the pair of affinity domains (e.g., any of the exemplary first domains described herein of any of the exemplary pairs of affinity domains described herein).

In some embodiments of any of the multi-chain chimeric polypeptides described herein, the first chimeric polypeptide further includes one or more (e.g., two, three, four, five, six, seven, eight, nine, or ten) additional target-binding domains at the N-terminal and/or C-terminal end of the first chimeric polypeptide. In some embodiments, at least one of the one or more additional target-binding domains (e.g., any of the exemplary target-binding domains described herein or known in the art) directly abuts the first domain of the pair of affinity domains (e.g., any of the exemplary first domains described herein of any of the exemplary pairs of affinity domains described herein) in the first chimeric polypeptide. In some embodiments, the first chimeric polypeptide further includes a linker sequence (e.g., any of the exemplary linker sequences described herein or known in the art) between the at least one of the one or more additional target-binding domains (e.g., any of the exemplary target-binding domains described herein or known in the art) and the first domain of the pair of affinity domains (e.g., any of the exemplary first domains described herein of any of the exemplary pairs of affinity domains described herein). In some embodiments, the at least one of the one or more additional target-binding domains (e.g., any of the exemplary target-binding domains described herein or known in the art) directly abuts the first target-binding domain (e.g., any of the exemplary target-binding domains described herein or known in the art) in the first chimeric polypeptide. In some embodiments, the first chimeric polypeptide further comprises a linker sequence (e.g., any of the exemplary linker sequences described herein

or known in the art) between the at least one of the one or more additional target-binding domains (e.g., any of the exemplary target-binding domains described herein or known in the art) and the first target-binding domain (e.g., any of the exemplary target-binding domains described herein or known in the art).

In some embodiments of any of the multi-chain chimeric polypeptides described herein, at least one of the one or more additional target-binding domains (e.g., any of the exemplary target-binding domains described herein or known in the art) is disposed at the N- and/or C-terminus of the first chimeric polypeptide, and at least one of the one or more additional target-binding domains (e.g., any of the exemplary target-binding domains described herein or known in the art) is positioned between the soluble tissue factor domain (e.g., any of the exemplary soluble tissue factor domains described herein or known in the art) and the first domain of the pair of affinity domains (e.g., any of the exemplary first domains of any of the exemplary pairs of affinity domains described herein) in the first chimeric polypeptide. In some embodiments, the at least one additional target-binding domain (e.g., any of the exemplary target-binding domains described herein or known in the art) of the one or more additional target-binding domains disposed at the N-terminus directly abuts the first target-binding domain (e.g., any of the exemplary target-binding domains described herein or known in the art) or the first domain of the pair of affinity domains (e.g., any of the exemplary first domains described herein of any of the exemplary pairs of affinity domains described herein) in the first chimeric polypeptide. In some embodiments, the first chimeric polypeptide further comprises a linker sequence (e.g., any of the linker sequences described herein or known in the art) disposed between the at least one additional target-binding domain (e.g., any of the exemplary target-binding domains described herein or known in the art) and the first target-binding domain (e.g., any of the exemplary target-binding domains described herein or known in the art) or the first domain of the pair of affinity domains (e.g., any of the exemplary first domains described herein of any of the exemplary pairs of affinity domains described herein) in the first chimeric polypeptide. In some embodiments, the at least one additional target-binding domain (e.g., any of the exemplary target-binding domains described herein or known in the art) of the one or more additional target-binding domains disposed at the C-terminus directly abuts the first

target-binding domain (e.g., any of the exemplary target-binding domains described herein or known in the art) or the first domain of the pair of affinity domains (e.g., any of the exemplary first domains of any of the exemplary pairs of affinity domains described herein) in the first chimeric polypeptide. In some embodiments, the first chimeric polypeptide further includes a linker sequence (e.g., any of the exemplary linker sequences described herein or known in the art) disposed between the at least one additional target-binding domain (e.g., any of the exemplary target-binding domains described herein or known in the art) and the first target-binding domain (e.g., any of the exemplary target-binding domains described herein or known in the art) or the first domain of the pair of affinity domains (e.g., any of the exemplary first domains described herein of any of the exemplary pairs of affinity domains described herein) in the first chimeric polypeptide. In some embodiments, the at least one of the one or more additional target-binding domains (e.g., any of the exemplary target-binding domains described herein or known in the art) positioned between the soluble tissue factor domain (e.g., any of the exemplary soluble tissue factor domains described herein) and the first domain of the pair of affinity domains (e.g., any of the first domains described herein or any of the exemplary pairs of affinity domains described herein), directly abuts the soluble tissue factor domain and/or the first domain of the pair of affinity domains. In some embodiments, the first chimeric polypeptide further comprises a linker sequence (e.g., any of the exemplary linker sequences described herein or known in the art) disposed (i) between the soluble tissue factor domain (e.g., any of the exemplary soluble tissue factor domains described herein) and the at least one of the one or more additional target-binding domains (e.g., any of the exemplary target-binding domains described herein or known in the art) positioned between the soluble tissue factor domain (e.g., any of the exemplary soluble tissue factor domains described herein) and the first domain of the pair of affinity domains (e.g., any of the exemplary first domains of any of the exemplary pairs of affinity domains described herein), and/or (ii) between the first domain of the pair of affinity domains and the at least one of the one or more additional target-binding domains positioned between the soluble tissue factor domain and the first domain of the pair of affinity domains.

In some embodiments of any of the multi-chain chimeric polypeptides described herein, the second chimeric polypeptide further includes one or more (e.g., two, three, four, five, six, seven, eight, nine, or ten) additional target-binding domains (e.g., any of the exemplary target-binding domains described herein or known in the art) at the N-terminal end and/or the C-terminal end of the second chimeric polypeptide. In some embodiments, at least one of the one or more additional target-binding domains (e.g., any of the exemplary target-binding domains described herein or known in the art) directly abuts the second domain of the pair of affinity domains (e.g., any of the exemplary second domains of any of the exemplary pairs of affinity domains described herein) in the second chimeric polypeptide. In some embodiments, the second chimeric polypeptide further includes a linker sequence (e.g., any of the exemplary linker sequences described herein or known in the art) between at least one of the one or more additional target-binding domains (e.g., any of the exemplary target-binding domains described herein or known in the art) and the second domain of the pair of affinity domains (e.g., any of the second domains described herein of any of the exemplary pairs of affinity domains described herein) in the second chimeric polypeptide. In some embodiments, at least one of the one or more additional target-binding domains (e.g., any of the exemplary target-binding domains described herein or known in the art) directly abuts the second target-binding domain (e.g., any of the target-binding domains described herein or known in the art) in the second chimeric polypeptide. In some embodiments, the second chimeric polypeptide further includes a linker sequence (e.g., any of the exemplary linker sequences described herein or known in the art) between at least one of the one or more additional target-binding domains (e.g., any of the exemplary target binding domains described herein or known in the art) and the second target-binding domain (e.g., any of the exemplary target binding domains described herein or known in the art) in the second chimeric polypeptide.

In some embodiments of any of the multi-chain chimeric polypeptides described herein, two or more (e.g., three or more, four or more, five or more, six or more, seven or more, eight or more, nine or more, or ten or more) of the first target-binding domain, the second target-binding domain, and the one or more additional target-binding domains bind specifically to the same antigen. In some embodiments, two or more (e.g., three or

more, four or more, five or more, six or more, seven or more, eight or more, nine or more, or ten or more) of the first target-binding domain, the second target-binding domain, and the one or more additional target-binding domains bind specifically to the same epitope. In some embodiments, two or more (e.g., three or more, four or more, five or more, six or more, seven or more, eight or more, nine or more, or ten or more) of the first target-binding domain, the second target-binding domain, and the one or more additional target-binding domains include the same amino acid sequence. In some embodiments, the first target-binding domain, the second target-binding domain, and the one or more additional target-binding domains each bind specifically to the same antigen. In some embodiments, the first target-binding domain, the second target-binding domain, and the one or more additional target-binding domains each bind specifically to the same epitope. In some embodiments, the first target-binding domain, the second target-binding domain, and the one or more additional target-binding domains each include the same amino acid sequence.

In some embodiments of any of the multi-chain chimeric polypeptides described herein, the first target-binding domain, the second target-binding domain, and the one or more additional target-binding domains bind specifically to different antigens. In some embodiments of any of the multi-chain chimeric polypeptides described herein, one or more (e.g., two or more, three or more, four or more, five or more, six or more, seven or more, eight or more, nine or more, or ten or more) of the first target-binding domain, the second target-binding domain, and the one or more target-binding domains is an antigen-binding domain. In some embodiments, the first target-binding domain, the second target-binding domain, and the one or more additional target-binding domains are each an antigen-binding domain (e.g., a scFv or a single-domain antibody).

Pairs of Affinity Domains

In some embodiments, a multi-chain chimeric polypeptide includes: 1) a first chimeric polypeptide that includes a first domain of a pair of affinity domains, and 2) a second chimeric polypeptide that includes a second domain of a pair of affinity domains such that 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 some embodiments, the pair of affinity domains is a sushi domain from an alpha chain of human IL-15 receptor (IL15Rα) and a soluble IL-15. A sushi domain, also known as a short consensus repeat or type 1 glycoprotein motif, is a common motif in protein-protein interaction. Sushi domains have been identified on a number of protein-binding molecules, including complement components C1r, C1s, factor H, and C2m, as well as the nonimmunologic molecules factor XIII and β2-glycoprotein. A typical Sushi domain has approximately 60 amino acid residues and contains four cysteines (Ranganathan, Pac. Symp Biocomput. 2000:155-67). The first cysteine can form a disulfide bond with the third cysteine, and the second cysteine can form a disulfide bridge with the fourth cysteine. In some embodiments in which one member of the pair of affinity domains is a soluble IL-15, the soluble IL15 has a D8N or D8A amino acid substitution. In some embodiments in which one member of the pair of affinity domains is an alpha chain of human IL-15 receptor (IL15Rα), the human IL15Rα is a mature full-length IL15Rα. In some embodiments, the pair of affinity domains is barnase and barnstar. In some embodiments, the pair of affinity domains is a PKA and an AKAP. In some embodiments, the pair of affinity domains is an adapter/docking tag module based on mutated RNase I fragments (Rossi, *Proc Natl Acad Sci USA*. 103:6841-6846, 2006; Sharkey et al., *Cancer Res*. 68:5282-5290, 2008; Rossi et al., *Trends Pharmacol Sci*. 33:474-481, 2012) or SNARE modules based on interactions of the proteins syntaxin, synaptotagmin, synaptobrevin, and SNAP25 (Deyev et al., *Nat Biotechnol*. 1486-1492, 2003).

In some embodiments, a first chimeric polypeptide of a multi-chain chimeric polypeptide includes a first domain of a pair of affinity domains and a second chimeric polypeptide of the multi-chain chimeric polypeptide includes a second domain of a pair of affinity domains, wherein the first domain of the pair of affinity domains and the second domain of the pair of affinity domains bind to each other with a dissociation equilibrium constant (K_D) of less than 1 x 10^{-7} M, less than 1 x 10^{-8} M, less than 1 x 10^{-9} M, less than 1 x 10^{-10} M, less than 1 x 10^{-11} M, less than 1 x 10^{-12} M, or less than 1 x 10^{-13} M. In some embodiments, the first domain of the pair of affinity domains and the second domain of the pair of affinity domains bind to each other with a K_D of about 1 x 10^{-4} M to about 1 x 10^{-6} M, about 1 x 10^{-5} M to about 1 x 10^{-7} M, about 1 x 10^{-6} M to about 1 x 10^{-8}

M, about 1 x 10^{-7} M to about 1 x 10^{-9} M, about 1 x 10^{-8} M to about 1 x 10^{-10} M, about 1 x 10^{-9} M to about 1 x 10^{-11} M, about 1 x 10^{-10} M to about 1 x 10^{-12} M, about 1 x 10^{-11} M to about 1 x 10^{-13} M, about 1 x 10^{-4} M to about 1 x 10^{-5} M, about 1 x 10^{-5} M to about 1 x 10^{-6} M, about 1 x 10^{-6} M to about 1 x 10^{-7} M, about 1 x 10^{-7} M to about 1 x 10^{-8} M, about 1 x 10^{-8} M to about 1 x 10^{-9} M, about 1 x 10^{-9} M to about 1 x 10^{-10} M, about 1 x 10^{-10} M to about 1 x 10^{-11} M, about 1 x 10^{-11} M to about 1 x 10^{-12} M, or about 1 x 10^{-12} M to about 1 x 10^{-13} M (inclusive). Any of a variety of different methods known in the art can be used to determine the K_D value of the binding of the first domain of the pair of affinity domains and the second domain of the pair of affinity domains (e.g., an electrophoretic mobility shift assay, a filter binding assay, surface plasmon resonance, and a biomolecular binding kinetics assay, etc.).

In some embodiments, a first chimeric polypeptide of a multi-chain chimeric polypeptide includes a first domain of a pair of affinity domains and a second chimeric polypeptide of the multi-chain chimeric polypeptide includes a second domain of a pair of affinity domains, wherein the first domain of the pair of affinity domains, the second domain of the pair of affinity domains, or both is about 10 to 100 amino acids in length. For example, a first domain of a pair of affinity domains, a second domain of a pair of affinity domains, or both can be about 10 to 100 amino acids in length, about 15 to 100 amino acids in length, about 20 to 100 amino acids in length, about 25 to 100 amino acids in length, about 30 to 100 amino acids in length, about 35 to 100 amino acids in length, about 40 to 100 amino acids in length, about 45 to 100 amino acids in length, about 50 to 100 amino acids in length, about 55 to 100 amino acids in length, about 60 to 100 amino acids in length, about 65 to 100 amino acids in length, about 70 to 100 amino acids in length, about 75 to 100 amino acids in length, about 80 to 100 amino acids in length, about 85 to 100 amino acids in length, about 90 to 100 amino acids in length, about 95 to 100 amino acids in length, about 10 to 95 amino acids in length, about 10 to 90 amino acids in length, about 10 to 85 amino acids in length, about 10 to 80 amino acids in length, about 10 to 75 amino acids in length, about 10 to 70 amino acids in length, about 10 to 65 amino acids in length, about 10 to 60 amino acids in length, about 10 to 55 amino acids in length, about 10 to 50 amino acids in length, about 10 to 45 amino acids in length, about 10 to 40 amino acids in length, about 10 to 35 amino acids in length, about

10 to 30 amino acids in length, about 10 to 25 amino acids in length, about 10 to 20 amino acids in length, about 10 to 15 amino acids in length, about 20 to 30 amino acids in length, about 30 to 40 amino acids in length, about 40 to 50 amino acids in length, about 50 to 60 amino acids in length, about 60 to 70 amino acids in length, about 70 to 80 amino acids in length, about 80 to 90 amino acids in length, about 90 to 100 amino acids in length, about 20 to 90 amino acids in length, about 30 to 80 amino acids in length, about 40 to 70 amino acids in length, about 50 to 60 amino acids in length, or any range in between. In some embodiments, a first domain of a pair of affinity domains, a second domain of a pair of affinity domains, or both is about 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acids in length.

In some embodiments, any of the first and/or second domains of a pair of affinity domains disclosed herein can include one or more additional amino acids (e.g., 1, 2, 3, 5, 6, 7, 8, 9, 10, or more amino acids) at its N-terminus and/or C-terminus, so long as the function of the first and/or second domains of a pair of affinity domains remains intact. For example, a sushi domain from an alpha chain of human IL-15 receptor (IL15Rα) can include one or more additional amino acids at the N-terminus and/or the C-terminus, while still retaining the ability to bind to a soluble IL-15. Additionally or alternatively, a soluble IL-15 can include one or more additional amino acids at the N-terminus and/or the C-terminus, while still retaining the ability to bind to a sushi domain from an alpha chain of human IL-15 receptor (IL15Rα).

A non-limiting example of a sushi domain from an alpha chain of IL-15 receptor alpha (IL15Rα) can include a sequence that is at least 70% identical, at least 75% identical, at least 80% identical, at least 85% identical, at least 90% identical, at least 95% identical, at least 99% identical, or 100% identical to ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAH WTTPSLKCIR (SEQ ID NO: 28). In some embodiments, a sushi domain from an alpha chain of IL15Rα can be encoded by a nucleic acid including ATTACATGCCCCCCTCCCATGAGCGTGGAGCACGCCGACATCTGGGTGAAGAG CTATAGCCTCTACAGCCGGGAGAGGTATATCTGTAACAGCGGCTTCAAGAGGA AGGCCGGCACCAGCAGCCTCACCGAGTGCGTGCTGAATAAGGCTACCAACGT GGCTCACTGGACAACACCCTCTTTAAAGTGCATCCGG (SEQ ID NO: 29).

In some embodiments, a soluble IL-15 can include a sequence that is at least 70% identical, at least 75% identical, at least 80% identical, at least 85% identical, at least 90% identical, at least 95% identical, at least 99% identical, or 100% identical to NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGD ASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINT S (SEQ ID NO: 14). In some embodiments, a soluble IL-15 can be encoded by a nucleic acid including the sequence of AACTGGGTGAACGTCATCAGCGATTTAAAGAAGATCGAAGATTTAATTCAGTC CATGCATATCGACGCCACTTTATACACAGAATCCGACGTGCACCCCTCTTGTAA GGTGACCGCCATGAAATGTTTTTTACTGGAGCTGCAAGTTATCTCTTTAGAGAG CGGAGACGCTAGCATCCACGACACCGTGGAGAATTTAATCATTTTAGCCAATA ACTCTTTATCCAGCAACGGCAACGTGACAGAGTCCGGCTGCAAGGAGTGCGA AGAGCTGGAGGAGAAGAACATCAAGGAGTTTCTGCAATCCTTTGTGCACATTG TCCAGATGTTCATCAATACCTCC (SEQ ID NO: 30).

Signal Sequence

In some embodiments, a multi-chain chimeric polypeptide includes a first chimeric polypeptide that includes a signal sequence at its N-terminal end. In some embodiments, a multi-chain chimeric polypeptide includes a second chimeric polypeptide that includes a signal sequence at its N-terminal end. In some embodiments, both the first chimeric polypeptide of a multi-chain chimeric polypeptide and a second chimeric polypeptide of the multi-chain chimeric polypeptide include a signal sequence. As will be understood by those of ordinary skill in the art, a signal sequence is an amino acid sequence that is present at the N-terminus of a number of endogenously produced proteins that directs the protein to the secretory pathway (e.g., the protein is directed to reside in certain intracellular organelles, to reside in the cell membrane, or to be secreted from the cell). Signal sequences are heterogeneous and differ greatly in their primary amino acid sequences. However, signal sequences are typically 16 to 30 amino acids in length and include a hydrophilic, usually positively charged N-terminal region, a central hydrophobic domain, and a C-terminal region that contains the cleavage site for signal peptidase.

In some embodiments, a first chimeric polypeptide of a multi-chain chimeric polypeptide, a second chimeric polypeptide of the multi-chain chimeric polypeptide, or both includes a signal sequence having an amino acid sequence MKWVTFISLLFLFSSAYS (SEQ ID NO: 31). In some embodiments, a first chimeric polypeptide of a multi-chain chimeric polypeptide, a second chimeric polypeptide of the multi-chain chimeric polypeptide, or both includes a signal sequence encoded by the nucleic acid sequence ATGAAATGGGTGACCTTTATTTCTTTACTGTTCCTCTTTAGCAGCGCCTACTCC (SEQ ID NO: 32), ATGAAGTGGGTCACATTTATCTCTTTACTGTTCCTCTTCTCCAGCGCCTACAGC (SEQ ID NO: 33), or ATGAAATGGGTGACCTTTATTTCTTTACTGTTCCTCTTTAGCAGCGCCTACTCC (SEQ ID NO: 34).

In some embodiments, a first chimeric polypeptide of a multi-chain chimeric polypeptide, a second chimeric polypeptide of the multi-chain chimeric polypeptide, or both includes a signal sequence having an amino acid sequence MKCLLYLAFLFLGVNC (SEQ ID NO: 35). In some embodiments, a first chimeric polypeptide of a multi-chain chimeric polypeptide, a second chimeric polypeptide of the multi-chain chimeric polypeptide, or both includes a signal sequence having an amino acid sequence MGQIVTMFEALPHIIDEVINIVIIVLIIITSIKAVYNFATCGILALVSFLFLAGRSCG (SEQ ID NO: 36). In some embodiments, a first chimeric polypeptide of a multi-chain chimeric polypeptide, a second chimeric polypeptide of the multi-chain chimeric polypeptide, or both includes a signal sequence having an amino acid sequence MPNHQSGSPTGSSDLLLSGKKQRPHLALRRKRRREMRKINRKVRRMNLAPIKEK TAWQHLQALISEAEEVLKTSQTPQNSLTLFLALLSVLGPPVTG (SEQ ID NO: 37). In some embodiments, a first chimeric polypeptide of a multi-chain chimeric polypeptide, a second chimeric polypeptide of the multi-chain chimeric polypeptide, or both includes a signal sequence having an amino acid sequence MDSKGSSQKGSRLLLLLVVSNLLLCQGVVS (SEQ ID NO: 38). Those of ordinary skill in the art will be aware of other appropriate signal sequences for use in a first

chimeric polypeptide and/or a second chimeric polypeptide of multi-chain chimeric polypeptides described herein.

In some embodiments, a first chimeric polypeptide of a multi-chain chimeric polypeptide, a second chimeric polypeptide of the multi-chain chimeric polypeptide, or both includes a signal sequence that is about 10 to 100 amino acids in length. For example, a signal sequence can be about 10 to 100 amino acids in length, about 15 to 100 amino acids in length, about 20 to 100 amino acids in length, about 25 to 100 amino acids in length, about 30 to 100 amino acids in length, about 35 to 100 amino acids in length, about 40 to 100 amino acids in length, about 45 to 100 amino acids in length, about 50 to 100 amino acids in length, about 55 to 100 amino acids in length, about 60 to 100 amino acids in length, about 65 to 100 amino acids in length, about 70 to 100 amino acids in length, about 75 to 100 amino acids in length, about 80 to 100 amino acids in length, about 85 to 100 amino acids in length, about 90 to 100 amino acids in length, about 95 to 100 amino acids in length, about 10 to 95 amino acids in length, about 10 to 90 amino acids in length, about 10 to 85 amino acids in length, about 10 to 80 amino acids in length, about 10 to 75 amino acids in length, about 10 to 70 amino acids in length, about 10 to 65 amino acids in length, about 10 to 60 amino acids in length, about 10 to 55 amino acids in length, about 10 to 50 amino acids in length, about 10 to 45 amino acids in length, about 10 to 40 amino acids in length, about 10 to 35 amino acids in length, about 10 to 30 amino acids in length, about 10 to 25 amino acids in length, about 10 to 20 amino acids in length, about 10 to 15 amino acids in length, about 20 to 30 amino acids in length, about 30 to 40 amino acids in length, about 40 to 50 amino acids in length, about 50 to 60 amino acids in length, about 60 to 70 amino acids in length, about 70 to 80 amino acids in length, about 80 to 90 amino acids in length, about 90 to 100 amino acids in length, about 20 to 90 amino acids in length, about 30 to 80 amino acids in length, about 40 to 70 amino acids in length, about 50 to 60 amino acids in length, or any range in between. In some embodiments, a signal sequence is about 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acids in length.

In some embodiments, any of the signal sequences disclosed herein can include one or more additional amino acids (e.g., 1, 2, 3, 5, 6, 7, 8, 9, 10, or more amino acids) at its N-terminus and/or C-terminus, so long as the function of the signal sequence remains

intact. For example, a signal sequence having the amino acid sequence MKCLLYLAFLFLGVNC (SEQ ID NO: 35) can include one or more additional amino acids at the N-terminus or C-terminus, while still retaining the ability to direct a first chimeric polypeptide of a multi-chain chimeric polypeptide, a second chimeric polypeptide of the multi-chain chimeric polypeptide, or both to the secretory pathway.

In some embodiments, a first chimeric polypeptide of a multi-chain chimeric polypeptide, a second chimeric polypeptide of the multi-chain chimeric polypeptide, or both includes a signal sequence that directs the multi-chain chimeric polypeptide into the extracellular space. Such embodiments are useful in producing multi-chain chimeric polypeptides that are relatively easy to be isolated and/or purified.

Peptide Tags

In some embodiments, a multi-chain chimeric polypeptide includes a first chimeric polypeptide that includes a peptide tag (e.g., at the N-terminal end or the C-terminal end of the first chimeric polypeptide). In some embodiments, a multi-chain chimeric polypeptide includes a second chimeric polypeptide that includes a peptide tag (e.g., at the N-terminal end or the C-terminal end of the second chimeric polypeptide). In some embodiments, both the first chimeric polypeptide of a multi-chain chimeric polypeptide and a second chimeric polypeptide of the multi-chain chimeric polypeptide include a peptide tag. In some embodiments, a first chimeric polypeptide of a multi-chain chimeric polypeptide, a second chimeric polypeptide of the multi-chain chimeric polypeptide, or both include two or more peptide tags.

Exemplary peptide tags that can be included in a first chimeric polypeptide of a multi-chain chimeric polypeptide, a second chimeric polypeptide of the multi-chain chimeric polypeptide, or both include, without limitation, AviTag (GLNDIFEAQKIEWHE; SEQ ID NO: 39), a calmodulin-tag (KRRWKKNFIAVSAANRFKKISSSGAL; SEQ ID NO: 40), a polyglutamate tag (EEEEEE; SEQ ID NO: 41), an E-tag (GAPVPYPDPLEPR; SEQ ID NO: 42), a FLAG-tag (DYKDDDDK; SEQ ID NO: 43), an HA-tag, a peptide from hemagglutinin (YPYDVPDYA; SEQ ID NO: 44), a his-tag (HHHHH (SEQ ID NO: 45); HHHHHH (SEQ ID NO: 46); HHHHHHH (SEQ ID NO: 47); HHHHHHHH (SEQ ID NO: 48);

HHHHHHHHH (SEQ ID NO: 49); or HHHHHHHHHH (SEQ ID NO: 50)), a myc-tag (EQKLISEEDL; SEQ ID NO: 51), NE-tag (TKENPRSNQEESYDDNES; SEQ ID NO: 52), S-tag, (KETAAAKFERQHMDS; SEQ ID NO: 53), SBP-tag (MDEKTTGWRGGHVVEGLAGELEQLRARLEHHPQGQREP; SEQ ID NO: 54), Softag 1 (SLAELLNAGLGGS; SEQ ID NO: 55), Softag 3 (TQDPSRVG; SEQ ID NO: 56), Spot-tag (PDRVRAVSHWSS; SEQ ID NO: 57), Strep-tag (WSHPQFEK; SEQ ID NO: 58), TC tag (CCPGCC; SEQ ID NO: 59), Ty tag (EVHTNQDPLD; SEQ ID NO: 60), V5 tag (GKPIPNPLLGLDST; SEQ ID NO: 61), VSV-tag (YTDIEMNRLGK; SEQ ID NO: 62), and Xpress tag (DLYDDDDK; SEQ ID NO: 63). In some embodiments, tissue factor protein is a peptide tag.

Peptide tags that can be included in a first chimeric polypeptide of a multi-chain chimeric polypeptide, a second chimeric polypeptide of the multi-chain chimeric polypeptide, or both can be used in any of a variety of applications related to the multi-chain chimeric polypeptide. For example, a peptide tag can be used in the purification of a multi-chain chimeric polypeptide. As one non-limiting example, a first chimeric polypeptide of a multi-chain chimeric polypeptide (e.g., a recombinantly expressed first chimeric polypeptide), a second chimeric polypeptide of the multi-chain chimeric polypeptide (e.g., a recombinantly expressed second chimeric polypeptide), or both can include a myc tag; the multi-chain chimeric polypeptide that includes the myc-tagged first chimeric polypeptide, the myc-tagged second chimeric polypeptide, or both can be purified using an antibody that recognizes the myc tag(s). One non-limiting example of an antibody that recognizes a myc tag is 9E10, available from the non-commercial Developmental Studies Hybridoma Bank. As another non-limiting example, a first chimeric polypeptide of a multi-chain chimeric polypeptide (e.g., a recombinantly expressed first chimeric polypeptide), a second chimeric polypeptide of the multi-chain chimeric polypeptide (e.g., a recombinantly expressed second chimeric polypeptide), or both can include a histidine tag; the multi-chain chimeric polypeptide that includes the histidine-tagged first chimeric polypeptide, the histidine-tagged second chimeric polypeptide, or both can be purified using a nickel or cobalt chelate. Those of ordinary skill in the art will be aware of other suitable tags and agent that bind those tags for use in purifying multi-chain chimeric polypeptide. In some embodiments, a peptide tag is

removed from the first chimeric polypeptide and/or the second chimeric polypeptide of the multi-chain chimeric polypeptide after purification. In some embodiments, a peptide tag is not removed from the first chimeric polypeptide and/or the second chimeric polypeptide of the multi-chain chimeric polypeptide after purification.

Peptide tags that can be included in a first chimeric polypeptide of a multi-chain chimeric polypeptide, a second chimeric polypeptide of the multi-chain chimeric polypeptide, or both can be used, for example, in immunoprecipitation of the multi-chain chimeric polypeptide, imaging of the multi-chain chimeric polypeptide (e.g., via Western blotting, ELISA, flow cytometry, and/or immunocytochemistry), and/or solubilization of the multi-chain chimeric polypeptide.

In some embodiments, a first chimeric polypeptide of a multi-chain chimeric polypeptide, a second chimeric polypeptide of the multi-chain chimeric polypeptide, or both includes a peptide tag that is about 10 to 100 amino acids in length. For example, a peptide tag can be about 10 to 100 amino acids in length, about 15 to 100 amino acids in length, about 20 to 100 amino acids in length, about 25 to 100 amino acids in length, about 30 to 100 amino acids in length, about 35 to 100 amino acids in length, about 40 to 100 amino acids in length, about 45 to 100 amino acids in length, about 50 to 100 amino acids in length, about 55 to 100 amino acids in length, about 60 to 100 amino acids in length, about 65 to 100 amino acids in length, about 70 to 100 amino acids in length, about 75 to 100 amino acids in length, about 80 to 100 amino acids in length, about 85 to 100 amino acids in length, about 90 to 100 amino acids in length, about 95 to 100 amino acids in length, about 10 to 95 amino acids in length, about 10 to 90 amino acids in length, about 10 to 85 amino acids in length, about 10 to 80 amino acids in length, about 10 to 75 amino acids in length, about 10 to 70 amino acids in length, about 10 to 65 amino acids in length, about 10 to 60 amino acids in length, about 10 to 55 amino acids in length, about 10 to 50 amino acids in length, about 10 to 45 amino acids in length, about 10 to 40 amino acids in length, about 10 to 35 amino acids in length, about 10 to 30 amino acids in length, about 10 to 25 amino acids in length, about 10 to 20 amino acids in length, about 10 to 15 amino acids in length, about 20 to 30 amino acids in length, about 30 to 40 amino acids in length, about 40 to 50 amino acids in length, about 50 to 60 amino acids in length, about 60 to 70 amino acids in length, about 70 to 80 amino acids in

length, about 80 to 90 amino acids in length, about 90 to 100 amino acids in length, about 20 to 90 amino acids in length, about 30 to 80 amino acids in length, about 40 to 70 amino acids in length, about 50 to 60 amino acids in length, or any range in between. In some embodiments, a peptide tag is about 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acids in length.

Peptide tags included in a first chimeric polypeptide of a multi-chain chimeric polypeptide, a second chimeric polypeptide of the multi-chain chimeric polypeptide, or both can be of any suitable length. For example, peptide tags can be 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more amino acids in length. In embodiments in which a multi-chain chimeric polypeptide includes two or more peptide tags, the two or more peptide tags can be of the same or different lengths. In some embodiments, any of the peptide tags disclosed herein may include one or more additional amino acids (e.g., 1, 2, 3, 5, 6, 7, 8, 9, 10, or more amino acids) at the N-terminus and/or C-terminus, so long as the function of the peptide tag remains intact. For example, a myc tag having the amino acid sequence EQKLISEEDL (SEQ ID NO: 64) can include one or more additional amino acids (e.g., at the N-terminus and/or the C- terminus of the peptide tag), while still retaining the ability to be bound by an antibody (e.g., 9E10).

Exemplary Multi-Chain Chimeric Polypeptides- Type A

In some embodiments of any of the multi-chain chimeric polypeptides described herein, the first target-binding domain and the second targeting-binding domain each independently bind specifically to a receptor of IL-18 or a receptor of IL-12. In some examples of these multi-chain chimeric polypeptides, the first target-binding domain and the soluble tissue factor domain directly abut each other in the first chimeric polypeptide. In some examples of these multi-chain chimeric polypeptides, the first chimeric polypeptide further comprises a linker sequence (e.g., any of the exemplary linkers described herein) between the first target-binding domain and the soluble tissue factor domain in the first chimeric polypeptide.

In some embodiments of these multi-chain chimeric polypeptides, 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 embodiments of these multi-

chain chimeric polypeptides, the second chimeric polypeptide further includes a linker sequence (e.g., any of the exemplary linkers described herein) between the second domain of the pair of affinity domains and the second target-binding domain in the second chimeric polypeptide.

In some embodiments of these multi-chain chimeric polypeptides, the soluble tissue factor domain can be any of the exemplary soluble tissue factor domains described herein. In some embodiments of these multi-chain chimeric polypeptides, the pair of affinity domains can be any of the exemplary pairs of affinity domains described herein.

In some embodiments of these multi-chain chimeric polypeptides, one or both of the first target-binding domain and the second target-binding domain is an agonistic antigen-binding domain. In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain and the second target-binding domain are each agonistic antigen-binding domains. In some embodiments of these multi-chain chimeric polypeptides, the antigen-binding domain includes a scFv or single-domain antibody.

In some embodiments of these multi-chain chimeric polypeptides, one or both of the first target-binding domain and the second target-binding domain is a soluble IL-15 or a soluble IL-18. In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain and the second target-binding domain are each independently a soluble IL-15 or a soluble IL-18. In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain and the second target-binding domain both bind specifically to a receptor of IL-18 or a receptor of IL-12. In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain and the second target-binding domain bind specifically to the same epitope. In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain and the second target-binding domain include the same amino acid sequence.

In some embodiments of these multi-chain chimeric polypeptides, 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. In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain binds specifically to a

receptor for IL-18, and the second target-binding domain bind specifically to a receptor for IL-12.

In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain includes a soluble IL-18 (e.g., a soluble human IL-18).

In some embodiments of these multi-chain chimeric polypeptides, the soluble human IL-18 includes a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

YFGKLESKLSVIRNLNDQVLFIDQGNRPLFEDMTDSDCRDNAPRTIFIISMYKDSQ PRGMAVTISVKCEKISTLSCENKIISFKEMNPPDNIKDTKSDIIFFQRSVPGHDNKM QFESSSYEGYFLACEKERDLFKLILKKEDELGDRSIMFTVQNED (SEQ ID NO: 16).

In some embodiments of these multi-chain chimeric polypeptides, the soluble human IL-18 is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

TACTTCGGCAAACTGGAATCCAAGCTGAGCGTGATCCGGAATTTAAACGACC AAGTTCTGTTTATCGATCAAGGTAACCGGCCTCTGTTCGAGGACATGACCGAC TCCGATTGCCGGGACAATGCCCCCCGGACCATCTTCATTATCTCCATGTACAA GGACAGCCAGCCCCGGGGCATGGCTGTGACAATTAGCGTGAAGTGTGAGAA AATCAGCACTTTATCTTGTGAGAACAAGATCATCTCCTTTAAGGAAATGAACC CCCCCGATAACATCAAGGACACCAAGTCCGATATCATCTTCTTCCAGCGGTCC GTGCCCGGTCACGATAACAAGATGCAGTTCGAATCCTCCTCCTACGAGGGCT ACTTTTTAGCTTGTGAAAAGGAGAGGGATTTATTCAAGCTGATCCTCAAGAA GGAGGACGAGCTGGGCGATCGTTCCATCATGTTCACCGTCCAAAACGAGGAT (SEQ ID NO: 65).

In some embodiments of these multi-chain chimeric polypeptides, the second target-binding domain includes a soluble IL-12 (e.g., a soluble human IL-12). In some embodiments of these multi-chain chimeric polypeptides, the soluble human IL-15 includes a sequence of soluble human IL-12β (p40) and a sequence of soluble human IL-12α (p35). In some embodiments of these multi-chain chimeric polypeptides, the soluble IL-15 human IL-15 further includes a linker sequence (e.g., any of the exemplary linker sequences described herein) between the sequence of soluble IL-12β (p40) and the

sequence of soluble human IL-12α (p35). In some examples of these multi-chain chimeric polypeptides, the linker sequence comprises GGGGSGGGGSGGGGS (SEQ ID NO: 7).

In some embodiments of these multi-chain chimeric polypeptides, the sequence of soluble human IL-12β (p40) comprises a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

IWELKKDVYVVELDWYPDAPGEMVVLTCDTPEEDGITWTLDQSSEVLGSGKTLT
IQVKEFGDAGQYTCHKGGEVLSHSLLLLHKKEDGIWSTDILKDQKEPKNKTFLR
CEAKNYSGRFTCWWLTTISTDLTFSVKSSRGSSDPQGVTCGAATLSAERVRGDN
KEYEYSVECQEDSACPAAEESLPIEVMVDAVHKLKYENYTSSFFIRDIIKPDPPKN
LQLKPLKNSRQVEVSWEYPDTWSTPHSYFSLTFCVQVQGKSKREKKDRVFTDKT
SATVICRKNASISVRAQDRYYSSSWSEWASVPCS (SEQ ID NO: 66).

In some embodiments of these multi-chain chimeric polypeptides, the soluble human IL-12β (p40) is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATTTGGGAACTGAAGAAGGACGTCTACGTGGTCGAACTGGACTGGTATCCCG
ATGCTCCCGGCGAAATGGTGGTGCTCACTTGTGACACCCCCGAAGAAGACGG
CATCACTTGGACCCTCGATCAGAGCAGCGAGGTGCTGGGCTCCGGAAAGACC
CTCACAATCCAAGTTAAGGAGTTCGGAGACGCTGGCCAATACACATGCCACA
AGGGAGGCGAGGTGCTCAGCCATTCCTTATTATTATTACACAAGAAGGAAGA
CGGAATCTGGTCCACCGACATTTTAAAAGATCAGAAGGAGCCCAAGAATAAG
ACCTTTTTAAGGTGTGAGGCCAAAAACTACAGCGGTCGTTTCACTTGTTGGTG
GCTGACCACCATTTCCACCGATTTAACCTTCTCCGTGAAAAGCAGCCGGGGA
AGCTCCGACCCTCAAGGTGTGACATGTGGAGCCGCTACCCTCAGCGCTGAGA
GGGTTCGTGGCGATAACAAGGAATACGAGTACAGCGTGGAGTGCCAAGAAG
ATAGCGCTTGTCCCGCTGCCGAAGAATCTTTACCCATTGAGGTGATGGTGGAC
GCCGTGCACAAACTCAAGTACGAGAACTACACCTCCTCCTTCTTTATCCGGGA
CATCATTAAGCCCGATCCTCCTAAGAATTTACAGCTGAAGCCTCTCAAAAATA
GCCGGCAAGTTGAGGTCTCTTGGGAATATCCCGACACTTGGAGCACACCCCA
CAGCTACTTCTCTTTAACCTTTTGTGTGCAAGTTCAAGGTAAAAGCAAGCGGG
AGAAGAAAGACCGGGTGTTTACCGACAAAACCAGCGCCACCGTCATCTGTCG
GAAGAACGCCTCCATCAGCGTGAGGGCTCAAGATCGTTATTACTCCAGCAGC
TGGTCCGAGTGGGCCAGCGTGCCTTGTTCC (SEQ ID NO: 67).

In some embodiments of these multi-chain chimeric polypeptides, the soluble human IL-12α (p35) includes a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

RNLPVATPDPGMFPCLHHSQNLLRAVSNMLQKARQTLEFYPCTSEEIDHEDITKD
KTSTVEACLPLELTKNESCLNSRETSFITNGSCLASRKTSFMMALCLSSIYEDLKM
YQVEFKTMNAKLLMDPKRQIFLDQNMLAVIDELMQALNFNSETVPQKSSLEEPD
FYKTKIKLCILLHAFRIRAVTIDRVMSYLNAS (SEQ ID NO: 68).

In some embodiments of these multi-chain chimeric polypeptides, the soluble human IL-12α (p35) is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

CGTAACCTCCCCGTGGCTACCCCCGATCCCGGAATGTTCCCTTGTTTACACCA
CAGCCAGAATTTACTGAGGGCCGTGAGCAACATGCTGCAGAAAGCTAGGCAG
ACTTTAGAATTTTACCCTTGCACCAGCGAGGAGATCGACCATGAAGATATCA
CCAAGGACAAGACATCCACCGTGGAGGCTTGTTTACCTCTGGAGCTGACAAA
GAACGAGTCTTGTCTCAACTCTCGTGAAACCAGCTTCATCACAAATGGCTCTT
GTTTAGCTTCCCGGAAGACCTCCTTTATGATGGCTTTATGCCTCAGCTCCATCT
ACGAGGATTTAAAGATGTACCAAGTGGAGTTCAAGACCATGAACGCCAAGCT
GCTCATGGACCCTAAACGGCAGATCTTTTTAGACCAGAACATGCTGGCTGTG
ATTGATGAGCTGATGCAAGCTTTAAACTTCAACTCCGAGACCGTCCCTCAGA
AGTCCTCCCTCGAGGAGCCCGATTTTTACAAGACAAAGATCAAACTGTGCAT
TTTACTCCACGCCTTTAGGATCCGGGCCGTGACCATTGACCGGGTCATGAGCT
ATTTAAACGCCAGC (SEQ ID NO: 69).

In some embodiments, the first chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

YFGKLESKLSVIRNLNDQVLFIDQGNRPLFEDMTDSDCRDNAPRTIFIISMYKDSQ
PRGMAVTISVKCEKISTLSCENKIISFKEMNPPDNIKDTKSDIIFFQRSVPGHDNKM
QFESSSYEGYFLACEKERDLFKLILKKEDELGDRSIMFTVQNEDSGTTNTVAAYN
LTWKSTNFKTILEWEPKPVNQVYTVQISTKSGDWKSKCFYTTDTECDLTDEIVKD
VKQTYLARVFSYPAGNVESTGSAGEPLYENSPEFTPYLETNLGQPTIQSFEQVGT

KVNVTVEDERTLVRRNNTFLSLRDVFGKDLIYTLYYWKSSSSGKKTAKTNTNEF
LIDVDKGENYCFSVQAVIPSRTVNRKSTDSPVECMGQEKGEFRENWVNVISDLK
KIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLI
ILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS (SEQ ID NO:
70).

In some embodiments, a first chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

TACTTCGGCAAACTGGAATCCAAGCTGAGCGTGATCCGGAATTTAAACGACC
AAGTTCTGTTTATCGATCAAGGTAACCGGCCTCTGTTCGAGGACATGACCGAC
TCCGATTGCCGGGACAATGCCCCCCGGACCATCTTCATTATCTCCATGTACAA
GGACAGCCAGCCCCGGGGCATGGCTGTGACAATTAGCGTGAAGTGTGAGAA
AATCAGCACTTTATCTTGTGAGAACAAGATCATCTCCTTTAAGGAAATGAACC
CCCCCGATAACATCAAGGACACCAAGTCCGATATCATCTTCTTCCAGCGGTCC
GTGCCCGGTCACGATAACAAGATGCAGTTCGAATCCTCCTCCTACGAGGGCT
ACTTTTTAGCTTGTGAAAAGGAGAGGGATTTATTCAAGCTGATCCTCAAGAA
GGAGGACGAGCTGGGCGATCGTTCCATCATGTTCACCGTCCAAAACGAGGAT
AGCGGCACAACCAACACAGTCGCTGCCTATAACCTCACTTGGAAGAGCACCA
ACTTCAAAACCATCCTCGAATGGGAACCCAAACCCGTTAACCAAGTTTACAC
CGTGCAGATCAGCACCAAGTCCGGCGACTGGAAGTCCAAATGTTTCTATACC
ACCGACACCGAGTGCGATCTCACCGATGAGATCGTGAAAGATGTGAAACAGA
CCTACCTCGCCCGGGTGTTTAGCTACCCCGCCGGCAATGTGGAGAGCACTGG
TTCCGCTGGCGAGCCTTTATACGAGAACAGCCCCGAATTTACCCCTTACCTCG
AGACCAATTTAGGACAGCCCACCATCCAAAGCTTTGAGCAAGTTGGCACAAA
GGTGAATGTGACAGTGGAGGACGAGCGGACTTTAGTGCGGCGGAACAACAC
CTTTCTCAGCCTCCGGGATGTGTTCGGCAAAGATTTAATCTACACACTGTATT
ACTGGAAGTCCTCTTCCTCCGGCAAGAAGACAGCTAAAACCAACACAAACGA
GTTTTTAATCGACGTGGATAAAGGCGAAAACTACTGTTTCAGCGTGCAAGCT
GTGATCCCCTCCCGGACCGTGAATAGGAAAAGCACCGATAGCCCCGTTGAGT
GCATGGGCCAAGAAAAGGGCGAGTTCCGGGAGAACTGGGTGAACGTCATCA
GCGATTTAAAGAAGATCGAAGATTTAATTCAGTCCATGCATATCGACGCCAC
TTTATACACAGAATCCGACGTGCACCCCTCTTGTAAGGTGACCGCCATGAAAT
GTTTTTTACTGGAGCTGCAAGTTATCTCTTTAGAGAGCGGAGACGCTAGCATC
CACGACACCGTGGAGAATTTAATCATTTTAGCCAATAACTCTTTATCCAGCAA
CGGCAACGTGACAGAGTCCGGCTGCAAGGAGTGCGAAGAGCTGGAGGAGAA
GAACATCAAGGAGTTTCTGCAATCCTTTGTGCACATTGTCCAGATGTTCATCA
ATACCTCC (SEQ ID NO: 71).

In some embodiments, a first chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

MKWVTFISLLFLFSSAYSYFGKLESKLSVIRNLNDQVLFIDQGNRPLFEDMTDSD
CRDNAPRTIFIISMYKDSQPRGMAVTISVKCEKISTLSCENKIISFKEMNPPDNIKD
TKSDIIFFQRSVPGHDNKMQFESSSYEGYFLACEKERDLFKLILKKEDELGDRSIM
FTVQNEDSGTTNTVAAYNLTWKSTNFKTILEWEPKPVNQVYTVQISTKSGDWKS
KCFYTTDTECDLTDEIVKDVKQTYLARVFSYPAGNVESTGSAGEPLYENSPEFTP
YLETNLGQPTIQSFEQVGTKVNVTVEDERTLVRRNNTFLSLRDVFGKDLIYTLYY
WKSSSSGKKTAKTNTNEFLIDVDKGENYCFSVQAVIPSRTVNRKSTDSPVECMG
QEKGEFRENWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLEL
QVISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFV
HIVQMFINTS (SEQ ID NO: 72).

In some embodiments, a first chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATGAAGTGGGTCACATTTATCTCTTTACTGTTCCTCTTCTCCAGCGCCTACAGC
TACTTCGGCAAACTGGAATCCAAGCTGAGCGTGATCCGGAATTTAAACGACC
AAGTTCTGTTTATCGATCAAGGTAACCGGCCTCTGTTCGAGGACATGACCGAC
TCCGATTGCCGGGACAATGCCCCCCGGACCATCTTCATTATCTCCATGTACAA
GGACAGCCAGCCCCGGGGCATGGCTGTGACAATTAGCGTGAAGTGTGAGAA
AATCAGCACTTTATCTTGTGAGAACAAGATCATCTCCTTTAAGGAAATGAACC
CCCCCGATAACATCAAGGACACCAAGTCCGATATCATCTTCTTCCAGCGGTCC
GTGCCCGGTCACGATAACAAGATGCAGTTCGAATCCTCCTCCTACGAGGGCT
ACTTTTTAGCTTGTGAAAAGGAGAGGGATTTATTCAAGCTGATCCTCAAGAA
GGAGGACGAGCTGGGCGATCGTTCCATCATGTTCACCGTCCAAAACGAGGAT
AGCGGCACAACCAACACAGTCGCTGCCTATAACCTCACTTGGAAGAGCACCA
ACTTCAAAACCATCCTCGAATGGGAACCCAAACCCGTTAACCAAGTTTACAC
CGTGCAGATCAGCACCAAGTCCGGCGACTGGAAGTCCAAATGTTTCTATACC
ACCGACACCGAGTGCGATCTCACCGATGAGATCGTGAAAGATGTGAAACAGA
CCTACCTCGCCCGGGTGTTTAGCTACCCCGCCGGCAATGTGGAGAGCACTGG
TTCCGCTGGCGAGCCTTTATACGAGAACAGCCCCGAATTTACCCCTTACCTCG
AGACCAATTTAGGACAGCCCACCATCCAAAGCTTTGAGCAAGTTGGCACAAA
GGTGAATGTGACAGTGGAGGACGAGCGGACTTTAGTGCGGCGGAACAACAC
CTTTCTCAGCCTCCGGGATGTGTTCGGCAAAGATTTAATCTACACACTGTATT

ACTGGAAGTCCTCTTCCTCCGGCAAGAAGACAGCTAAAACCAACACAAACGA
GTTTTTAATCGACGTGGATAAAGGCGAAAACTACTGTTTCAGCGTGCAAGCT
GTGATCCCCTCCCGGACCGTGAATAGGAAAAGCACCGATAGCCCCGTTGAGT
GCATGGGCCAAGAAAAGGGCGAGTTCCGGGAGAACTGGGTGAACGTCATCA
GCGATTTAAAGAAGATCGAAGATTTAATTCAGTCCATGCATATCGACGCCAC
TTTATACACAGAATCCGACGTGCACCCCTCTTGTAAGGTGACCGCCATGAAAT
GTTTTTTACTGGAGCTGCAAGTTATCTCTTTAGAGAGCGGAGACGCTAGCATC
CACGACACCGTGGAGAATTTAATCATTTTAGCCAATAACTCTTTATCCAGCAA
CGGCAACGTGACAGAGTCCGGCTGCAAGGAGTGCGAAGAGCTGGAGGAGAA
GAACATCAAGGAGTTTCTGCAATCCTTTGTGCACATTGTCCAGATGTTCATCA
ATACCTCC (SEQ ID NO: 73).

In some embodiments, the second chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

IWELKKDVYVVELDWYPDAPGEMVVLTCDTPEEDGITWTLDQSSEVLGSGKTLT
IQVKEFGDAGQYTCHKGGEVLSHSLLLLHKKEDGIWSTDILKDQKEPKNKTFLR
CEAKNYSGRFTCWWLTTISTDLTFSVKSSRGSSDPQGVTCGAATLSAERVRGDN
KEYEYSVECQEDSACPAAEESLPIEVMVDAVHKLKYENYTSSFFIRDIIKPDPPKN
LQLKPLKNSRQVEVSWEYPDTWSTPHSYFSLTFCVQVQGKSKREKKDRVFTDKT
SATVICRKNASISVRAQDRYYSSSWSEWASVPCSGGGGSGGGGSGGGGSRNLPV
ATPDPGMFPCLHHSQNLLRAVSNMLQKARQTLEFYPCTSEEIDHEDITKDKTSTV
EACLPLELTKNESCLNSRETSFITNGSCLASRKTSFMMALCLSSIYEDLKMYQVEF
KTMNAKLLMDPKRQIFLDQNMLAVIDELMQALNFNSETVPQKSSLEEPDFYKTK
IKLCILLHAFRIRAVTIDRVMSYLNASITCPPPMSVEHADIWVKSYSLYSRERYICN
SGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR (SEQ ID NO: 74).

In some embodiments, a second chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATTTGGGAACTGAAGAAGGACGTCTACGTGGTCGAACTGGACTGGTATCCCG
ATGCTCCCGGCGAAATGGTGGTGCTCACTTGTGACACCCCCGAAGAAGACGG
CATCACTTGGACCCTCGATCAGAGCAGCGAGGTGCTGGGCTCCGGAAAGACC
CTCACAATCCAAGTTAAGGAGTTCGGAGACGCTGGCCAATACACATGCCACA
AGGGAGGCGAGGTGCTCAGCCATTCCTTATTATTATTACACAAGAAGGAAGA
CGGAATCTGGTCCACCGACATTTTAAAAGATCAGAAGGAGCCCAAGAATAAG

ACCTTTTTAAGGTGTGAGGCCAAAAACTACAGCGGTCGTTTCACTTGTTGGTG
GCTGACCACCATTTCCACCGATTTAACCTTCTCCGTGAAAAGCAGCCGGGGA
AGCTCCGACCCTCAAGGTGTGACATGTGGAGCCGCTACCCTCAGCGCTGAGA
GGGTTCGTGGCGATAACAAGGAATACGAGTACAGCGTGGAGTGCCAAGAAG
ATAGCGCTTGTCCCGCTGCCGAAGAATCTTTACCCATTGAGGTGATGGTGGAC
GCCGTGCACAAACTCAAGTACGAGAACTACACCTCCTCCTTCTTTATCCGGGA
CATCATTAAGCCCGATCCTCCTAAGAATTTACAGCTGAAGCCTCTCAAAAATA
GCCGGCAAGTTGAGGTCTCTTGGGAATATCCCGACACTTGGAGCACACCCCA
CAGCTACTTCTCTTTAACCTTTTGTGTGCAAGTTCAAGGTAAAAGCAAGCGGG
AGAAGAAAGACCGGGTGTTTACCGACAAAACCAGCGCCACCGTCATCTGTCG
GAAGAACGCCTCCATCAGCGTGAGGGCTCAAGATCGTTATTACTCCAGCAGC
TGGTCCGAGTGGGCCAGCGTGCCTTGTTCCGGCGGTGGAGGATCCGGAGGAG
GTGGCTCCGGCGGCGGAGGATCTCGTAACCTCCCCGTGGCTACCCCCGATCC
CGGAATGTTCCCTTGTTTACACCACAGCCAGAATTTACTGAGGGCCGTGAGC
AACATGCTGCAGAAAGCTAGGCAGACTTTAGAATTTTACCCTTGCACCAGCG
AGGAGATCGACCATGAAGATATCACCAAGGACAAGACATCCACCGTGGAGG
CTTGTTTACCTCTGGAGCTGACAAAGAACGAGTCTTGTCTCAACTCTCGTGAA
ACCAGCTTCATCACAAATGGCTCTTGTTTAGCTTCCCGGAAGACCTCCTTTAT
GATGGCTTTATGCCTCAGCTCCATCTACGAGGATTTAAAGATGTACCAAGTGG
AGTTCAAGACCATGAACGCCAAGCTGCTCATGGACCCTAAACGGCAGATCTT
TTTAGACCAGAACATGCTGGCTGTGATTGATGAGCTGATGCAAGCTTTAAACT
TCAACTCCGAGACCGTCCCTCAGAAGTCCTCCCTCGAGGAGCCCGATTTTTAC
AAGACAAAGATCAAACTGTGCATTTTACTCCACGCCTTTAGGATCCGGGCCG
TGACCATTGACCGGGTCATGAGCTATTTAAACGCCAGCATTACATGCCCCCCT
CCCATGAGCGTGGAGCACGCCGACATCTGGGTGAAGAGCTATAGCCTCTACA
GCCGGGAGAGGTATATCTGTAACAGCGGCTTCAAGAGGAAGGCCGGCACCA
GCAGCCTCACCGAGTGCGTGCTGAATAAGGCTACCAACGTGGCTCACTGGAC
AACACCCTCTTTAAAGTGCATCCGG (SEQ ID NO: 75).

In some embodiments, a second chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

MKWVTFISLLFLFSSAYSIWELKKDVYVVELDWYPDAPGEMVVLTCDTPEEDGI
TWTLDQSSEVLGSGKTLTIQVKEFGDAGQYTCHKGGEVLSHSLLLLHKKEDGIW
STDILKDQKEPKNKTFLRCEAKNYSGRFTCWWLTTISTDLTFSVKSSRGSSDPQG
VTCGAATLSAERVRGDNKEYEYSVECQEDSACPAAEESLPIEVMVDAVHKLKYE
NYTSSFFIRDIIKPDPPKNLQLKPLKNSRQVEVSWEYPDTWSTPHSYFSLTFCVQV
QGKSKREKKDRVFTDKTSATVICRKNASISVRAQDRYYSSSWSEWASVPCSGGG
GSGGGGSGGGGSRNLPVATPDPGMFPCLHHSQNLLRAVSNMLQKARQTLEFYP
CTSEEIDHEDITKDKTSTVEACLPLELTKNESCLNSRETSFITNGSCLASRKTSFMM

ALCLSSIYEDLKMYQVEFKTMNAKLLMDPKRQIFLDQNMLAVIDELMQALNFNS
ETVPQKSSLEEPDFYKTKIKLCILLHAFRIRAVTIDRVMSYLNASITCPPPMSVEHA
DIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR
(SEQ ID NO: 76).

In some embodiments, a second chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATGAAATGGGTGACCTTTATTTCTTTACTGTTCCTCTTTAGCAGCGCCTACTCC
ATTTGGGAACTGAAGAAGGACGTCTACGTGGTCGAACTGGACTGGTATCCCG
ATGCTCCCGGCGAAATGGTGGTGCTCACTTGTGACACCCCCGAAGAAGACGG
CATCACTTGGACCCTCGATCAGAGCAGCGAGGTGCTGGGCTCCGGAAAGACC
CTCACAATCCAAGTTAAGGAGTTCGGAGACGCTGGCCAATACACATGCCACA
AGGGAGGCGAGGTGCTCAGCCATTCCTTATTATTATTACACAAGAAGGAAGA
CGGAATCTGGTCCACCGACATTTTAAAAGATCAGAAGGAGCCCAAGAATAAG
ACCTTTTTAAGGTGTGAGGCCAAAAACTACAGCGGTCGTTTCACTTGTTGGTG
GCTGACCACCATTTCCACCGATTTAACCTTCTCCGTGAAAAGCAGCCGGGGA
AGCTCCGACCCTCAAGGTGTGACATGTGGAGCCGCTACCCTCAGCGCTGAGA
GGGTTCGTGGCGATAACAAGGAATACGAGTACAGCGTGGAGTGCCAAGAAG
ATAGCGCTTGTCCCGCTGCCGAAGAATCTTTACCCATTGAGGTGATGGTGGAC
GCCGTGCACAAACTCAAGTACGAGAACTACACCTCCTCCTTCTTTATCCGGGA
CATCATTAAGCCCGATCCTCCTAAGAATTTACAGCTGAAGCCTCTCAAAAATA
GCCGGCAAGTTGAGGTCTCTTGGGAATATCCCGACACTTGGAGCACACCCCA
CAGCTACTTCTCTTTAACCTTTTGTGTGCAAGTTCAAGGTAAAAGCAAGCGGG
AGAAGAAAGACCGGGTGTTTACCGACAAAACCAGCGCCACCGTCATCTGTCG
GAAGAACGCCTCCATCAGCGTGAGGGCTCAAGATCGTTATTACTCCAGCAGC
TGGTCCGAGTGGGCCAGCGTGCCTTGTTCCGGCGGTGGAGGATCCGGAGGAG
GTGGCTCCGGCGGCGGAGGATCTCGTAACCTCCCCGTGGCTACCCCCGATCC
CGGAATGTTCCCTTGTTTACACCACAGCCAGAATTTACTGAGGGCCGTGAGC
AACATGCTGCAGAAAGCTAGGCAGACTTTAGAATTTTACCCTTGCACCAGCG
AGGAGATCGACCATGAAGATATCACCAAGGACAAGACATCCACCGTGGAGG
CTTGTTTACCTCTGGAGCTGACAAAGAACGAGTCTTGTCTCAACTCTCGTGAA
ACCAGCTTCATCACAAATGGCTCTTGTTTAGCTTCCCGGAAGACCTCCTTTAT
GATGGCTTTATGCCTCAGCTCCATCTACGAGGATTTAAAGATGTACCAAGTGG
AGTTCAAGACCATGAACGCCAAGCTGCTCATGGACCCTAAACGGCAGATCTT
TTTAGACCAGAACATGCTGGCTGTGATTGATGAGCTGATGCAAGCTTTAAACT
TCAACTCCGAGACCGTCCCTCAGAAGTCCTCCCTCGAGGAGCCCGATTTTTAC
AAGACAAAGATCAAACTGTGCATTTTACTCCACGCCTTTAGGATCCGGGCCG
TGACCATTGACCGGGTCATGAGCTATTTAAACGCCAGCATTACATGCCCCCCT
CCCATGAGCGTGGAGCACGCCGACATCTGGGTGAAGAGCTATAGCCTCTACA

GCCGGGAGAGGTATATCTGTAACAGCGGCTTCAAGAGGAAGGCCGGCACCA
GCAGCCTCACCGAGTGCGTGCTGAATAAGGCTACCAACGTGGCTCACTGGAC
AACACCCTCTTTAAAGTGCATCCGG (SEQ ID NO: 77).

Exemplary Multi-Chain Chimeric Polypeptides- Type B

In some embodiments of any of the multi-chain chimeric polypeptides described herein, the first target-binding domain and the second targeting-binding domain each independently bind specifically to a receptor of IL-21 or to TGF-β. In some examples of these multi-chain chimeric polypeptides, the first target-binding domain and the soluble tissue factor domain directly abut each other in the first chimeric polypeptide. In some examples of these multi-chain chimeric polypeptides, the first chimeric polypeptide further comprises a linker sequence (e.g., any of the exemplary linkers described herein) between the first target-binding domain and the soluble tissue factor domain in the first chimeric polypeptide.

In some embodiments of these multi-chain chimeric polypeptides, 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 embodiments of these multi-chain chimeric polypeptides, the first chimeric polypeptide further includes a linker sequence (e.g., any of the exemplary linkers described herein) between the soluble tissue factor domain and the first domain of the pair of affinity domains in the first chimeric polypeptide.

In some embodiments of these multi-chain chimeric polypeptides, 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 embodiments of these multi-chain chimeric polypeptides, the second chimeric polypeptide further includes a linker sequence (e.g., any of the exemplary linkers described herein) between the second domain of the pair of affinity domains and the second target-binding domain in the second chimeric polypeptide.

In some embodiments of these multi-chain chimeric polypeptides, the soluble tissue factor domain can be any of the exemplary soluble tissue factor domains described herein. In some embodiments of these multi-chain chimeric polypeptides, the pair of affinity domains can be any of the exemplary pairs of affinity domains described herein.

In some embodiments of these multi-chain chimeric polypeptides, one or both of the first target-binding domain and the second target-binding domain is a soluble IL-21 (e.g., a soluble human IL-21 polypeptide) or a soluble TGF-β receptor (e.g., a soluble TGFRβRII receptor). In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain and the second target-binding domain are each independently a soluble IL-21 or a soluble TGF-β receptor (e.g., a soluble TGFRβRII receptor). In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain and the second target-binding domain both bind specifically to a receptor of IL-21 or to TGF-β. In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain and the second target-binding domain bind specifically to the same epitope. In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain and the second target-binding domain include the same amino acid sequence.

In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain binds specifically to a receptor for IL-21, and the second target-binding domain binds specifically to TGF-β. In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain binds specifically to TGF-β, and the second target-binding domain bind specifically to a receptor for IL-21.

In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain includes a soluble IL-21 (e.g., a soluble human IL-21). In some embodiments of these multi-chain chimeric polypeptides, the soluble human IL-21 includes a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

QGQDRHMIRMRQLIDIVDQLKNYVNDLVPEFLPAPEDVETNCEWSAFSCFQKAQ LKSANTGNNERIINVSIKKLKRKPPSTNAGRRQKHRLTCPSCDSYEKKPPKEFLER FKSLLQKMIHQHLSSRTHGSEDS (SEQ ID NO: 78).

In some embodiments of these multi-chain chimeric polypeptides, the soluble human IL-21 is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least

90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

CAGGGCCAGGACAGGCACATGATCCGGATGAGGCAGCTCATCGACATCGTCG
ACCAGCTGAAGAACTACGTGAACGACCTGGTGCCCGAGTTTCTGCCTGCCCC
CGAGGACGTGGAGACCAACTGCGAGTGGTCCGCCTTCTCCTGCTTTCAGAAG
GCCCAGCTGAAGTCCGCCAACACCGGCAACAACGAGCGGATCATCAACGTG
AGCATCAAGAAGCTGAAGCGGAAGCCTCCCTCCACAAACGCCGGCAGGAGG
CAGAAGCACAGGCTGACCTGCCCCAGCTGTGACTCCTACGAGAAGAAGCCCC
CCAAGGAGTTCCTGGAGAGGTTCAAGTCCCTGCTGCAGAAGATGATCCATCA
GCACCTGTCCTCCAGGACCCACGGCTCCGAGGACTCC (SEQ ID NO: 79).

In some embodiments of these multi-chain chimeric polypeptides, the second target-binding domain includes a soluble TGF-β receptor (e.g., a soluble TGFRβRII receptor (e.g., a soluble human TGFRβRII receptor)). In some embodiments of these multi-chain chimeric polypeptides, the soluble human TGFRβRII includes a first sequence of soluble human TGFRβRII and a second sequence of soluble human TGFRβRII. In some embodiments of these multi-chain chimeric polypeptides, the soluble human TGFRβRII includes a linker disposed between the first sequence of soluble human TGFRβRII and the second sequence of soluble human TGFRβRII. In some examples of these multi-chain chimeric polypeptides, the linker includes the sequence GGGGSGGGGSGGGGS (SEQ ID NO: 7).

In some embodiments of these multi-chain chimeric polypeptides, the first sequence of soluble human TGFRβRII receptor comprises a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

IPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICE
KPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGET
FFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 80).

In some embodiments of these multi-chain chimeric polypeptides, the second sequence of soluble human TGFRβRII receptor comprises a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

IPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICE KPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGET FFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 81).

In some embodiments of these multi-chain chimeric polypeptides, the first sequence of soluble human TGFRβRII receptor is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATCCCCCCCCATGTGCAAAAGAGCGTGAACAACGATATGATCGTGACCGACA ACAACGGCGCCGTGAAGTTTCCCCAGCTCTGCAAGTTCTGCGATGTCAGGTTC AGCACCTGCGATAATCAGAAGTCCTGCATGTCCAACTGCACGATCACCTCCA TCTGCGAGAAGCCCCAAGAAGTGTGCGTGGCCGTGTGGCGGAAAAATGACG AGAACATCACCCTGGAGACCGTGTGTCACGACCCCAAGCTCCCTTATCACGA CTTCATTCTGGAGGACGCTGCCTCCCCCAAATGCATCATGAAGGAGAAGAAG AAGCCCGGAGAGACCTTCTTTATGTGTTCCTGTAGCAGCGACGAGTGTAACG ACAACATCATCTTCAGCGAAGAGTACAACACCAGCAACCCTGAT (SEQ ID NO: 82).

In some embodiments of these multi-chain chimeric polypeptides, the second sequence of soluble human TGFRβRII receptor is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATTCCTCCCCACGTGCAGAAGAGCGTGAATAATGACATGATCGTGACCGATA ACAATGGCGCCGTGAAATTTCCCCAGCTGTGCAAATTCTGCGATGTGAGGTTT TCCACCTGCGACAACCAGAAGTCCTGTATGAGCAACTGCACAATCACCTCCA TCTGTGAGAAGCCTCAGGAGGTGTGCGTGGCTGTCTGGCGGAAGAATGACGA GAATATCACCCTGGAAACCGTCTGCCACGATCCCAAGCTGCCCTACCACGAT TTCATCCTGGAAGACGCCGCCAGCCCTAAGTGCATCATGAAAGAGAAAAAGA AGCCTGGCGAGACCTTTTTCATGTGCTCCTGCAGCAGCGACGAATGCAACGA CAATATCATCTTTAGCGAGGAATACAATACCAGCAACCCCGAC (SEQ ID NO: 83).

In some embodiments of these multi-chain chimeric polypeptides, the soluble human TGFRβRII receptor is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical,

at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATCCCCCCCCATGTGCAAAAGAGCGTGAACAACGATATGATCGTGACCGACA
ACAACGGCGCCGTGAAGTTTCCCCAGCTCTGCAAGTTCTGCGATGTCAGGTTC
AGCACCTGCGATAATCAGAAGTCCTGCATGTCCAACTGCACGATCACCTCCA
TCTGCGAGAAGCCCCAAGAAGTGTGCGTGGCCGTGTGGCGGAAAAATGACG
AGAACATCACCCTGGAGACCGTGTGTCACGACCCCAAGCTCCCTTATCACGA
CTTCATTCTGGAGGACGCTGCCTCCCCCAAATGCATCATGAAGGAGAAGAAG
AAGCCCGGAGAGACCTTCTTTATGTGTTCCTGTAGCAGCGACGAGTGTAACG
ACAACATCATCTTCAGCGAAGAGTACAACACCAGCAACCCTGATGGAGGTGG
CGGATCCGGAGGTGGAGGTTCTGGTGGAGGTGGGAGTATTCCTCCCCACGTG
CAGAAGAGCGTGAATAATGACATGATCGTGACCGATAACAATGGCGCCGTGA
AATTTCCCCAGCTGTGCAAATTCTGCGATGTGAGGTTTTCCACCTGCGACAAC
CAGAAGTCCTGTATGAGCAACTGCACAATCACCTCCATCTGTGAGAAGCCTC
AGGAGGTGTGCGTGGCTGTCTGGCGGAAGAATGACGAGAATATCACCCTGGA
AACCGTCTGCCACGATCCCAAGCTGCCCTACCACGATTTCATCCTGGAAGAC
GCCGCCAGCCCTAAGTGCATCATGAAAGAGAAAAAGAAGCCTGGCGAGACC
TTTTTCATGTGCTCCTGCAGCAGCGACGAATGCAACGACAATATCATCTTTAG
CGAGGAATACAATACCAGCAACCCCGAC (SEQ ID NO: 84).

In some embodiments of these multi-chain chimeric polypeptides, the human TGFβRII receptor includes a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

IPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICE
KPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGET
FFMCSCSSDECNDNIIFSEEYNTSNPDGGGGSGGGGSGGGGSIPPHVQKSVNNDM
IVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRK
NDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECND
NIIFSEEYNTSNPD (SEQ ID NO: 85).

In some embodiments, the first chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

QGQDRHMIRMRQLIDIVDQLKNYVNDLVPEFLPAPEDVETNCEWSAFSCFQKAQ
LKSANTGNNERIINVSIKKLKRKPPSTNAGRRQKHRLTCPSCDSYEKKPPKEFLER

FKSLLQKMIHQHLSSRTHGSEDSSGTTNTVAAYNLTWKSTNFKTILEWEPKPVNQ
VYTVQISTKSGDWKSKCFYTTDTECDLTDEIVKDVKQTYLARVFSYPAGNVEST
GSAGEPLYENSPEFTPYLETNLGQPTIQSFEQVGTKVNVTVEDERTLVRRNNTFLS
LRDVFGKDLIYTLYYWKSSSSGKKTAKTNTNEFLIDVDKGENYCFSVQAVIPSRT
VNRKSTDSPVECMGQEKGEFRENWVNVISDLKKIEDLIQSMHIDATLYTESDVHP
SCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKECE
ELEEKNIKEFLQSFVHIVQMFINTS (SEQ ID NO: 86).

In some embodiments, a first chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

CAGGGCCAGGACAGGCACATGATCCGGATGAGGCAGCTCATCGACATCGTCG
ACCAGCTGAAGAACTACGTGAACGACCTGGTGCCCGAGTTTCTGCCTGCCCC
CGAGGACGTGGAGACCAACTGCGAGTGGTCCGCCTTCTCCTGCTTTCAGAAG
GCCCAGCTGAAGTCCGCCAACACCGGCAACAACGAGCGGATCATCAACGTG
AGCATCAAGAAGCTGAAGCGGAAGCCTCCCTCCACAAACGCCGGCAGGAGG
CAGAAGCACAGGCTGACCTGCCCCAGCTGTGACTCCTACGAGAAGAAGCCCC
CCAAGGAGTTCCTGGAGAGGTTCAAGTCCCTGCTGCAGAAGATGATCCATCA
GCACCTGTCCTCCAGGACCCACGGCTCCGAGGACTCCTCCGGCACCACCAAT
ACCGTGGCCGCTTATAACCTCACATGGAAGAGCACCAACTTCAAGACAATTC
TGGAATGGGAACCCAAGCCCGTCAATCAAGTTTACACCGTGCAGATCTCCAC
CAAATCCGGAGACTGGAAGAGCAAGTGCTTCTACACAACAGACACCGAGTGT
GATTTAACCGACGAAATCGTCAAGGACGTCAAGCAAACCTATCTGGCTCGGG
TCTTTTCCTACCCCGCTGGCAATGTCGAGTCCACCGGCTCCGCTGGCGAGCCT
CTCTACGAGAATTCCCCCGAATTCACCCCTTATTTAGAGACCAATTTAGGCCA
GCCTACCATCCAGAGCTTCGAGCAAGTTGGCACCAAGGTGAACGTCACCGTC
GAGGATGAAAGGACTTTAGTGCGGCGGAATAACACATTTTTATCCCTCCGGG
ATGTGTTCGGCAAAGACCTCATCTACACACTGTACTATTGGAAGTCCAGCTCC
TCCGGCAAAAAGACCGCTAAGACCAACACCAACGAGTTTTTAATTGACGTGG
ACAAAGGCGAGAACTACTGCTTCAGCGTGCAAGCCGTGATCCCTTCTCGTAC
CGTCAACCGGAAGAGCACAGATTCCCCCGTTGAGTGCATGGGCCAAGAAAA
GGGCGAGTTCCGGGAGAACTGGGTGAACGTCATCAGCGATTTAAAGAAGATC
GAAGATTTAATTCAGTCCATGCATATCGACGCCACTTTATACACAGAATCCGA
CGTGCACCCCTCTTGTAAGGTGACCGCCATGAAATGTTTTTTACTGGAGCTGC
AAGTTATCTCTTTAGAGAGCGGAGACGCTAGCATCCACGACACCGTGGAGAA
TTTAATCATTTTAGCCAATAACTCTTTATCCAGCAACGGCAACGTGACAGAGT
CCGGCTGCAAGGAGTGCGAAGAGCTGGAGGAGAAGAACATCAAGGAGTTTC
TGCAATCCTTTGTGCACATTGTCCAGATGTTCATCAATACCTCC (SEQ ID NO: 87).

In some embodiments, a first chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

MKWVTFISLLFLFSSAYSQGQDRHMIRMRQLIDIVDQLKNYVNDLVPEFLPAPED
VETNCEWSAFSCFQKAQLKSANTGNNERIINVSIKKLKRKPPSTNAGRRQKHRLT
CPSCDSYEKKPPKEFLERFKSLLQKMIHQHLSSRTHGSEDSSGTTNTVAAYNLTW
KSTNFKTILEWEPKPVNQVYTVQISTKSGDWKSKCFYTTDTECDLTDEIVKDVKQ
TYLARVFSYPAGNVESTGSAGEPLYENSPEFTPYLETNLGQPTIQSFEQVGTKVN
VTVEDERTLVRRNNTFLSLRDVFGKDLIYTLYYWKSSSSGKKTAKTNTNEFLIDV
DKGENYCFSVQAVIPSRTVNRKSTDSPVECMGQEKGEFRENWVNVISDLKKIED
LIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILAN
NSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS (SEQ ID NO: 88).

In some embodiments, a first chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATGAAGTGGGTGACCTTCATCAGCCTGCTGTTCCTGTTCTCCAGCGCCTACTC
CCAGGGCCAGGACAGGCACATGATCCGGATGAGGCAGCTCATCGACATCGTC
GACCAGCTGAAGAACTACGTGAACGACCTGGTGCCCGAGTTTCTGCCTGCCC
CCGAGGACGTGGAGACCAACTGCGAGTGGTCCGCCTTCTCCTGCTTTCAGAA
GGCCCAGCTGAAGTCCGCCAACACCGGCAACAACGAGCGGATCATCAACGT
GAGCATCAAGAAGCTGAAGCGGAAGCCTCCCTCCACAAACGCCGGCAGGAG
GCAGAAGCACAGGCTGACCTGCCCCAGCTGTGACTCCTACGAGAAGAAGCCC
CCCAAGGAGTTCCTGGAGAGGTTCAAGTCCCTGCTGCAGAAGATGATCCATC
AGCACCTGTCCTCCAGGACCCACGGCTCCGAGGACTCCTCCGGCACCACCAA
TACCGTGGCCGCTTATAACCTCACATGGAAGAGCACCAACTTCAAGACAATT
CTGGAATGGGAACCCAAGCCCGTCAATCAAGTTTACACCGTGCAGATCTCCA
CCAAATCCGGAGACTGGAAGAGCAAGTGCTTCTACACAACAGACACCGAGT
GTGATTTAACCGACGAAATCGTCAAGGACGTCAAGCAAACCTATCTGGCTCG
GGTCTTTTCCTACCCCGCTGGCAATGTCGAGTCCACCGGCTCCGCTGGCGAGC
CTCTCTACGAGAATTCCCCCGAATTCACCCCTTATTTAGAGACCAATTTAGGC
CAGCCTACCATCCAGAGCTTCGAGCAAGTTGGCACCAAGGTGAACGTCACCG
TCGAGGATGAAAGGACTTTAGTGCGGCGGAATAACACATTTTTATCCCTCCG
GGATGTGTTCGGCAAAGACCTCATCTACACACTGTACTATTGGAAGTCCAGCT
CCTCCGGCAAAAAGACCGCTAAGACCAACACCAACGAGTTTTTAATTGACGT
GGACAAAGGCGAGAACTACTGCTTCAGCGTGCAAGCCGTGATCCCTTCTCGT

ACCGTCAACCGGAAGAGCACAGATTCCCCCGTTGAGTGCATGGGCCAAGAAA
AGGGCGAGTTCCGGGAGAACTGGGTGAACGTCATCAGCGATTTAAAGAAGAT
CGAAGATTTAATTCAGTCCATGCATATCGACGCCACTTTATACACAGAATCCG
ACGTGCACCCCTCTTGTAAGGTGACCGCCATGAAATGTTTTTTACTGGAGCTG
CAAGTTATCTCTTTAGAGAGCGGAGACGCTAGCATCCACGACACCGTGGAGA
ATTTAATCATTTTAGCCAATAACTCTTTATCCAGCAACGGCAACGTGACAGAG
TCCGGCTGCAAGGAGTGCGAAGAGCTGGAGGAGAAGAACATCAAGGAGTTT
CTGCAATCCTTTGTGCACATTGTCCAGATGTTCATCAATACCTCC (SEQ ID NO: 89).

In some embodiments, the second chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

IPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICE
KPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGET
FFMCSCSSDECNDNIIFSEEYNTSNPDGGGGSGGGGSGGGGSIPPHVQKSVNNDM
IVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRK
NDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECND
NIIFSEEYNTSNPDITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLT
ECVLNKATNVAHWTTPSLKCIR (SEQ ID NO: 90).

In some embodiments, a second chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATCCCCCCCCATGTGCAAAAGAGCGTGAACAACGATATGATCGTGACCGACA
ACAACGGCGCCGTGAAGTTTCCCCAGCTCTGCAAGTTCTGCGATGTCAGGTTC
AGCACCTGCGATAATCAGAAGTCCTGCATGTCCAACTGCACGATCACCTCCA
TCTGCGAGAAGCCCCAAGAAGTGTGCGTGGCCGTGTGGCGGAAAAATGACG
AGAACATCACCCTGGAGACCGTGTGTCACGACCCCAAGCTCCCTTATCACGA
CTTCATTCTGGAGGACGCTGCCTCCCCCAAATGCATCATGAAGGAGAAGAAG
AAGCCCGGAGAGACCTTCTTTATGTGTTCCTGTAGCAGCGACGAGTGTAACG
ACAACATCATCTTCAGCGAAGAGTACAACACCAGCAACCCTGATGGAGGTGG
CGGATCCGGAGGTGGAGGTTCTGGTGGAGGTGGGAGTATTCCTCCCCACGTG
CAGAAGAGCGTGAATAATGACATGATCGTGACCGATAACAATGGCGCCGTGA
AATTTCCCCAGCTGTGCAAATTCTGCGATGTGAGGTTTTCCACCTGCGACAAC
CAGAAGTCCTGTATGAGCAACTGCACAATCACCTCCATCTGTGAGAAGCCTC

AGGAGGTGTGCGTGGCTGTCTGGCGGAAGAATGACGAGAATATCACCCTGGA
AACCGTCTGCCACGATCCCAAGCTGCCCTACCACGATTTCATCCTGGAAGAC
GCCGCCAGCCCTAAGTGCATCATGAAAGAGAAAAAGAAGCCTGGCGAGACC
TTTTTCATGTGCTCCTGCAGCAGCGACGAATGCAACGACAATATCATCTTTAG
CGAGGAATACAATACCAGCAACCCCGACATCACGTGTCCTCCTCCTATGTCC
GTGGAACACGCAGACATCTGGGTCAAGAGCTACAGCTTGTACTCCAGGGAGC
GGTACATTTGTAACTCTGGTTTCAAGCGTAAAGCCGGCACGTCCAGCCTGAC
GGAGTGCGTGTTGAACAAGGCCACGAATGTCGCCCACTGGACAACCCCCAGT
CTCAAATGTATTAGA (SEQ ID NO: 91).

In some embodiments, a second chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

MKWVTFISLLFLFSSAYSIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFST
CDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILED
AASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPDGGGGSGGGGSG
GGGSIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSI
TSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKK
PGETFFMCSCSSDECNDNIIFSEEYNTSNPDITCPPPMSVEHADIWVKSYSLYSRER
YICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR (SEQ ID NO: 92).

In some embodiments, a second chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATGAAGTGGGTGACCTTCATCAGCCTGCTGTTCCTGTTCTCCAGCGCCTACTC
CATCCCCCCCCCATGTGCAAAAGAGCGTGAACAACGATATGATCGTGACCGAC
AACAACGGCGCCGTGAAGTTTCCCCAGCTCTGCAAGTTCTGCGATGTCAGGTT
CAGCACCTGCGATAATCAGAAGTCCTGCATGTCCAACTGCACGATCACCTCC
ATCTGCGAGAAGCCCCAAGAAGTGTGCGTGGCCGTGTGGCGGAAAAATGAC
GAGAACATCACCCTGGAGACCGTGTGTCACGACCCCAAGCTCCCTTATCACG
ACTTCATTCTGGAGGACGCTGCCTCCCCCAAATGCATCATGAAGGAGAAGAA
GAAGCCCGGAGAGACCTTCTTTATGTGTTCCTGTAGCAGCGACGAGTGTAAC
GACAACATCATCTTCAGCGAAGAGTACAACACCAGCAACCCTGATGGAGGTG
GCGGATCCGGAGGTGGAGGTTCTGGTGGAGGTGGGAGTATTCCTCCCCACGT
GCAGAAGAGCGTGAATAATGACATGATCGTGACCGATAACAATGGCGCCGTG
AAATTTCCCCAGCTGTGCAAATTCTGCGATGTGAGGTTTTCCACCTGCGACAA
CCAGAAGTCCTGTATGAGCAACTGCACAATCACCTCCATCTGTGAGAAGCCT

CAGGAGGTGTGCGTGGCTGTCTGGCGGAAGAATGACGAGAATATCACCCTGG
AAACCGTCTGCCACGATCCCAAGCTGCCCTACCACGATTTCATCCTGGAAGA
CGCCGCCAGCCCTAAGTGCATCATGAAAGAGAAAAAGAAGCCTGGCGAGAC
CTTTTTCATGTGCTCCTGCAGCAGCGACGAATGCAACGACAATATCATCTTTA
GCGAGGAATACAATACCAGCAACCCCGACATCACGTGTCCTCCTCCTATGTC
CGTGGAACACGCAGACATCTGGGTCAAGAGCTACAGCTTGTACTCCAGGGAG
CGGTACATTTGTAACTCTGGTTTCAAGCGTAAAGCCGGCACGTCCAGCCTGAC
GGAGTGCGTGTTGAACAAGGCCACGAATGTCGCCCACTGGACAACCCCCAGT
CTCAAATGTATTAGA (SEQ ID NO: 93).

Exemplary Multi-Chain Chimeric Polypeptides- Type C

In some embodiments of any of the multi-chain chimeric polypeptides described herein, the first target-binding domain and the second targeting-binding domain each independently bind specifically to a receptor of IL-7 or a receptor of IL-21. In some examples of these multi-chain chimeric polypeptides, the first target-binding domain and the soluble tissue factor domain directly abut each other in the first chimeric polypeptide. In some examples of these multi-chain chimeric polypeptides, the first chimeric polypeptide further comprises a linker sequence (e.g., any of the exemplary linkers described herein) between the first target-binding domain and the soluble tissue factor domain in the first chimeric polypeptide.

In some embodiments of these multi-chain chimeric polypeptides, 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 embodiments of these multi-chain chimeric polypeptides, the first chimeric polypeptide further includes a linker sequence (e.g., any of the exemplary linkers described herein) between the soluble tissue factor domain and the first domain of the pair of affinity domains in the first chimeric polypeptide.

In some embodiments of these multi-chain chimeric polypeptides, 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 embodiments of these multi-chain chimeric polypeptides, the second chimeric polypeptide further includes a linker sequence (e.g., any of the exemplary linkers described herein) between the second domain of the pair of affinity domains and the second target-binding domain in the second chimeric polypeptide.

In some embodiments of these multi-chain chimeric polypeptides, the soluble tissue factor domain can be any of the exemplary soluble tissue factor domains described herein. In some embodiments of these multi-chain chimeric polypeptides, the pair of affinity domains can be any of the exemplary pairs of affinity domains described herein.

In some embodiments of these multi-chain chimeric polypeptides, one or both of the first target-binding domain and the second target-binding domain is a soluble IL-21 (e.g., a soluble human IL-21 polypeptide) or a soluble IL-7 (e.g., a soluble human IL-7 polypeptide). In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain and the second target-binding domain are each independently a soluble IL-21 or a soluble IL-7. In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain and the second target-binding domain both bind specifically to a receptor of IL-21 or a receptor of IL-7. In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain and the second target-binding domain bind specifically to the same epitope. In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain and the second target-binding domain include the same amino acid sequence.

In some embodiments of these multi-chain chimeric polypeptides, 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. In some embodiments of these multi-chain chimeric polypeptides, 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.

In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain includes a soluble IL-21 (e.g., a soluble human IL-21).

In some embodiments of these multi-chain chimeric polypeptides, the soluble human IL-21 includes a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

QGQDRHMIRMRQLIDIVDQLKNYVNDLVPEFLPAPEDVETNCEWSAFSCFQKAQ LKSANTGNNERIINVSIKKLKRKPPSTNAGRRQKHRLTCPSCDSYEKKPPKEFLER FKSLLQKMIHQHLSSRTHGSEDS (SEQ ID NO: 78).

In some embodiments of these multi-chain chimeric polypeptides, the soluble human IL-21 is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

CAAGGTCAAGATCGCCACATGATTAGAATGCGTCAACTTATAGATATTGTTG
ATCAGCTGAAAAATTATGTGAATGACTTGGTCCCTGAATTTCTGCCAGCTCCA
GAAGATGTAGAGACAAACTGTGAGTGGTCAGCTTTTTCCTGTTTTCAGAAGG
CCCAACTAAAGTCAGCAAATACAGGAAACAATGAAAGGATAATCAATGTATC
AATTAAAAAGCTGAAGAGGAAACCACCTTCCACAAATGCAGGGAGAAGACA
GAAACACAGACTAACATGCCCTTCATGTGATTCTTATGAGAAAAAACCACCC
AAAGAATTCCTAGAAAGATTCAAATCACTTCTCCAAAAGATGATTCATCAGC
ATCTGTCCTCTAGAACACACGGAAGTGAAGATTCC (SEQ ID NO: 94).

In some embodiments of these multi-chain chimeric polypeptides, the soluble human IL-21 is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

CAGGGCCAGGACAGGCACATGATCCGGATGAGGCAGCTCATCGACATCGTCG
ACCAGCTGAAGAACTACGTGAACGACCTGGTGCCCGAGTTTCTGCCTGCCCC
CGAGGACGTGGAGACCAACTGCGAGTGGTCCGCCTTCTCCTGCTTTCAGAAG
GCCCAGCTGAAGTCCGCCAACACCGGCAACAACGAGCGGATCATCAACGTG
AGCATCAAGAAGCTGAAGCGGAAGCCTCCCTCCACAAACGCCGGCAGGAGG
CAGAAGCACAGGCTGACCTGCCCCAGCTGTGACTCCTACGAGAAGAAGCCCC
CCAAGGAGTTCCTGGAGAGGTTCAAGTCCCTGCTGCAGAAGATGATCCATCA
GCACCTGTCCTCCAGGACCCACGGCTCCGAGGACTCC (SEQ ID NO: 79).

In some embodiments of these multi-chain chimeric polypeptides, the sequence of soluble human IL-7 comprises a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

DCDIEGKDGKQYESVLMVSIDQLLDSMKEIGSNCLNNEFNFFKRHICDANKEGM
FLFRAARKLRQFLKMNSTGDFDLHLLKVSEGTTILLNCTGQVKGRKPAALGEAQ
PTKSLEENKSLKEQKKLNDLCFLKRLLQEIKTCWNKILMGTKEH (SEQ ID NO:
11).

In some embodiments of these multi-chain chimeric polypeptides, the soluble human IL-7 is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

GATTGTGATATTGAAGGTAAAGATGGCAAACAATATGAGAGTGTTCTAATGG
TCAGCATCGATCAATTATTGGACAGCATGAAAGAAATTGGTAGCAATTGCCT
GAATAATGAATTTAACTTTTTTAAAAGACATATCTGTGATGCTAATAAGGAA
GGTATGTTTTTATTCCGTGCTGCTCGCAAGTTGAGGCAATTTCTTAAAATGAA
TAGCACTGGTGATTTTGATCTCCACTTATTAAAAGTTTCAGAAGGCACAACAA
TACTGTTGAACTGCACTGGCCAGGTTAAAGGAAGAAAACCAGCTGCCCTGGG
TGAAGCCCAACCAACAAAGAGTTTGGAAGAAAATAAATCTTTAAAGGAACA
GAAAAAACTGAATGACTTGTGTTTCCTAAAGAGACTATTACAAGAGATAAAA
ACTTGTTGGAATAAAATTTTGATGGGCACTAAAGAACAC (SEQ ID NO: 95).

In some embodiments, the first chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

QGQDRHMIRMRQLIDIVDQLKNYVNDLVPEFLPAPEDVETNCEWSAFSCFQKAQ
LKSANTGNNERIINVSIKKLKRKPPSTNAGRRQKHRLTCPSCDSYEKKPPKEFLER
FKSLLQKMIHQHLSSRTHGSEDSSGTTNTVAAYNLTWKSTNFKTILEWEPKPVNQ
VYTVQISTKSGDWKSKCFYTTDTECDLTDEIVKDVKQTYLARVFSYPAGNVEST
GSAGEPLYENSPEFTPYLETNLGQPTIQSFEQVGTKVNVTVEDERTLVRRNNTFLS
LRDVFGKDLIYTLYYWKSSSSGKKTAKTNTNEFLIDVDKGENYCFSVQAVIPSRT
VNRKSTDSPVECMGQEKGEFRENWVNVISDLKKIEDLIQSMHIDATLYTESDVHP
SCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKECE
ELEEKNIKEFLQSFVHIVQMFINTS (SEQ ID NO: 96).

In some embodiments, a first chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

CAAGGTCAAGATCGCCACATGATTAGAATGCGTCAACTTATAGATATTGTTG
ATCAGCTGAAAAATTATGTGAATGACTTGGTCCCTGAATTTCTGCCAGCTCCA
GAAGATGTAGAGACAAACTGTGAGTGGTCAGCTTTTTCCTGTTTTCAGAAGG

CCCAACTAAAGTCAGCAAATACAGGAAACAATGAAAGGATAATCAATGTATC
AATTAAAAAGCTGAAGAGGAAACCACCTTCCACAAATGCAGGGAGAAGACA
GAAACACAGACTAACATGCCCTTCATGTGATTCTTATGAGAAAAAACCACCC
AAAGAATTCCTAGAAAGATTCAAATCACTTCTCCAAAAGATGATTCATCAGC
ATCTGTCCTCTAGAACACACGGAAGTGAAGATTCCTCAGGCACTACAAATAC
TGTGGCAGCATATAATTTAACTTGGAAATCAACTAATTTCAAGACAATTTTGG
AGTGGGAACCCAAACCCGTCAATCAAGTCTACACTGTTCAAATAAGCACTAA
GTCAGGAGATTGGAAAAGCAAATGCTTTTACACAACAGACACAGAGTGTGAC
CTCACCGACGAGATTGTGAAGGATGTGAAGCAGACGTACTTGGCACGGGTCT
TCTCCTACCCGGCAGGGAATGTGGAGAGCACCGGTTCTGCTGGGGAGCCTCT
GTATGAGAACTCCCCAGAGTTCACACCTTACCTGGAGACAAACCTCGGACAG
CCAACAATTCAGAGTTTTGAACAGGTGGGAACAAAAGTGAATGTGACCGTAG
AAGATGAACGGACTTTAGTCAGAAGGAACAACACTTTCCTAAGCCTCCGGGA
TGTTTTTGGCAAGGACTTAATTTATACACTTTATTATTGGAAATCTTCAAGTTC
AGGAAAGAAAACAGCCAAAACAAACACTAATGAGTTTTTGATTGATGTGGAT
AAAGGAGAAAACTACTGTTTCAGTGTTCAAGCAGTGATTCCCTCCCGAACAG
TTAACCGGAAGAGTACAGACAGCCCGGTAGAGTGTATGGGCCAGGAGAAAG
GGGAATTCAGAGAAAACTGGGTGAACGTCATCAGCGATTTAAAGAAGATCG
AAGATTTAATTCAGTCCATGCATATCGACGCCACTTTATACACAGAATCCGAC
GTGCACCCCTCTTGTAAGGTGACCGCCATGAAATGTTTTTTACTGGAGCTGCA
AGTTATCTCTTTAGAGAGCGGAGACGCTAGCATCCACGACACCGTGGAGAAT
TTAATCATTTTAGCCAATAACTCTTTATCCAGCAACGGCAACGTGACAGAGTC
CGGCTGCAAGGAGTGCGAAGAGCTGGAGGAGAAGAACATCAAGGAGTTTCT
GCAATCCTTTGTGCACATTGTCCAGATGTTCATCAATACCTCC (SEQ ID NO: 97).

In some embodiments, a first chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

MGVKVLFALICIAVAEAQGQDRHMIRMRQLIDIVDQLKNYVNDLVPEFLPAPED
VETNCEWSAFSCFQKAQLKSANTGNNERIINVSIKKLKRKPPSTNAGRRQKHRLT
CPSCDSYEKKPPKEFLERFKSLLQKMIHQHLSSRTHGSEDSSGTTNTVAAYNLTW
KSTNFKTILEWEPKPVNQVYTVQISTKSGDWKSKCFYTTDTECDLTDEIVKDVKQ
TYLARVFSYPAGNVESTGSAGEPLYENSPEFTPYLETNLGQPTIQSFEQVGTKVN
VTVEDERTLVRRNNTFLSLRDVFGKDLIYTLYYWKSSSSGKKTAKTNTNEFLIDV
DKGENYCFSVQAVIPSRTVNRKSTDSPVECMGQEKGEFRENWVNVISDLKKIED
LIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILAN
NSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS (SEQ ID NO: 98).

In some embodiments, a first chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATGGGAGTGAAAGTTCTTTTTGCCCTTATTTGTATTGCTGTGGCCGAGGCCCA
AGGTCAAGATCGCCACATGATTAGAATGCGTCAACTTATAGATATTGTTGATC
AGCTGAAAAATTATGTGAATGACTTGGTCCCTGAATTTCTGCCAGCTCCAGAA
GATGTAGAGACAAACTGTGAGTGGTCAGCTTTTTCCTGTTTTCAGAAGGCCCA
ACTAAAGTCAGCAAATACAGGAAACAATGAAAGGATAATCAATGTATCAATT
AAAAAGCTGAAGAGGAAACCACCTTCCACAAATGCAGGGAGAAGACAGAAA
CACAGACTAACATGCCCTTCATGTGATTCTTATGAGAAAAAACCACCCAAAG
AATTCCTAGAAAGATTCAAATCACTTCTCCAAAAGATGATTCATCAGCATCTG
TCCTCTAGAACACACGGAAGTGAAGATTCCTCAGGCACTACAAATACTGTGG
CAGCATATAATTTAACTTGGAAATCAACTAATTTCAAGACAATTTTGGAGTGG
GAACCCAAACCCGTCAATCAAGTCTACACTGTTCAAATAAGCACTAAGTCAG
GAGATTGGAAAAGCAAATGCTTTTACACAACAGACACAGAGTGTGACCTCAC
CGACGAGATTGTGAAGGATGTGAAGCAGACGTACTTGGCACGGGTCTTCTCC
TACCCGGCAGGGAATGTGGAGAGCACCGGTTCTGCTGGGGAGCCTCTGTATG
AGAACTCCCCAGAGTTCACACCTTACCTGGAGACAAACCTCGGACAGCCAAC
AATTCAGAGTTTTGAACAGGTGGGAACAAAAGTGAATGTGACCGTAGAAGAT
GAACGGACTTTAGTCAGAAGGAACAACACTTTCCTAAGCCTCCGGGATGTTT
TTGGCAAGGACTTAATTTATACACTTTATTATTGGAAATCTTCAAGTTCAGGA
AAGAAAACAGCCAAAACAAACACTAATGAGTTTTTGATTGATGTGGATAAAG
GAGAAAACTACTGTTTCAGTGTTCAAGCAGTGATTCCCTCCCGAACAGTTAAC
CGGAAGAGTACAGACAGCCCGGTAGAGTGTATGGGCCAGGAGAAAGGGGAA
TTCAGAGAAAACTGGGTGAACGTCATCAGCGATTTAAAGAAGATCGAAGATT
TAATTCAGTCCATGCATATCGACGCCACTTTATACACAGAATCCGACGTGCAC
CCCTCTTGTAAGGTGACCGCCATGAAATGTTTTTTACTGGAGCTGCAAGTTAT
CTCTTTAGAGAGCGGAGACGCTAGCATCCACGACACCGTGGAGAATTTAATC
ATTTTAGCCAATAACTCTTTATCCAGCAACGGCAACGTGACAGAGTCCGGCT
GCAAGGAGTGCGAAGAGCTGGAGGAGAAGAACATCAAGGAGTTTCTGCAAT
CCTTTGTGCACATTGTCCAGATGTTCATCAATACCTCC (SEQ ID NO: 99)

In some embodiments, the second chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

DCDIEGKDGKQYESVLMVSIDQLLDSMKEIGSNCLNNEFNFFKRHICDANKEGM
FLFRAARKLRQFLKMNSTGDFDLHLLKVSEGTTILLNCTGQVKGRKPAALGEAQ
PTKSLEENKSLKEQKKLNDLCFLKRLLQEIKTCWNKILMGTKEHITCPPPMSVEH
ADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR
(SEQ ID NO: 100)

In some embodiments, a second chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

GATTGTGATATTGAAGGTAAAGATGGCAAACAATATGAGAGTGTTCTAATGG
TCAGCATCGATCAATTATTGGACAGCATGAAAGAAATTGGTAGCAATTGCCT
GAATAATGAATTTAACTTTTTTAAAAGACATATCTGTGATGCTAATAAGGAA
GGTATGTTTTTATTCCGTGCTGCTCGCAAGTTGAGGCAATTTCTTAAAATGAA
TAGCACTGGTGATTTTGATCTCCACTTATTAAAAGTTTCAGAAGGCACAACAA
TACTGTTGAACTGCACTGGCCAGGTTAAAGGAAGAAAACCAGCTGCCCTGGG
TGAAGCCCAACCAACAAAGAGTTTGGAAGAAAATAAATCTTTAAAGGAACA
GAAAAAACTGAATGACTTGTGTTTCCTAAAGAGACTATTACAAGAGATAAAA
ACTTGTTGGAATAAAATTTTGATGGGCACTAAAGAACACATCACGTGCCCTC
CCCCCATGTCCGTGGAACACGCAGACATCTGGGTCAAGAGCTACAGCTTGTA
CTCCAGGGAGCGGTACATTTGTAACTCTGGTTTCAAGCGTAAAGCCGGCACG
TCCAGCCTGACGGAGTGCGTGTTGAACAAGGCCACGAATGTCGCCCACTGGA
CAACCCCCAGTCTCAAATGCATTAGA (SEQ ID NO: 101).

In some embodiments, a second chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

MGVKVLFALICIAVAEADCDIEGKDGKQYESVLMVSIDQLLDSMKEIGSNCLNN
EFNFFKRHICDANKEGMFLFRAARKLRQFLKMNSTGDFDLHLLKVSEGTTILLNC
TGQVKGRKPAALGEAQPTKSLEENKSLKEQKKLNDLCFLKRLLQEIKTCWNKIL
MGTKEHITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNK
ATNVAHWTTPSLKCIR (SEQ ID NO: 102).

In some embodiments, a second chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at

least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATGGGAGTGAAAGTTCTTTTTGCCCTTATTTGTATTGCTGTGGCCGAGGCCGA
TTGTGATATTGAAGGTAAAGATGGCAAACAATATGAGAGTGTTCTAATGGTC
AGCATCGATCAATTATTGGACAGCATGAAAGAAATTGGTAGCAATTGCCTGA
ATAATGAATTTAACTTTTTTAAAAGACATATCTGTGATGCTAATAAGGAAGGT
ATGTTTTTATTCCGTGCTGCTCGCAAGTTGAGGCAATTTCTTAAAATGAATAG
CACTGGTGATTTTGATCTCCACTTATTAAAAGTTTCAGAAGGCACAACAATAC
TGTTGAACTGCACTGGCCAGGTTAAAGGAAGAAAACCAGCTGCCCTGGGTGA
AGCCCAACCAACAAAGAGTTTGGAAGAAAATAAATCTTTAAAGGAACAGAA
AAAACTGAATGACTTGTGTTTCCTAAAGAGACTATTACAAGAGATAAAAACT
TGTTGGAATAAAATTTTGATGGGCACTAAAGAACACATCACGTGCCCTCCCC
CCATGTCCGTGGAACACGCAGACATCTGGGTCAAGAGCTACAGCTTGTACTC
CAGGGAGCGGTACATTTGTAACTCTGGTTTCAAGCGTAAAGCCGGCACGTCC
AGCCTGACGGAGTGCGTGTTGAACAAGGCCACGAATGTCGCCCACTGGACAA
CCCCCAGTCTCAAATGCATTAGA (SEQ ID NO: 103).

Exemplary Multi-Chain Chimeric Polypeptides- Type D

In some embodiments of any of the multi-chain chimeric polypeptides described herein, the first target-binding domain and the second targeting-binding domain each independently bind specifically to a receptor of IL-7 or a receptor of IL-21. In some examples of these multi-chain chimeric polypeptides, the first target-binding domain and the soluble tissue factor domain directly abut each other in the first chimeric polypeptide. In some examples of these multi-chain chimeric polypeptides, the first chimeric polypeptide further comprises a linker sequence (e.g., any of the exemplary linkers described herein) between the first target-binding domain and the soluble tissue factor domain in the first chimeric polypeptide.

In some embodiments of these multi-chain chimeric polypeptides, 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 embodiments of these multi-chain chimeric polypeptides, the first chimeric polypeptide further includes a linker sequence (e.g., any of the exemplary linkers described herein) between the soluble tissue factor domain and the first domain of the pair of affinity domains in the first chimeric polypeptide.

In some embodiments of these multi-chain chimeric polypeptides, 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 embodiments of these multi-chain chimeric polypeptides, the second chimeric polypeptide further includes a linker sequence (e.g., any of the exemplary linkers described herein) between the second domain of the pair of affinity domains and the second target-binding domain in the second chimeric polypeptide.

In some embodiments of these multi-chain chimeric polypeptides, the soluble tissue factor domain can be any of the exemplary soluble tissue factor domains described herein. In some embodiments of these multi-chain chimeric polypeptides, the pair of affinity domains can be any of the exemplary pairs of affinity domains described herein.

In some embodiments of these multi-chain chimeric polypeptides, one or both of the first target-binding domain and the second target-binding domain is a soluble IL-21 (e.g., a soluble human IL-21 polypeptide) or a soluble IL-7 (e.g., a soluble human IL-7 polypeptide). In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain and the second target-binding domain are each independently a soluble IL-21 or a soluble IL-7. In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain and the second target-binding domain both bind specifically to a receptor of IL-21 or a receptor of IL-7. In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain and the second target-binding domain bind specifically to the same epitope. In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain and the second target-binding domain include the same amino acid sequence.

In some embodiments of these multi-chain chimeric polypeptides, 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. In some embodiments of these multi-chain chimeric polypeptides, 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.

In some embodiments of these multi-chain chimeric polypeptides, the soluble human IL-21 includes a sequence that is at least 80% identical (e.g., at least 82%

identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

QGQDRHMIRMRQLIDIVDQLKNYVNDLVPEFLPAPEDVETNCEWSAFSCFQKAQ
LKSANTGNNERIINVSIKKLKRKPPSTNAGRRQKHRLTCPSCDSYEKKPPKEFLER
FKSLLQKMIHQHLSSRTHGSEDS (SEQ ID NO: 78).

In some embodiments of these multi-chain chimeric polypeptides, the soluble human IL-21 is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

CAAGGTCAAGATCGCCACATGATTAGAATGCGTCAACTTATAGATATTGTTG
ATCAGCTGAAAAATTATGTGAATGACTTGGTCCCTGAATTTCTGCCAGCTCCA
GAAGATGTAGAGACAAACTGTGAGTGGTCAGCTTTTTCCTGTTTTCAGAAGG
CCCAACTAAAGTCAGCAAATACAGGAAACAATGAAAGGATAATCAATGTATC
AATTAAAAAGCTGAAGAGGAAACCACCTTCCACAAATGCAGGGAGAAGACA
GAAACACAGACTAACATGCCCTTCATGTGATTCTTATGAGAAAAAACCACCC
AAAGAATTCCTAGAAAGATTCAAATCACTTCTCCAAAAGATGATTCATCAGC
ATCTGTCCTCTAGAACACACGGAAGTGAAGATTCC (SEQ ID NO: 94).

In some embodiments of these multi-chain chimeric polypeptides, the soluble human IL-21 is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

CAGGGCCAGGACAGGCACATGATCCGGATGAGGCAGCTCATCGACATCGTCG
ACCAGCTGAAGAACTACGTGAACGACCTGGTGCCCGAGTTTCTGCCTGCCCC
CGAGGACGTGGAGACCAACTGCGAGTGGTCCGCCTTCTCCTGCTTTCAGAAG
GCCCAGCTGAAGTCCGCCAACACCGGCAACAACGAGCGGATCATCAACGTG
AGCATCAAGAAGCTGAAGCGGAAGCCTCCCTCCACAAACGCCGGCAGGAGG
CAGAAGCACAGGCTGACCTGCCCCAGCTGTGACTCCTACGAGAAGAAGCCCC
CCAAGGAGTTCCTGGAGAGGTTCAAGTCCCTGCTGCAGAAGATGATCCATCA
GCACCTGTCCTCCAGGACCCACGGCTCCGAGGACTCC (SEQ ID NO: 79).

In some embodiments of these multi-chain chimeric polypeptides, the sequence of soluble human IL-7 comprises a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least

90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

DCDIEGKDGKQYESVLMVSIDQLLDSMKEIGSNCLNNEFNFFKRHICDANKEGM
FLFRAARKLRQFLKMNSTGDFDLHLLKVSEGTTILLNCTGQVKGRKPAALGEAQ
PTKSLEENKSLKEQKKLNDLCFLKRLLQEIKTCWNKILMGTKEH (SEQ ID NO: 11).

In some embodiments of these multi-chain chimeric polypeptides, the soluble human IL-7 is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

GATTGTGATATTGAAGGTAAAGATGGCAAACAATATGAGAGTGTTCTAATGG
TCAGCATCGATCAATTATTGGACAGCATGAAAGAAATTGGTAGCAATTGCCT
GAATAATGAATTTAACTTTTTTAAAAGACATATCTGTGATGCTAATAAGGAA
GGTATGTTTTTATTCCGTGCTGCTCGCAAGTTGAGGCAATTTCTTAAAATGAA
TAGCACTGGTGATTTTGATCTCCACTTATTAAAAGTTTCAGAAGGCACAACAA
TACTGTTGAACTGCACTGGCCAGGTTAAAGGAAGAAAACCAGCTGCCCTGGG
TGAAGCCCAACCAACAAAGAGTTTGGAAGAAAATAAATCTTTAAAGGAACA
GAAAAAACTGAATGACTTGTGTTTCCTAAAGAGACTATTACAAGAGATAAAA
ACTTGTTGGAATAAAATTTTGATGGGCACTAAAGAACAC (SEQ ID NO: 95).

In some embodiments, the first chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

DCDIEGKDGKQYESVLMVSIDQLLDSMKEIGSNCLNNEFNFFKRHICDANKEGM
FLFRAARKLRQFLKMNSTGDFDLHLLKVSEGTTILLNCTGQVKGRKPAALGEAQ
PTKSLEENKSLKEQKKLNDLCFLKRLLQEIKTCWNKILMGTKEHSGTTNTVAAY
NLTWKSTNFKTILEWEPKPVNQVYTVQISTKSGDWKSKCFYTTDTECDLTDEIVK
DVKQTYLARVFSYPAGNVESTGSAGEPLYENSPEFTPYLETNLGQPTIQSFEQVG
TKVNVTVEDERTLVRRNNTFLSLRDVFGKDLIYTLYYWKSSSSGKKTAKTNTNE
FLIDVDKGENYCFSVQAVIPSRTVNRKSTDSPVECMGQEKGEFRENWVNVISDL
KKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVEN
LIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS (SEQ ID NO: 104).

In some embodiments, a first chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

GATTGCGACATCGAGGGCAAGGACGGCAAGCAGTACGAGAGCGTGCTGATG
GTGTCCATCGACCAGCTGCTGGACAGCATGAAGGAGATCGGCTCCAACTGCC
TCAACAACGAGTTCAACTTCTTCAAGCGGCACATCTGCGACGCCAACAAGGA
GGGCATGTTCCTGTTCAGGGCCGCCAGGAAACTGCGGCAGTTCCTGAAGATG
AACTCCACCGGCGACTTCGACCTGCACCTGCTGAAGGTGTCCGAGGGCACCA
CCATCCTGCTGAACTGCACCGGACAGGTGAAGGGCCGGAAACCTGCTGCTCT
GGGAGAGGCCCAACCCACCAAGAGCCTGGAGGAGAACAAGTCCCTGAAGGA
GCAGAAGAAGCTGAACGACCTGTGCTTCCTGAAGAGGCTGCTGCAGGAGATC
AAGACCTGCTGGAACAAGATCCTGATGGGCACCAAGGAGCATAGCGGCACA
ACCAACACAGTCGCTGCCTATAACCTCACTTGGAAGAGCACCAACTTCAAAA
CCATCCTCGAATGGGAACCCAAACCCGTTAACCAAGTTTACACCGTGCAGAT
CAGCACCAAGTCCGGCGACTGGAAGTCCAAATGTTTCTATACCACCGACACC
GAGTGCGATCTCACCGATGAGATCGTGAAAGATGTGAAACAGACCTACCTCG
CCCGGGTGTTTAGCTACCCCGCCGGCAATGTGGAGAGCACTGGTTCCGCTGG
CGAGCCTTTATACGAGAACAGCCCCGAATTTACCCCTTACCTCGAGACCAATT
TAGGACAGCCCACCATCCAAAGCTTTGAGCAAGTTGGCACAAAGGTGAATGT
GACAGTGGAGGACGAGCGGACTTTAGTGCGGCGGAACAACACCTTTCTCAGC
CTCCGGGATGTGTTCGGCAAAGATTTAATCTACACACTGTATTACTGGAAGTC
CTCTTCCTCCGGCAAGAAGACAGCTAAAACCAACACAAACGAGTTTTTAATC
GACGTGGATAAAGGCGAAAACTACTGTTTCAGCGTGCAAGCTGTGATCCCCT
CCCGGACCGTGAATAGGAAAAGCACCGATAGCCCCGTTGAGTGCATGGGCCA
AGAAAAGGGCGAGTTCCGGGAGAACTGGGTGAACGTCATCAGCGATTTAAA
GAAGATCGAAGATTTAATTCAGTCCATGCATATCGACGCCACTTTATACACA
GAATCCGACGTGCACCCCTCTTGTAAGGTGACCGCCATGAAATGTTTTTTACT
GGAGCTGCAAGTTATCTCTTTAGAGAGCGGAGACGCTAGCATCCACGACACC
GTGGAGAATTTAATCATTTTAGCCAATAACTCTTTATCCAGCAACGGCAACGT
GACAGAGTCCGGCTGCAAGGAGTGCGAAGAGCTGGAGGAGAAGAACATCAA
GGAGTTTCTGCAATCCTTTGTGCACATTGTCCAGATGTTCATCAATACCTCC
(SEQ ID NO: 105).

In some embodiments, a first chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

MKWVTFISLLFLFSSAYSDCDIEGKDGKQYESVLMVSIDQLLDSMKEIGSNCLNN
EFNFFKRHICDANKEGMFLFRAARKLRQFLKMNSTGDFDLHLLKVSEGTTILLNC
TGQVKGRKPAALGEAQPTKSLEENKSLKEQKKLNDLCFLKRLLQEIKTCWNKIL
MGTKEHSGTTNTVAAYNLTWKSTNFKTILEWEPKPVNQVYTVQISTKSGDWKS
KCFYTTDTECDLTDEIVKDVKQTYLARVFSYPAGNVESTGSAGEPLYENSPEFTP
YLETNLGQPTIQSFEQVGTKVNVTVEDERTLVRRNNTFLSLRDVFGKDLIYTLYY
WKSSSSGKKTAKTNTNEFLIDVDKGENYCFSVQAVIPSRTVNRKSTDSPVECMG
QEKGEFRENWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLEL
QVISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFV
HIVQMFINTS (SEQ ID NO: 106).

In some embodiments, a first chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATGAAGTGGGTGACCTTCATCAGCCTGCTGTTCCTGTTCTCCAGCGCCTACTC
CGATTGCGACATCGAGGGCAAGGACGGCAAGCAGTACGAGAGCGTGCTGAT
GGTGTCCATCGACCAGCTGCTGGACAGCATGAAGGAGATCGGCTCCAACTGC
CTCAACAACGAGTTCAACTTCTTCAAGCGGCACATCTGCGACGCCAACAAGG
AGGGCATGTTCCTGTTCAGGGCCGCCAGGAAACTGCGGCAGTTCCTGAAGAT
GAACTCCACCGGCGACTTCGACCTGCACCTGCTGAAGGTGTCCGAGGGCACC
ACCATCCTGCTGAACTGCACCGGACAGGTGAAGGGCCGGAAACCTGCTGCTC
TGGGAGAGGCCCAACCCACCAAGAGCCTGGAGGAGAACAAGTCCCTGAAGG
AGCAGAAGAAGCTGAACGACCTGTGCTTCCTGAAGAGGCTGCTGCAGGAGAT
CAAGACCTGCTGGAACAAGATCCTGATGGGCACCAAGGAGCATAGCGGCAC
AACCAACACAGTCGCTGCCTATAACCTCACTTGGAAGAGCACCAACTTCAAA
ACCATCCTCGAATGGGAACCCAAACCCGTTAACCAAGTTTACACCGTGCAGA
TCAGCACCAAGTCCGGCGACTGGAAGTCCAAATGTTTCTATACCACCGACAC
CGAGTGCGATCTCACCGATGAGATCGTGAAAGATGTGAAACAGACCTACCTC
GCCCGGGTGTTTAGCTACCCCGCCGGCAATGTGGAGAGCACTGGTTCCGCTG
GCGAGCCTTTATACGAGAACAGCCCCGAATTTACCCCTTACCTCGAGACCAA
TTTAGGACAGCCCACCATCCAAAGCTTTGAGCAAGTTGGCACAAAGGTGAAT
GTGACAGTGGAGGACGAGCGGACTTTAGTGCGGCGGAACAACACCTTTCTCA
GCCTCCGGGATGTGTTCGGCAAAGATTTAATCTACACACTGTATTACTGGAAG
TCCTCTTCCTCCGGCAAGAAGACAGCTAAAACCAACACAAACGAGTTTTTAA
TCGACGTGGATAAAGGCGAAAACTACTGTTTCAGCGTGCAAGCTGTGATCCC
CTCCCGGACCGTGAATAGGAAAAGCACCGATAGCCCCGTTGAGTGCATGGGC
CAAGAAAAGGGCGAGTTCCGGGAGAACTGGGTGAACGTCATCAGCGATTTA
AAGAAGATCGAAGATTTAATTCAGTCCATGCATATCGACGCCACTTTATACA
CAGAATCCGACGTGCACCCCTCTTGTAAGGTGACCGCCATGAAATGTTTTTTA
CTGGAGCTGCAAGTTATCTCTTTAGAGAGCGGAGACGCTAGCATCCACGACA

CCGTGGAGAATTTAATCATTTTAGCCAATAACTCTTTATCCAGCAACGGCAAC
GTGACAGAGTCCGGCTGCAAGGAGTGCGAAGAGCTGGAGGAGAAGAACATC
AAGGAGTTTCTGCAATCCTTTGTGCACATTGTCCAGATGTTCATCAATACCTC
C (SEQ ID NO: 107).

In some embodiments, the second chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

QGQDRHMIRMRQLIDIVDQLKNYVNDLVPEFLPAPEDVETNCEWSAFSCFQKAQ
LKSANTGNNERIINVSIKKLKRKPPSTNAGRRQKHRLTCPSCDSYEKKPPKEFLER
FKSLLQKMIHQHLSSRTHGSEDSITCPPPMSVEHADIWVKSYSLYSRERYICNSGF
KRKAGTSSLTECVLNKATNVAHWTTPSLKCIR (SEQ ID NO: 108).

In some embodiments, a second chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

CAGGGCCAGGACAGGCACATGATCCGGATGAGGCAGCTCATCGACATCGTCG
ACCAGCTGAAGAACTACGTGAACGACCTGGTGCCCGAGTTTCTGCCTGCCCC
CGAGGACGTGGAGACCAACTGCGAGTGGTCCGCCTTCTCCTGCTTTCAGAAG
GCCCAGCTGAAGTCCGCCAACACCGGCAACAACGAGCGGATCATCAACGTG
AGCATCAAGAAGCTGAAGCGGAAGCCTCCCTCCACAAACGCCGGCAGGAGG
CAGAAGCACAGGCTGACCTGCCCCAGCTGTGACTCCTACGAGAAGAAGCCCC
CCAAGGAGTTCCTGGAGAGGTTCAAGTCCCTGCTGCAGAAGATGATCCATCA
GCACCTGTCCTCCAGGACCCACGGCTCCGAGGACTCCATTACATGCCCCCCTC
CCATGAGCGTGGAGCACGCCGACATCTGGGTGAAGAGCTATAGCCTCTACAG
CCGGGAGAGGTATATCTGTAACAGCGGCTTCAAGAGGAAGGCCGGCACCAG
CAGCCTCACCGAGTGCGTGCTGAATAAGGCTACCAACGTGGCTCACTGGACA
ACACCCTCTTTAAAGTGCATCCGG (SEQ ID NO: 109).

In some embodiments, a second chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

MKWVTFISLLFLFSSAYSQGQDRHMIRMRQLIDIVDQLKNYVNDLVPEFLPAPED
VETNCEWSAFSCFQKAQLKSANTGNNERIINVSIKKLKRKPPSTNAGRRQKHRLT
CPSCDSYEKKPPKEFLERFKSLLQKMIHQHLSSRTHGSEDSITCPPPMSVEHADIW
VKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR (SEQ
ID NO: 110).

In some embodiments, a second chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATGAAGTGGGTGACCTTCATCAGCCTGCTGTTCCTGTTCTCCAGCGCCTACTC
CCAGGGCCAGGACAGGCACATGATCCGGATGAGGCAGCTCATCGACATCGTC
GACCAGCTGAAGAACTACGTGAACGACCTGGTGCCCGAGTTTCTGCCTGCCC
CCGAGGACGTGGAGACCAACTGCGAGTGGTCCGCCTTCTCCTGCTTTCAGAA
GGCCCAGCTGAAGTCCGCCAACACCGGCAACAACGAGCGGATCATCAACGT
GAGCATCAAGAAGCTGAAGCGGAAGCCTCCCTCCACAAACGCCGGCAGGAG
GCAGAAGCACAGGCTGACCTGCCCCAGCTGTGACTCCTACGAGAAGAAGCCC
CCCAAGGAGTTCCTGGAGAGGTTCAAGTCCCTGCTGCAGAAGATGATCCATC
AGCACCTGTCCTCCAGGACCCACGGCTCCGAGGACTCCATTACATGCCCCCCT
CCCATGAGCGTGGAGCACGCCGACATCTGGGTGAAGAGCTATAGCCTCTACA
GCCGGGAGAGGTATATCTGTAACAGCGGCTTCAAGAGGAAGGCCGGCACCA
GCAGCCTCACCGAGTGCGTGCTGAATAAGGCTACCAACGTGGCTCACTGGAC
AACACCCTCTTTAAAGTGCATCCGG (SEQ ID NO: 111).

Exemplary Multi-Chain Chimeric Polypeptides- Type E

In some embodiments of any of the multi-chain chimeric polypeptides described herein, the first target-binding domain and the second targeting-binding domain each independently bind specifically to a receptor for IL-18 (e.g., a soluble human IL-18), a receptor for IL-12 (e.g., a soluble human IL-12), or CD16 (e.g., an anti-CD16 scFv). In some embodiments of these multi-chain chimeric polypeptides described herein, the first chimeric polypeptide further includes the additional target-binding domain. In some embodiments of these multi-chain chimeric polypeptides described herein, the second chimeric polypeptide further includes the additional target-binding domain. In some embodiments of these multi-chain chimeric polypeptides described herein, the additional target-binding domain binds specifically to CD16 or a receptor for IL-12.

In some examples of these multi-chain chimeric polypeptides, the first target-binding domain and the soluble tissue factor domain directly abut each other in the first chimeric polypeptide. In some examples of these multi-chain chimeric polypeptides, the first chimeric polypeptide further comprises a linker sequence (e.g., any of the exemplary linkers described herein) between the first target-binding domain and the soluble tissue factor domain in the first chimeric polypeptide.

In some embodiments of these multi-chain chimeric polypeptides, 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 embodiments of these multi-chain chimeric polypeptides, the first chimeric polypeptide further includes a linker sequence (e.g., any of the exemplary linkers described herein) between the soluble tissue factor domain and the first domain of the pair of affinity domains in the first chimeric polypeptide.

In some embodiments of these multi-chain chimeric polypeptides, 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 embodiments of these multi-chain chimeric polypeptides, the second chimeric polypeptide further includes a linker sequence (e.g., any of the exemplary linkers described herein) between the second domain of the pair of affinity domains and the second target-binding domain in the second chimeric polypeptide.

In some embodiments, the second chimeric polypeptide further comprises one or more additional target-binding domains at the N-terminal end or the C-terminal end of the second chimeric polypeptide.

In some embodiments of these multi-chain chimeric polypeptides, the additional target-binding domain and the second domain of the pair of affinity domains directly abut each other in the second chimeric polypeptide. In some embodiments of these multi-chain chimeric polypeptides, the second chimeric polypeptide further includes a linker sequence (e.g., any of the exemplary linkers described herein) between the second domain of the pair of affinity domains and the additional target-binding domain in the second chimeric polypeptide.

In some embodiments of these multi-chain chimeric polypeptides, the additional target-binding domain and the second target-binding domain directly abut each other in the second chimeric polypeptide. In some embodiments of these multi-chain chimeric polypeptides, the second chimeric polypeptide further includes a linker sequence (e.g., any of the exemplary linkers described herein) between the second target-binding domain and the additional target-binding domain in the second chimeric polypeptide.

In some embodiments of these multi-chain chimeric polypeptides, the soluble tissue factor domain can be any of the exemplary soluble tissue factor domains described herein. In some embodiments of these multi-chain chimeric polypeptides, the pair of affinity domains can be any of the exemplary pairs of affinity domains described herein.

In some embodiments of these multi-chain chimeric polypeptides, one or more of the first target-binding domain, the second target-binding domain and the additional antigen-binding domain is an agonistic antigen-binding domain. In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain, the second target-binding domain, and the additional antigen-binding domain are each agonistic antigen-binding domains. In some embodiments of these multi-chain chimeric polypeptides, the antigen-binding domain includes a scFv or single-domain antibody.

In some embodiments of these multi-chain chimeric polypeptides, one or both of the first target-binding domain and the second target-binding domain is a soluble IL-15 or a soluble IL-18. In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain and the second target-binding domain are each independently a soluble IL-15 or a soluble IL-18. In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain and the second target-binding domain both bind specifically to a receptor of IL-18 or a receptor of IL-12. In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain and the second target-binding domain bind specifically to the same epitope. In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain and the second target-binding domain include the same amino acid sequence.

In some embodiments of these multi-chain chimeric polypeptides, 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. In some embodiments of these multi-

chain chimeric polypeptides, the first target-binding domain binds specifically to a receptor for IL-18, and the second target-binding domain bind specifically to a receptor for IL-12. In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain binds specifically to CD16, and the second target-binding domain binds specifically to a receptor for IL-18. In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain binds specifically to a receptor for IL-18, and the second target-binding domain bind specifically to CD16.

In some embodiments of these multi-chain chimeric polypeptides, two or more of the first target-binding domain, the second target-binding domain, and the one or more additional target-binding domains bind specifically to the same antigen. In some embodiments, two or more of the first target-binding domain, the second target-binding domain, and the one or more additional target-binding domains bind specifically to the same epitope. In some embodiments, two or more of the first target-binding domain, the second target-binding domain, and the one or more additional target-binding domains comprise the same amino acid sequence.

In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain includes a soluble IL-18 (e.g., a soluble human IL-18).

In some embodiments of these multi-chain chimeric polypeptides, the soluble human IL-18 includes a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

YFGKLESKLSVIRNLNDQVLFIDQGNRPLFEDMTDSDCRDNAPRTIFIISMYKDSQ
PRGMAVTISVKCEKISTLSCENKIISFKEMNPPDNIKDTKSDIIFFQRSVPGHDNKM
QFESSSYEGYFLACEKERDLFKLILKKEDELGDRSIMFTVQNED (SEQ ID NO: 16).

In some embodiments of these multi-chain chimeric polypeptides, the soluble human IL-18 is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

TACTTCGGCAAACTGGAATCCAAGCTGAGCGTGATCCGGAATTTAAACGACC
AAGTTCTGTTTATCGATCAAGGTAACCGGCCTCTGTTCGAGGACATGACCGAC

TCCGATTGCCGGGACAATGCCCCCCGGACCATCTTCATTATCTCCATGTACAA
GGACAGCCAGCCCCGGGGCATGGCTGTGACAATTAGCGTGAAGTGTGAGAA
AATCAGCACTTTATCTTGTGAGAACAAGATCATCTCCTTTAAGGAAATGAACC
CCCCCGATAACATCAAGGACACCAAGTCCGATATCATCTTCTTCCAGCGGTCC
GTGCCCGGTCACGATAACAAGATGCAGTTCGAATCCTCCTCCTACGAGGGCT
ACTTTTTAGCTTGTGAAAAGGAGAGGGATTTATTCAAGCTGATCCTCAAGAA
GGAGGACGAGCTGGGCGATCGTTCCATCATGTTCACCGTCCAAAACGAGGAT
(SEQ ID NO: 65).

In some embodiments of these multi-chain chimeric polypeptides, the second target-binding domain includes a soluble IL-12 (e.g., a soluble human IL-12). In some embodiments of these multi-chain chimeric polypeptides, the soluble human IL-15 includes a sequence of soluble human IL-12β (p40) and a sequence of soluble human IL-12α (p35). In some embodiments of these multi-chain chimeric polypeptides, the soluble IL-15 (e.g., soluble human IL-15) further includes a linker sequence (e.g., any of the exemplary linker sequences described herein) between the sequence of soluble IL-12β (p40) and the sequence of soluble human IL-12α (p35). In some examples of these multi-chain chimeric polypeptides, the linker sequence comprises GGGGSGGGGSGGGGS (SEQ ID NO: 7).

In some embodiments of these multi-chain chimeric polypeptides, the sequence of soluble human IL-12β (p40) comprises a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

IWELKKDVYVVELDWYPDAPGEMVVLTCDTPEEDGITWTLDQSSEVLGSGKTLT
IQVKEFGDAGQYTCHKGGEVLSHSLLLLHKKEDGIWSTDILKDQKEPKNKTFLR
CEAKNYSGRFTCWWLTTISTDLTFSVKSSRGSSDPQGVTCGAATLSAERVRGDN
KEYEYSVECQEDSACPAAEESLPIEVMVDAVHKLKYENYTSSFFIRDIIKPDPPKN
LQLKPLKNSRQVEVSWEYPDTWSTPHSYFSLTFCVQVQGKSKREKKDRVFTDKT
SATVICRKNASISVRAQDRYYSSSWSEWASVPCS (SEQ ID NO: 66).

In some embodiments of these multi-chain chimeric polypeptides, the soluble human IL-12β (p40) is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATTTGGGAACTGAAGAAGGACGTCTACGTGGTCGAACTGGACTGGTATCCCG
ATGCTCCCGGCGAAATGGTGGTGCTCACTTGTGACACCCCCGAAGAAGACGG
CATCACTTGGACCCTCGATCAGAGCAGCGAGGTGCTGGGCTCCGGAAAGACC
CTCACAATCCAAGTTAAGGAGTTCGGAGACGCTGGCCAATACACATGCCACA
AGGGAGGCGAGGTGCTCAGCCATTCCTTATTATTATTACACAAGAAGGAAGA
CGGAATCTGGTCCACCGACATTTTAAAAGATCAGAAGGAGCCCAAGAATAAG
ACCTTTTTAAGGTGTGAGGCCAAAAACTACAGCGGTCGTTTCACTTGTTGGTG
GCTGACCACCATTTCCACCGATTTAACCTTCTCCGTGAAAAGCAGCCGGGGA
AGCTCCGACCCTCAAGGTGTGACATGTGGAGCCGCTACCCTCAGCGCTGAGA
GGGTTCGTGGCGATAACAAGGAATACGAGTACAGCGTGGAGTGCCAAGAAG
ATAGCGCTTGTCCCGCTGCCGAAGAATCTTTACCCATTGAGGTGATGGTGGAC
GCCGTGCACAAACTCAAGTACGAGAACTACACCTCCTCCTTCTTTATCCGGGA
CATCATTAAGCCCGATCCTCCTAAGAATTTACAGCTGAAGCCTCTCAAAAATA
GCCGGCAAGTTGAGGTCTCTTGGGAATATCCCGACACTTGGAGCACACCCCA
CAGCTACTTCTCTTTAACCTTTTGTGTGCAAGTTCAAGGTAAAAGCAAGCGGG
AGAAGAAAGACCGGGTGTTTACCGACAAAACCAGCGCCACCGTCATCTGTCG
GAAGAACGCCTCCATCAGCGTGAGGGCTCAAGATCGTTATTACTCCAGCAGC
TGGTCCGAGTGGGCCAGCGTGCCTTGTTCC (SEQ ID NO: 67).

In some embodiments of these multi-chain chimeric polypeptides, the soluble human IL-12α (p35) includes a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

RNLPVATPDPGMFPCLHHSQNLLRAVSNMLQKARQTLEFYPCTSEEIDHEDITKD
KTSTVEACLPLELTKNESCLNSRETSFITNGSCLASRKTSFMMALCLSSIYEDLKM
YQVEFKTMNAKLLMDPKRQIFLDQNMLAVIDELMQALNFNSETVPQKSSLEEPD
FYKTKIKLCILLHAFRIRAVTIDRVMSYLNAS (SEQ ID NO: 68).

In some embodiments of these multi-chain chimeric polypeptides, the soluble human IL-12α (p35) is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

CGTAACCTCCCCGTGGCTACCCCCGATCCCGGAATGTTCCCTTGTTTACACCA
CAGCCAGAATTTACTGAGGGCCGTGAGCAACATGCTGCAGAAAGCTAGGCAG
ACTTTAGAATTTTACCCTTGCACCAGCGAGGAGATCGACCATGAAGATATCA
CCAAGGACAAGACATCCACCGTGGAGGCTTGTTTACCTCTGGAGCTGACAAA
GAACGAGTCTTGTCTCAACTCTCGTGAAACCAGCTTCATCACAAATGGCTCTT
GTTTAGCTTCCCGGAAGACCTCCTTTATGATGGCTTTATGCCTCAGCTCCATCT

ACGAGGATTTAAAGATGTACCAAGTGGAGTTCAAGACCATGAACGCCAAGCT
GCTCATGGACCCTAAACGGCAGATCTTTTTAGACCAGAACATGCTGGCTGTG
ATTGATGAGCTGATGCAAGCTTTAAACTTCAACTCCGAGACCGTCCCTCAGA
AGTCCTCCCTCGAGGAGCCCGATTTTTACAAGACAAAGATCAAACTGTGCAT
TTTACTCCACGCCTTTAGGATCCGGGCCGTGACCATTGACCGGGTCATGAGCT
ATTTAAACGCCAGC (SEQ ID NO: 69).

In some embodiments of these multi-chain chimeric polypeptides, the additional target-binding domain includes an scFv that specifically binds to CD16 (e.g., an anti-CD16 scFv).

In some embodiments of these multi-chain chimeric polypeptides, the scFv that binds specifically to CD16 includes a light chain variable domain that includes a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

SELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVIYGKNNRPS
GIPDRFSGSSSGNTASLTITGAQAEDEADYYCNSRDSSGNHVVFGGGTKLTVGH
(SEQ ID NO: 112).

In some embodiments of these multi-chain chimeric polypeptides, the scFv that binds specifically to CD16 is encoded by a light chain variable domain sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

TCCGAGCTGACCCAGGACCCTGCTGTGTCCGTGGCTCTGGGCCAGACCGTGA
GGATCACCTGCCAGGGCGACTCCCTGAGGTCCTACTACGCCTCCTGGTACCA
GCAGAAGCCCGGCCAGGCTCCTGTGCTGGTGATCTACGGCAAGAACAACAGG
CCCTCCGGCATCCCTGACAGGTTCTCCGGATCCTCCTCCGGCAACACCGCCTC
CCTGACCATCACAGGCGCTCAGGCCGAGGACGAGGCTGACTACTACTGCAAC
TCCAGGGACTCCTCCGGCAACCATGTGGTGTTCGGCGGCGGCACCAAGCTGA
CCGTGGGCCAT (SEQ ID NO: 113).

In some embodiments of these multi-chain chimeric polypeptides, the scFv that binds specifically to CD16 includes a heavy chain variable domain that includes a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical,

at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

EVQLVESGGGVVRPGGSLRLSCAASGFTFDDYGMSWVRQAPGKGLEWVSGINW
NGGSTGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGRSLLFDY
WGQGTLVTVSR (SEQ ID NO: 114).

In some embodiments of these multi-chain chimeric polypeptides, the scFv that binds specifically to CD16 is encoded by a heavy chain variable domain sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

GAGGTGCAGCTGGTGGAGTCCGGAGGAGGAGTGGTGAGGCCTGGAGGCTCC
CTGAGGCTGAGCTGTGCTGCCTCCGGCTTCACCTTCGACGACTACGGCATGTC
CTGGGTGAGGCAGGCTCCTGGAAAGGGCCTGGAGTGGGTGTCCGGCATCAAC
TGGAACGGCGGATCCACCGGCTACGCCGATTCCGTGAAGGGCAGGTTCACCA
TCAGCAGGGACAACGCCAAGAACTCCCTGTACCTGCAGATGAACTCCCTGAG
GGCCGAGGACACCGCCGTGTACTACTGCGCCAGGGGCAGGTCCCTGCTGTTC
GACTACTGGGGACAGGGCACCCTGGTGACCGTGTCCAGG (SEQ ID NO: 115).

In some embodiments, the first chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

YFGKLESKLSVIRNLNDQVLFIDQGNRPLFEDMTDSDCRDNAPRTIFIISMYKDSQ
PRGMAVTISVKCEKISTLSCENKIISFKEMNPPDNIKDTKSDIIFFQRSVPGHDNKM
QFESSSYEGYFLACEKERDLFKLILKKEDELGDRSIMFTVQNEDSGTTNTVAAYN
LTWKSTNFKTILEWEPKPVNQVYTVQISTKSGDWKSKCFYTTDTECDLTDEIVKD
VKQTYLARVFSYPAGNVESTGSAGEPLYENSPEFTPYLETNLGQPTIQSFEQVGT
KVNVTVEDERTLVRRNNTFLSLRDVFGKDLIYTLYYWKSSSSGKKTAKTNTNEF
LIDVDKGENYCFSVQAVIPSRTVNRKSTDSPVECMGQEKGEFRENWVNVISDLK
KIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLI
ILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS (SEQ ID NO: 116).

In some embodiments, a first chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86%

identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

TACTTCGGCAAACTGGAATCCAAGCTGAGCGTGATCCGGAATTTAAACGACC
AAGTTCTGTTTATCGATCAAGGTAACCGGCCTCTGTTCGAGGACATGACCGAC
TCCGATTGCCGGGACAATGCCCCCCGGACCATCTTCATTATCTCCATGTACAA
GGACAGCCAGCCCCGGGGCATGGCTGTGACAATTAGCGTGAAGTGTGAGAA
AATCAGCACTTTATCTTGTGAGAACAAGATCATCTCCTTTAAGGAAATGAACC
CCCCCGATAACATCAAGGACACCAAGTCCGATATCATCTTCTTCCAGCGGTCC
GTGCCCGGTCACGATAACAAGATGCAGTTCGAATCCTCCTCCTACGAGGGCT
ACTTTTTAGCTTGTGAAAAGGAGAGGGATTTATTCAAGCTGATCCTCAAGAA
GGAGGACGAGCTGGGCGATCGTTCCATCATGTTCACCGTCCAAAACGAGGAT
AGCGGCACAACCAACACAGTCGCTGCCTATAACCTCACTTGGAAGAGCACCA
ACTTCAAAACCATCCTCGAATGGGAACCCAAACCCGTTAACCAAGTTTACAC
CGTGCAGATCAGCACCAAGTCCGGCGACTGGAAGTCCAAATGTTTCTATACC
ACCGACACCGAGTGCGATCTCACCGATGAGATCGTGAAAGATGTGAAACAGA
CCTACCTCGCCCGGGTGTTTAGCTACCCCGCCGGCAATGTGGAGAGCACTGG
TTCCGCTGGCGAGCCTTTATACGAGAACAGCCCCGAATTTACCCCTTACCTCG
AGACCAATTTAGGACAGCCCACCATCCAAAGCTTTGAGCAAGTTGGCACAAA
GGTGAATGTGACAGTGGAGGACGAGCGGACTTTAGTGCGGCGGAACAACAC
CTTTCTCAGCCTCCGGGATGTGTTCGGCAAAGATTTAATCTACACACTGTATT
ACTGGAAGTCCTCTTCCTCCGGCAAGAAGACAGCTAAAACCAACACAAACGA
GTTTTTAATCGACGTGGATAAAGGCGAAAACTACTGTTTCAGCGTGCAAGCT
GTGATCCCCTCCCGGACCGTGAATAGGAAAAGCACCGATAGCCCCGTTGAGT
GCATGGGCCAAGAAAAGGGCGAGTTCCGGGAGAACTGGGTGAACGTCATCA
GCGATTTAAAGAAGATCGAAGATTTAATTCAGTCCATGCATATCGACGCCAC
TTTATACACAGAATCCGACGTGCACCCCTCTTGTAAGGTGACCGCCATGAAAT
GTTTTTTACTGGAGCTGCAAGTTATCTCTTTAGAGAGCGGAGACGCTAGCATC
CACGACACCGTGGAGAATTTAATCATTTTAGCCAATAACTCTTTATCCAGCAA
CGGCAACGTGACAGAGTCCGGCTGCAAGGAGTGCGAAGAGCTGGAGGAGAA
GAACATCAAGGAGTTTCTGCAATCCTTTGTGCACATTGTCCAGATGTTCATCA
ATACCTCC (SEQ ID NO: 117).

In some embodiments, a first chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

MKWVTFISLLFLFSSAYSYFGKLESKLSVIRNLNDQVLFIDQGNRPLFEDMTDSD
CRDNAPRTIFIISMYKDSQPRGMAVTISVKCEKISTLSCENKIISFKEMNPPDNIKD

TKSDIIFFQRSVPGHDNKMQFESSSYEGYFLACEKERDLFKLILKKEDELGDRSIM
FTVQNEDSGTTNTVAAYNLTWKSTNFKTILEWEPKPVNQVYTVQISTKSGDWKS
KCFYTTDTECDLTDEIVKDVKQTYLARVFSYPAGNVESTGSAGEPLYENSPEFTP
YLETNLGQPTIQSFEQVGTKVNVTVEDERTLVRRNNTFLSLRDVFGKDLIYTLYY
WKSSSSGKKTAKTNTNEFLIDVDKGENYCFSVQAVIPSRTVNRKSTDSPVECMG
QEKGEFRENWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLEL
QVISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFV
HIVQMFINTS (SEQ ID NO: 118).

In some embodiments, a first chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATGAAGTGGGTCACATTTATCTCTTTACTGTTCCTCTTCTCCAGCGCCTACAGC
TACTTCGGCAAACTGGAATCCAAGCTGAGCGTGATCCGGAATTTAAACGACC
AAGTTCTGTTTATCGATCAAGGTAACCGGCCTCTGTTCGAGGACATGACCGAC
TCCGATTGCCGGGACAATGCCCCCCGGACCATCTTCATTATCTCCATGTACAA
GGACAGCCAGCCCCGGGGCATGGCTGTGACAATTAGCGTGAAGTGTGAGAA
AATCAGCACTTTATCTTGTGAGAACAAGATCATCTCCTTTAAGGAAATGAACC
CCCCCGATAACATCAAGGACACCAAGTCCGATATCATCTTCTTCCAGCGGTCC
GTGCCCGGTCACGATAACAAGATGCAGTTCGAATCCTCCTCCTACGAGGGCT
ACTTTTTAGCTTGTGAAAAGGAGAGGGATTTATTCAAGCTGATCCTCAAGAA
GGAGGACGAGCTGGGCGATCGTTCCATCATGTTCACCGTCCAAAACGAGGAT
AGCGGCACAACCAACACAGTCGCTGCCTATAACCTCACTTGGAAGAGCACCA
ACTTCAAAACCATCCTCGAATGGGAACCCAAACCCGTTAACCAAGTTTACAC
CGTGCAGATCAGCACCAAGTCCGGCGACTGGAAGTCCAAATGTTTCTATACC
ACCGACACCGAGTGCGATCTCACCGATGAGATCGTGAAAGATGTGAAACAGA
CCTACCTCGCCCGGGTGTTTAGCTACCCCGCCGGCAATGTGGAGAGCACTGG
TTCCGCTGGCGAGCCTTTATACGAGAACAGCCCCGAATTTACCCCTTACCTCG
AGACCAATTTAGGACAGCCCACCATCCAAAGCTTTGAGCAAGTTGGCACAAA
GGTGAATGTGACAGTGGAGGACGAGCGGACTTTAGTGCGGCGGAACAACAC
CTTTCTCAGCCTCCGGGATGTGTTCGGCAAAGATTTAATCTACACACTGTATT
ACTGGAAGTCCTCTTCCTCCGGCAAGAAGACAGCTAAAACCAACACAAACGA
GTTTTTAATCGACGTGGATAAAGGCGAAAACTACTGTTTCAGCGTGCAAGCT
GTGATCCCCTCCCGGACCGTGAATAGGAAAAGCACCGATAGCCCCGTTGAGT
GCATGGGCCAAGAAAAGGGCGAGTTCCGGGAGAACTGGGTGAACGTCATCA
GCGATTTAAAGAAGATCGAAGATTTAATTCAGTCCATGCATATCGACGCCAC
TTTATACACAGAATCCGACGTGCACCCCTCTTGTAAGGTGACCGCCATGAAAT
GTTTTTTACTGGAGCTGCAAGTTATCTCTTTAGAGAGCGGAGACGCTAGCATC
CACGACACCGTGGAGAATTTAATCATTTTAGCCAATAACTCTTTATCCAGCAA
CGGCAACGTGACAGAGTCCGGCTGCAAGGAGTGCGAAGAGCTGGAGGAGAA

GAACATCAAGGAGTTTCTGCAATCCTTTGTGCACATTGTCCAGATGTTCATCA
ATACCTCC (SEQ ID NO: 119).

In some embodiments, the second chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

IWELKKDVYVVELDWYPDAPGEMVVLTCDTPEEDGITWTLDQSSEVLGSGKTLT
IQVKEFGDAGQYTCHKGGEVLSHSLLLLHKKEDGIWSTDILKDQKEPKNKTFLR
CEAKNYSGRFTCWWLTTISTDLTFSVKSSRGSSDPQGVTCGAATLSAERVRGDN
KEYEYSVECQEDSACPAAEESLPIEVMVDAVHKLKYENYTSSFFIRDIIKPDPPKN
LQLKPLKNSRQVEVSWEYPDTWSTPHSYFSLTFCVQVQGKSKREKKDRVFTDKT
SATVICRKNASISVRAQDRYYSSSWSEWASVPCSGGGGSGGGGSGGGGSRNLPV
ATPDPGMFPCLHHSQNLLRAVSNMLQKARQTLEFYPCTSEEIDHEDITKDKTSTV
EACLPLELTKNESCLNSRETSFITNGSCLASRKTSFMMALCLSSIYEDLKMYQVEF
KTMNAKLLMDPKRQIFLDQNMLAVIDELMQALNFNSETVPQKSSLEEPDFYKTK
IKLCILLHAFRIRAVTIDRVMSYLNASITCPPPMSVEHADIWVKSYSLYSRERYICN
SGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRSELTQDPAVSVALGQTVRIT
CQGDSLRSYYASWYQQKPGQAPVLVIYGKNNRPSGIPDRFSGSSSGNTASLTITG
AQAEDEADYYCNSRDSSGNHVVFGGGTKLTVGHGGGGSGGGGSGGGGSEVQL
VESGGGVVRPGGSLRLSCAASGFTFDDYGMSWVRQAPGKGLEWVSGINWNGG
STGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGRSLLFDYWGQ
GTLVTVSR (SEQ ID NO: 120).

In some embodiments, a second chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATTTGGGAACTGAAGAAGGACGTCTACGTGGTCGAACTGGACTGGTATCCCG
ATGCTCCCGGCGAAATGGTGGTGCTCACTTGTGACACCCCCGAAGAAGACGG
CATCACTTGGACCCTCGATCAGAGCAGCGAGGTGCTGGGCTCCGGAAAGACC
CTCACAATCCAAGTTAAGGAGTTCGGAGACGCTGGCCAATACACATGCCACA
AGGGAGGCGAGGTGCTCAGCCATTCCTTATTATTATTACACAAGAAGGAAGA
CGGAATCTGGTCCACCGACATTTTAAAAGATCAGAAGGAGCCCAAGAATAAG
ACCTTTTTAAGGTGTGAGGCCAAAAACTACAGCGGTCGTTTCACTTGTTGGTG
GCTGACCACCATTTCCACCGATTTAACCTTCTCCGTGAAAAGCAGCCGGGGA
AGCTCCGACCCTCAAGGTGTGACATGTGGAGCCGCTACCCTCAGCGCTGAGA
GGGTTCGTGGCGATAACAAGGAATACGAGTACAGCGTGGAGTGCCAAGAAG

ATAGCGCTTGTCCCGCTGCCGAAGAATCTTTACCCATTGAGGTGATGGTGGAC
GCCGTGCACAAACTCAAGTACGAGAACTACACCTCCTCCTTCTTTATCCGGGA
CATCATTAAGCCCGATCCTCCTAAGAATTTACAGCTGAAGCCTCTCAAAAATA
GCCGGCAAGTTGAGGTCTCTTGGGAATATCCCGACACTTGGAGCACACCCCA
CAGCTACTTCTCTTTAACCTTTTGTGTGCAAGTTCAAGGTAAAAGCAAGCGGG
AGAAGAAAGACCGGGTGTTTACCGACAAAACCAGCGCCACCGTCATCTGTCG
GAAGAACGCCTCCATCAGCGTGAGGGCTCAAGATCGTTATTACTCCAGCAGC
TGGTCCGAGTGGGCCAGCGTGCCTTGTTCCGGCGGTGGAGGATCCGGAGGAG
GTGGCTCCGGCGGCGGAGGATCTCGTAACCTCCCCGTGGCTACCCCCGATCC
CGGAATGTTCCCTTGTTTACACCACAGCCAGAATTTACTGAGGGCCGTGAGC
AACATGCTGCAGAAAGCTAGGCAGACTTTAGAATTTTACCCTTGCACCAGCG
AGGAGATCGACCATGAAGATATCACCAAGGACAAGACATCCACCGTGGAGG
CTTGTTTACCTCTGGAGCTGACAAAGAACGAGTCTTGTCTCAACTCTCGTGAA
ACCAGCTTCATCACAAATGGCTCTTGTTTAGCTTCCCGGAAGACCTCCTTTAT
GATGGCTTTATGCCTCAGCTCCATCTACGAGGATTTAAAGATGTACCAAGTGG
AGTTCAAGACCATGAACGCCAAGCTGCTCATGGACCCTAAACGGCAGATCTT
TTTAGACCAGAACATGCTGGCTGTGATTGATGAGCTGATGCAAGCTTTAAACT
TCAACTCCGAGACCGTCCCTCAGAAGTCCTCCCTCGAGGAGCCCGATTTTTAC
AAGACAAAGATCAAACTGTGCATTTTACTCCACGCCTTTAGGATCCGGGCCG
TGACCATTGACCGGGTCATGAGCTATTTAAACGCCAGCATTACATGCCCCCCT
CCCATGAGCGTGGAGCACGCCGACATCTGGGTGAAGAGCTATAGCCTCTACA
GCCGGGAGAGGTATATCTGTAACAGCGGCTTCAAGAGGAAGGCCGGCACCA
GCAGCCTCACCGAGTGCGTGCTGAATAAGGCTACCAACGTGGCTCACTGGAC
AACACCCTCTTTAAAGTGCATCCGGTCCGAGCTGACCCAGGACCCTGCTGTGT
CCGTGGCTCTGGGCCAGACCGTGAGGATCACCTGCCAGGGCGACTCCCTGAG
GTCCTACTACGCCTCCTGGTACCAGCAGAAGCCCGGCCAGGCTCCTGTGCTG
GTGATCTACGGCAAGAACAACAGGCCCTCCGGCATCCCTGACAGGTTCTCCG
GATCCTCCTCCGGCAACACCGCCTCCCTGACCATCACAGGCGCTCAGGCCGA
GGACGAGGCTGACTACTACTGCAACTCCAGGGACTCCTCCGGCAACCATGTG
GTGTTCGGCGGCGGCACCAAGCTGACCGTGGGCCATGGCGGCGGCGGCTCCG
GAGGCGGCGGCAGCGGCGGAGGAGGATCCGAGGTGCAGCTGGTGGAGTCCG
GAGGAGGAGTGGTGAGGCCTGGAGGCTCCCTGAGGCTGAGCTGTGCTGCCTC
CGGCTTCACCTTCGACGACTACGGCATGTCCTGGGTGAGGCAGGCTCCTGGA
AAGGGCCTGGAGTGGGTGTCCGGCATCAACTGGAACGGCGGATCCACCGGCT
ACGCCGATTCCGTGAAGGGCAGGTTCACCATCAGCAGGGACAACGCCAAGA
ACTCCCTGTACCTGCAGATGAACTCCCTGAGGGCCGAGGACACCGCCGTGTA
CTACTGCGCCAGGGGCAGGTCCCTGCTGTTCGACTACTGGGGACAGGGCACC
CTGGTGACCGTGTCCAGG (SEQ ID NO: 121).

In some embodiments, a second chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least

94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

MKWVTFISLLFLFSSAYSIWELKKDVYVVELDWYPDAPGEMVVLTCDTPEEDGI
TWTLDQSSEVLGSGKTLTIQVKEFGDAGQYTCHKGGEVLSHSLLLLHKKEDGIW
STDILKDQKEPKNKTFLRCEAKNYSGRFTCWWLTTISTDLTFSVKSSRGSSDPQG
VTCGAATLSAERVRGDNKEYEYSVECQEDSACPAAEESLPIEVMVDAVHKLKYE
NYTSSFFIRDIIKPDPPKNLQLKPLKNSRQVEVSWEYPDTWSTPHSYFSLTFCVQV
QGKSKREKKDRVFTDKTSATVICRKNASISVRAQDRYYSSSWSEWASVPCSGGG
GSGGGGSGGGGSRNLPVATPDPGMFPCLHHSQNLLRAVSNMLQKARQTLEFYP
CTSEEIDHEDITKDKTSTVEACLPLELTKNESCLNSRETSFITNGSCLASRKTSFMM
ALCLSSIYEDLKMYQVEFKTMNAKLLMDPKRQIFLDQNMLAVIDELMQALNFNS
ETVPQKSSLEEPDFYKTKIKLCILLHAFRIRAVTIDRVMSYLNASITCPPPMSVEHA
DIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRSE
LTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVIYGKNNRPSGI
PDRFSGSSSGNTASLTITGAQAEDEADYYCNSRDSSGNHVVFGGGTKLTVGHGG
GGSGGGGSGGGGSEVQLVESGGGVVRPGGSLRLSCAASGFTFDDYGMSWVRQA
PGKGLEWVSGINWNGGSTGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAV
YYCARGRSLLFDYWGQGTLVTVSR (SEQ ID NO: 122).

In some embodiments, a second chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATGAAATGGGTGACCTTTATTTCTTTACTGTTCCTCTTTAGCAGCGCCTACTCC
ATTTGGGAACTGAAGAAGGACGTCTACGTGGTCGAACTGGACTGGTATCCCG
ATGCTCCCGGCGAAATGGTGGTGCTCACTTGTGACACCCCCGAAGAAGACGG
CATCACTTGGACCCTCGATCAGAGCAGCGAGGTGCTGGGCTCCGGAAAGACC
CTCACAATCCAAGTTAAGGAGTTCGGAGACGCTGGCCAATACACATGCCACA
AGGGAGGCGAGGTGCTCAGCCATTCCTTATTATTATTACACAAGAAGGAAGA
CGGAATCTGGTCCACCGACATTTTAAAAGATCAGAAGGAGCCCAAGAATAAG
ACCTTTTTAAGGTGTGAGGCCAAAAACTACAGCGGTCGTTTCACTTGTTGGTG
GCTGACCACCATTTCCACCGATTTAACCTTCTCCGTGAAAAGCAGCCGGGGA
AGCTCCGACCCTCAAGGTGTGACATGTGGAGCCGCTACCCTCAGCGCTGAGA
GGGTTCGTGGCGATAACAAGGAATACGAGTACAGCGTGGAGTGCCAAGAAG
ATAGCGCTTGTCCCGCTGCCGAAGAATCTTTACCCATTGAGGTGATGGTGGAC
GCCGTGCACAAACTCAAGTACGAGAACTACACCTCCTCCTTCTTTATCCGGGA
CATCATTAAGCCCGATCCTCCTAAGAATTTACAGCTGAAGCCTCTCAAAAATA
GCCGGCAAGTTGAGGTCTCTTGGGAATATCCCGACACTTGGAGCACACCCCA
CAGCTACTTCTCTTTAACCTTTTGTGTGCAAGTTCAAGGTAAAAGCAAGCGGG
AGAAGAAAGACCGGGTGTTTACCGACAAAACCAGCGCCACCGTCATCTGTCG
GAAGAACGCCTCCATCAGCGTGAGGGCTCAAGATCGTTATTACTCCAGCAGC

TGGTCCGAGTGGGCCAGCGTGCCTTGTTCCGGCGGTGGAGGATCCGGAGGAG
GTGGCTCCGGCGGCGGAGGATCTCGTAACCTCCCCGTGGCTACCCCCGATCC
CGGAATGTTCCCTTGTTTACACCACAGCCAGAATTTACTGAGGGCCGTGAGC
AACATGCTGCAGAAAGCTAGGCAGACTTTAGAATTTTACCCTTGCACCAGCG
AGGAGATCGACCATGAAGATATCACCAAGGACAAGACATCCACCGTGGAGG
CTTGTTTACCTCTGGAGCTGACAAAGAACGAGTCTTGTCTCAACTCTCGTGAA
ACCAGCTTCATCACAAATGGCTCTTGTTTAGCTTCCCGGAAGACCTCCTTTAT
GATGGCTTTATGCCTCAGCTCCATCTACGAGGATTTAAAGATGTACCAAGTGG
AGTTCAAGACCATGAACGCCAAGCTGCTCATGGACCCTAAACGGCAGATCTT
TTTAGACCAGAACATGCTGGCTGTGATTGATGAGCTGATGCAAGCTTTAAACT
TCAACTCCGAGACCGTCCCTCAGAAGTCCTCCCTCGAGGAGCCCGATTTTTAC
AAGACAAAGATCAAACTGTGCATTTTACTCCACGCCTTTAGGATCCGGGCCG
TGACCATTGACCGGGTCATGAGCTATTTAAACGCCAGCATTACATGCCCCCCT
CCCATGAGCGTGGAGCACGCCGACATCTGGGTGAAGAGCTATAGCCTCTACA
GCCGGGAGAGGTATATCTGTAACAGCGGCTTCAAGAGGAAGGCCGGCACCA
GCAGCCTCACCGAGTGCGTGCTGAATAAGGCTACCAACGTGGCTCACTGGAC
AACACCCTCTTTAAAGTGCATCCGGTCCGAGCTGACCCAGGACCCTGCTGTGT
CCGTGGCTCTGGGCCAGACCGTGAGGATCACCTGCCAGGGCGACTCCCTGAG
GTCCTACTACGCCTCCTGGTACCAGCAGAAGCCCGGCCAGGCTCCTGTGCTG
GTGATCTACGGCAAGAACAACAGGCCCTCCGGCATCCCTGACAGGTTCTCCG
GATCCTCCTCCGGCAACACCGCCTCCCTGACCATCACAGGCGCTCAGGCCGA
GGACGAGGCTGACTACTACTGCAACTCCAGGGACTCCTCCGGCAACCATGTG
GTGTTCGGCGGCGGCACCAAGCTGACCGTGGGCCATGGCGGCGGCGGCTCCG
GAGGCGGCGGCAGCGGCGGAGGAGGATCCGAGGTGCAGCTGGTGGAGTCCG
GAGGAGGAGTGGTGAGGCCTGGAGGCTCCCTGAGGCTGAGCTGTGCTGCCTC
CGGCTTCACCTTCGACGACTACGGCATGTCCTGGGTGAGGCAGGCTCCTGGA
AAGGGCCTGGAGTGGGTGTCCGGCATCAACTGGAACGGCGGATCCACCGGCT
ACGCCGATTCCGTGAAGGGCAGGTTCACCATCAGCAGGGACAACGCCAAGA
ACTCCCTGTACCTGCAGATGAACTCCCTGAGGGCCGAGGACACCGCCGTGTA
CTACTGCGCCAGGGGCAGGTCCCTGCTGTTCGACTACTGGGGACAGGGCACC
CTGGTGACCGTGTCCAGG (SEQ ID NO: 123).

Exemplary Multi-Chain Chimeric Polypeptides- Type F

In some embodiments of any of the multi-chain chimeric polypeptides described herein, the first target-binding domain and the second targeting-binding domain each independently bind specifically to a receptor for IL-7 (e.g., a soluble human IL-7), CD16 (e.g., an anti-CD16 scFv), or a receptor for IL-21 (e.g., a soluble human IL-21). In some embodiments of these multi-chain chimeric polypeptides described herein, the first chimeric polypeptide further includes the additional target-binding domain. In some embodiments of these multi-chain chimeric polypeptides described herein, the second chimeric polypeptide further includes the additional target-binding domain. In some

embodiments of these multi-chain chimeric polypeptides described herein, the additional target-binding domain binds specifically to CD16 or a receptor for IL-21.

In some examples of these multi-chain chimeric polypeptides, the first target-binding domain and the soluble tissue factor domain directly abut each other in the first chimeric polypeptide. In some examples of these multi-chain chimeric polypeptides, the first chimeric polypeptide further comprises a linker sequence (e.g., any of the exemplary linkers described herein) between the first target-binding domain and the soluble tissue factor domain in the first chimeric polypeptide.

In some embodiments of these multi-chain chimeric polypeptides, 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 embodiments of these multi-chain chimeric polypeptides, the first chimeric polypeptide further includes a linker sequence (e.g., any of the exemplary linkers described herein) between the soluble tissue factor domain and the first domain of the pair of affinity domains in the first chimeric polypeptide.

In some embodiments of these multi-chain chimeric polypeptides, 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 embodiments of these multi-chain chimeric polypeptides, the second chimeric polypeptide further includes a linker sequence (e.g., any of the exemplary linkers described herein) between the second domain of the pair of affinity domains and the second target-binding domain in the second chimeric polypeptide.

In some embodiments, the second chimeric polypeptide further comprises one or more additional target-binding domains at the N-terminal end or the C-terminal end of the second chimeric polypeptide.

In some embodiments of these multi-chain chimeric polypeptides, the additional target-binding domain and the second domain of the pair of affinity domains directly abut each other in the second chimeric polypeptide. In some embodiments of these multi-chain chimeric polypeptides, the second chimeric polypeptide further includes a linker sequence (e.g., any of the exemplary linkers described herein) between the second

domain of the pair of affinity domains and the additional target-binding domain in the second chimeric polypeptide.

In some embodiments of these multi-chain chimeric polypeptides, the additional target-binding domain and the second target-binding domain directly abut each other in the second chimeric polypeptide. In some embodiments of these multi-chain chimeric polypeptides, the second chimeric polypeptide further includes a linker sequence (e.g., any of the exemplary linkers described herein) between the second target-binding domain and the additional target-binding domain in the second chimeric polypeptide.

In some embodiments of these multi-chain chimeric polypeptides, the soluble tissue factor domain can be any of the exemplary soluble tissue factor domains described herein. In some embodiments of these multi-chain chimeric polypeptides, the pair of affinity domains can be any of the exemplary pairs of affinity domains described herein.

In some embodiments of these multi-chain chimeric polypeptides, one or more of the first target-binding domain, the second target-binding domain and the additional antigen-binding domain is an agonistic antigen-binding domain. In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain, the second target-binding domain, and the additional antigen-binding domain are each agonistic antigen-binding domains. In some embodiments of these multi-chain chimeric polypeptides, the antigen-binding domain includes a scFv or single-domain antibody.

In some embodiments of any of the multi-chain chimeric polypeptides described herein, the first target-binding domain binds specifically to a receptor IL-7 and the second target-binding domain binds specifically to CD16 or a receptor for IL-21. In some embodiments of any of the multi-chain chimeric polypeptides described herein, the first target-binding domain includes a soluble IL-7 protein. In some embodiments of any of the multi-chain chimeric polypeptides described herein, the soluble IL-7 protein is a soluble human IL-7. In some embodiments of any of the multi-chain chimeric polypeptides described herein, the second antigen-binding domain includes a target-binding domain that binds specifically to CD16. In some embodiments of any of the multi-chain chimeric polypeptides described herein, the second target-binding domain includes an scFv that binds specifically to CD16. In some embodiments of any of the multi-chain chimeric polypeptides described herein, the second target-binding domain

binds specifically to a receptor for IL-21. In some embodiments of any of the multi-chain chimeric polypeptides described herein, the second target-binding domain includes a soluble IL-21. In some embodiments of any of the multi-chain chimeric polypeptides described herein, the soluble IL-21 is a soluble human IL-21. In some embodiments of any of the multi-chain chimeric polypeptides described herein, the second chimeric polypeptide further includes an additional target-binding domain that binds specifically to a receptor for IL-21. In some embodiments of any of the multi-chain chimeric polypeptides described herein, the additional target-binding domain includes a soluble IL-21. In some embodiments of any of the multi-chain chimeric polypeptides described herein, the soluble IL-21 is a soluble human IL-21. In some embodiments of any of the multi-chain chimeric polypeptides described herein, the second chimeric polypeptide further includes an additional target-binding domain that binds specifically to CD16.

In some embodiments of these multi-chain chimeric polypeptides, two or more of the first target-binding domain, the second target-binding domain, and the one or more additional target-binding domains bind specifically to the same antigen. In some embodiments, two or more of the first target-binding domain, the second target-binding domain, and the one or more additional target-binding domains bind specifically to the same epitope. In some embodiments, two or more of the first target-binding domain, the second target-binding domain, and the one or more additional target-binding domains comprise the same amino acid sequence.

In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain includes a soluble IL-7 (e.g., a soluble human IL-7).

In some embodiments of these multi-chain chimeric polypeptides, the soluble human IL-7 includes a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

DCDIEGKDGKQYESVLMVSIDQLLDSMKEIGSNCLNNEFNFFKRHICDANKEGM
FLFRAARKLRQFLKMNSTGDFDLHLLKVSEGTTILLNCTGQVKGRKPAALGEAQ
PTKSLEENKSLKEQKKLNDLCFLKRLLQEIKTCWNKILMGTKEH (SEQ ID NO: 11).

In some embodiments of these multi-chain chimeric polypeptides, the soluble human IL-7 is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

GATTGTGATATTGAAGGTAAAGATGGCAAACAATATGAGAGTGTTCTAATGG
TCAGCATCGATCAATTATTGGACAGCATGAAAGAAATTGGTAGCAATTGCCT
GAATAATGAATTTAACTTTTTTAAAAGACATATCTGTGATGCTAATAAGGAA
GGTATGTTTTTATTCCGTGCTGCTCGCAAGTTGAGGCAATTTCTTAAAATGAA
TAGCACTGGTGATTTTGATCTCCACTTATTAAAAGTTTCAGAAGGCACAACAA
TACTGTTGAACTGCACTGGCCAGGTTAAAGGAAGAAAACCAGCTGCCCTGGG
TGAAGCCCAACCAACAAAGAGTTTGGAAGAAAATAAATCTTTAAAGGAACA
GAAAAAACTGAATGACTTGTGTTTCCTAAAGAGACTATTACAAGAGATAAAA
ACTTGTTGGAATAAAATTTTGATGGGCACTAAAGAACAC (SEQ ID NO: 95).

In some embodiments of these multi-chain chimeric polypeptides, the soluble human IL-7 is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

GATTGCGACATCGAGGGCAAGGACGGCAAGCAGTACGAGAGCGTGCTGATG
GTGTCCATCGACCAGCTGCTGGACAGCATGAAGGAGATCGGCTCCAACTGCC
TCAACAACGAGTTCAACTTCTTCAAGCGGCACATCTGCGACGCCAACAAGGA
GGGCATGTTCCTGTTCAGGGCCGCCAGGAAACTGCGGCAGTTCCTGAAGATG
AACTCCACCGGCGACTTCGACCTGCACCTGCTGAAGGTGTCCGAGGGCACCA
CCATCCTGCTGAACTGCACCGGACAGGTGAAGGGCCGGAAACCTGCTGCTCT
GGGAGAGGCCCAACCCACCAAGAGCCTGGAGGAGAACAAGTCCCTGAAGGA
GCAGAAGAAGCTGAACGACCTGTGCTTCCTGAAGAGGCTGCTGCAGGAGATC
AAGACCTGCTGGAACAAGATCCTGATGGGCACCAAGGAGCAT (SEQ ID NO: 124).

In some embodiments of these multi-chain chimeric polypeptides, the sequence of soluble human IL-21 comprises a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

QGQDRHMIRMRQLIDIVDQLKNYVNDLVPEFLPAPEDVETNCEWSAFSCFQKAQ
LKSANTGNNERIINVSIKKLKRKPPSTNAGRRQKHRLTCPSCDSYEKKPPKEFLER
FKSLLQKMIHQHLSSRTHGSEDS (SEQ ID NO: 78).

In some embodiments of these multi-chain chimeric polypeptides, the soluble human IL-21 is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

CAAGGTCAAGATCGCCACATGATTAGAATGCGTCAACTTATAGATATTGTTG
ATCAGCTGAAAAATTATGTGAATGACTTGGTCCCTGAATTTCTGCCAGCTCCA
GAAGATGTAGAGACAAACTGTGAGTGGTCAGCTTTTTCCTGTTTTCAGAAGG
CCCAACTAAAGTCAGCAAATACAGGAAACAATGAAAGGATAATCAATGTATC
AATTAAAAAGCTGAAGAGGAAACCACCTTCCACAAATGCAGGGAGAAGACA
GAAACACAGACTAACATGCCCTTCATGTGATTCTTATGAGAAAAAACCACCC
AAAGAATTCCTAGAAAGATTCAAATCACTTCTCCAAAAGATGATTCATCAGC
ATCTGTCCTCTAGAACACACGGAAGTGAAGATTCC (SEQ ID NO: 94).

In some embodiments of these multi-chain chimeric polypeptides, the soluble human IL-21 is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

CAGGGCCAGGACAGGCACATGATCCGGATGAGGCAGCTCATCGACATCGTCG
ACCAGCTGAAGAACTACGTGAACGACCTGGTGCCCGAGTTTCTGCCTGCCCC
CGAGGACGTGGAGACCAACTGCGAGTGGTCCGCCTTCTCCTGCTTTCAGAAG
GCCCAGCTGAAGTCCGCCAACACCGGCAACAACGAGCGGATCATCAACGTG
AGCATCAAGAAGCTGAAGCGGAAGCCTCCCTCCACAAACGCCGGCAGGAGG
CAGAAGCACAGGCTGACCTGCCCCAGCTGTGACTCCTACGAGAAGAAGCCCC
CCAAGGAGTTCCTGGAGAGGTTCAAGTCCCTGCTGCAGAAGATGATCCATCA
GCACCTGTCCTCCAGGACCCACGGCTCCGAGGACTCC (SEQ ID NO: 79)

In some embodiments of these multi-chain chimeric polypeptides, the additional target-binding domain includes an scFv that specifically binds to CD16 (e.g., an anti-CD16 scFv).

In some embodiments of these multi-chain chimeric polypeptides, the scFv that binds specifically to CD16 includes a light chain variable domain that includes a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical,

at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

SELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVIYGKNNRPS GIPDRFSGSSSGNTASLTITGAQAEDEADYYCNSRDSSGNHVVFGGGTKLTVGH (SEQ ID NO: 112).

In some embodiments of these multi-chain chimeric polypeptides, the scFv that binds specifically to CD16 is encoded by a light chain variable domain sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

TCCGAGCTGACCCAGGACCCTGCTGTGTCCGTGGCTCTGGGCCAGACCGTGA GGATCACCTGCCAGGGCGACTCCCTGAGGTCCTACTACGCCTCCTGGTACCA GCAGAAGCCCGGCCAGGCTCCTGTGCTGGTGATCTACGGCAAGAACAACAGG CCCTCCGGCATCCCTGACAGGTTCTCCGGATCCTCCTCCGGCAACACCGCCTC CCTGACCATCACAGGCGCTCAGGCCGAGGACGAGGCTGACTACTACTGCAAC TCCAGGGACTCCTCCGGCAACCATGTGGTGTTCGGCGGCGGCACCAAGCTGA CCGTGGGCCAT (SEQ ID NO: 113).

In some embodiments of these multi-chain chimeric polypeptides, the scFv that binds specifically to CD16 includes a heavy chain variable domain that includes a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

EVQLVESGGGVVRPGGSLRLSCAASGFTFDDYGMSWVRQAPGKGLEWVSGINW NGGSTGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGRSLLFDY WGQGTLVTVSR (SEQ ID NO: 114).

In some embodiments of these multi-chain chimeric polypeptides, the scFv that binds specifically to CD16 is encoded by a heavy chain variable domain sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

GAGGTGCAGCTGGTGGAGTCCGGAGGAGGAGTGGTGAGGCCTGGAGGCTCC
CTGAGGCTGAGCTGTGCTGCCTCCGGCTTCACCTTCGACGACTACGGCATGTC
CTGGGTGAGGCAGGCTCCTGGAAAGGGCCTGGAGTGGGTGTCCGGCATCAAC
TGGAACGGCGGATCCACCGGCTACGCCGATTCCGTGAAGGGCAGGTTCACCA
TCAGCAGGGACAACGCCAAGAACTCCCTGTACCTGCAGATGAACTCCCTGAG
GGCCGAGGACACCGCCGTGTACTACTGCGCCAGGGGCAGGTCCCTGCTGTTC
GACTACTGGGGACAGGGCACCCTGGTGACCGTGTCCAGG (SEQ ID NO: 115).

In some embodiments, the first chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

DCDIEGKDGKQYESVLMVSIDQLLDSMKEIGSNCLNNEFNFFKRHICDANKEGM
FLFRAARKLRQFLKMNSTGDFDLHLLKVSEGTTILLNCTGQVKGRKPAALGEAQ
PTKSLEENKSLKEQKKLNDLCFLKRLLQEIKTCWNKILMGTKEHSGTTNTVAAY
NLTWKSTNFKTILEWEPKPVNQVYTVQISTKSGDWKSKCFYTTDTECDLTDEIVK
DVKQTYLARVFSYPAGNVESTGSAGEPLYENSPEFTPYLETNLGQPTIQSFEQVG
TKVNVTVEDERTLVRRNNTFLSLRDVFGKDLIYTLYYWKSSSSGKKTAKTNTNE
FLIDVDKGENYCFSVQAVIPSRTVNRKSTDSPVECMGQEKGEFRENWVNVISDL
KKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVEN
LIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS (SEQ ID NO: 125).

In some embodiments, a first chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

GATTGCGACATCGAGGGCAAGGACGGCAAGCAGTACGAGAGCGTGCTGATG
GTGTCCATCGACCAGCTGCTGGACAGCATGAAGGAGATCGGCTCCAACTGCC
TCAACAACGAGTTCAACTTCTTCAAGCGGCACATCTGCGACGCCAACAAGGA
GGGCATGTTCCTGTTCAGGGCCGCCAGGAAACTGCGGCAGTTCCTGAAGATG
AACTCCACCGGCGACTTCGACCTGCACCTGCTGAAGGTGTCCGAGGGCACCA
CCATCCTGCTGAACTGCACCGGACAGGTGAAGGGCCGGAAACCTGCTGCTCT
GGGAGAGGCCCAACCCACCAAGAGCCTGGAGGAGAACAAGTCCCTGAAGGA
GCAGAAGAAGCTGAACGACCTGTGCTTCCTGAAGAGGCTGCTGCAGGAGATC
AAGACCTGCTGGAACAAGATCCTGATGGGCACCAAGGAGCATAGCGGCACA
ACCAACACAGTCGCTGCCTATAACCTCACTTGGAAGAGCACCAACTTCAAAA
CCATCCTCGAATGGGAACCCAAACCCGTTAACCAAGTTTACACCGTGCAGAT

CAGCACCAAGTCCGGCGACTGGAAGTCCAAATGTTTCTATACCACCGACACC
GAGTGCGATCTCACCGATGAGATCGTGAAAGATGTGAAACAGACCTACCTCG
CCCGGGTGTTTAGCTACCCCGCCGGCAATGTGGAGAGCACTGGTTCCGCTGG
CGAGCCTTTATACGAGAACAGCCCCGAATTTACCCCTTACCTCGAGACCAATT
TAGGACAGCCCACCATCCAAAGCTTTGAGCAAGTTGGCACAAAGGTGAATGT
GACAGTGGAGGACGAGCGGACTTTAGTGCGGCGGAACAACACCTTTCTCAGC
CTCCGGGATGTGTTCGGCAAAGATTTAATCTACACACTGTATTACTGGAAGTC
CTCTTCCTCCGGCAAGAAGACAGCTAAAACCAACACAAACGAGTTTTTAATC
GACGTGGATAAAGGCGAAAACTACTGTTTCAGCGTGCAAGCTGTGATCCCCT
CCCGGACCGTGAATAGGAAAAGCACCGATAGCCCCGTTGAGTGCATGGGCCA
AGAAAAGGGCGAGTTCCGGGAGAACTGGGTGAACGTCATCAGCGATTTAAA
GAAGATCGAAGATTTAATTCAGTCCATGCATATCGACGCCACTTTATACACA
GAATCCGACGTGCACCCCTCTTGTAAGGTGACCGCCATGAAATGTTTTTTACT
GGAGCTGCAAGTTATCTCTTTAGAGAGCGGAGACGCTAGCATCCACGACACC
GTGGAGAATTTAATCATTTTAGCCAATAACTCTTTATCCAGCAACGGCAACGT
GACAGAGTCCGGCTGCAAGGAGTGCGAAGAGCTGGAGGAGAAGAACATCAA
GGAGTTTCTGCAATCCTTTGTGCACATTGTCCAGATGTTCATCAATACCTCC
(SEQ ID NO: 126).

In some embodiments, a first chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

MKWVTFISLLFLFSSAYSDCDIEGKDGKQYESVLMVSIDQLLDSMKEIGSNCLNN
EFNFFKRHICDANKEGMFLFRAARKLRQFLKMNSTGDFDLHLLKVSEGTTILLNC
TGQVKGRKPAALGEAQPTKSLEENKSLKEQKKLNDLCFLKRLLQEIKTCWNKIL
MGTKEHSGTTNTVAAYNLTWKSTNFKTILEWEPKPVNQVYTVQISTKSGDWKS
KCFYTTDTECDLTDEIVKDVKQTYLARVFSYPAGNVESTGSAGEPLYENSPEFTP
YLETNLGQPTIQSFEQVGTKVNVTVEDERTLVRRNNTFLSLRDVFGKDLIYTLYY
WKSSSSGKKTAKTNTNEFLIDVDKGENYCFSVQAVIPSRTVNRKSTDSPVECMG
QEKGEFRENWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLEL
QVISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFV
HIVQMFINTS (SEQ ID NO: 127).

In some embodiments, a first chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATGAAGTGGGTGACCTTCATCAGCCTGCTGTTCCTGTTCTCCAGCGCCTACTC
CGATTGCGACATCGAGGGCAAGGACGGCAAGCAGTACGAGAGCGTGCTGAT
GGTGTCCATCGACCAGCTGCTGGACAGCATGAAGGAGATCGGCTCCAACTGC
CTCAACAACGAGTTCAACTTCTTCAAGCGGCACATCTGCGACGCCAACAAGG
AGGGCATGTTCCTGTTCAGGGCCGCCAGGAAACTGCGGCAGTTCCTGAAGAT
GAACTCCACCGGCGACTTCGACCTGCACCTGCTGAAGGTGTCCGAGGGCACC
ACCATCCTGCTGAACTGCACCGGACAGGTGAAGGGCCGGAAACCTGCTGCTC
TGGGAGAGGCCCAACCCACCAAGAGCCTGGAGGAGAACAAGTCCCTGAAGG
AGCAGAAGAAGCTGAACGACCTGTGCTTCCTGAAGAGGCTGCTGCAGGAGAT
CAAGACCTGCTGGAACAAGATCCTGATGGGCACCAAGGAGCATAGCGGCAC
AACCAACACAGTCGCTGCCTATAACCTCACTTGGAAGAGCACCAACTTCAAA
ACCATCCTCGAATGGGAACCCAAACCCGTTAACCAAGTTTACACCGTGCAGA
TCAGCACCAAGTCCGGCGACTGGAAGTCCAAATGTTTCTATACCACCGACAC
CGAGTGCGATCTCACCGATGAGATCGTGAAAGATGTGAAACAGACCTACCTC
GCCCGGGTGTTTAGCTACCCCGCCGGCAATGTGGAGAGCACTGGTTCCGCTG
GCGAGCCTTTATACGAGAACAGCCCCGAATTTACCCCTTACCTCGAGACCAA
TTTAGGACAGCCCACCATCCAAAGCTTTGAGCAAGTTGGCACAAAGGTGAAT
GTGACAGTGGAGGACGAGCGGACTTTAGTGCGGCGGAACAACACCTTTCTCA
GCCTCCGGGATGTGTTCGGCAAAGATTTAATCTACACACTGTATTACTGGAAG
TCCTCTTCCTCCGGCAAGAAGACAGCTAAAACCAACACAAACGAGTTTTTAA
TCGACGTGGATAAAGGCGAAAACTACTGTTTCAGCGTGCAAGCTGTGATCCC
CTCCCGGACCGTGAATAGGAAAAGCACCGATAGCCCCGTTGAGTGCATGGGC
CAAGAAAAGGGCGAGTTCCGGGAGAACTGGGTGAACGTCATCAGCGATTTA
AAGAAGATCGAAGATTTAATTCAGTCCATGCATATCGACGCCACTTTATACA
CAGAATCCGACGTGCACCCCTCTTGTAAGGTGACCGCCATGAAATGTTTTTTA
CTGGAGCTGCAAGTTATCTCTTTAGAGAGCGGAGACGCTAGCATCCACGACA
CCGTGGAGAATTTAATCATTTTAGCCAATAACTCTTTATCCAGCAACGGCAAC
GTGACAGAGTCCGGCTGCAAGGAGTGCGAAGAGCTGGAGGAGAAGAACATC
AAGGAGTTTCTGCAATCCTTTGTGCACATTGTCCAGATGTTCATCAATACCTC
C (SEQ ID NO: 128).

In some embodiments, the second chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

SELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVIYGKNNRPS
GIPDRFSGSSSGNTASLTITGAQAEDEADYYCNSRDSSGNHVVFGGGTKLTVGHG
GGGSGGGGSGGGGSEVQLVESGGGVVRPGGSLRLSCAASGFTFDDYGMSWVRQ
APGKGLEWVSGINWNGGSTGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTA
VYYCARGRSLLFDYWGQGTLVTVSRITCPPPMSVEHADIWVKSYSLYSRERYIC
NSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRQGQDRHMIRMRQLIDIVD

QLKNYVNDLVPEFLPAPEDVETNCEWSAFSCFQKAQLKSANTGNNERIINVSIKK
LKRKPPSTNAGRRQKHRLTCPSCDSYEKKPPKEFLERFKSLLQKMIHQHLSSRTH
GSEDS (SEQ ID NO: 129).

In some embodiments, a second chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

TCCGAGCTGACCCAGGACCCTGCTGTGTCCGTGGCTCTGGGCCAGACCGTGA
GGATCACCTGCCAGGGCGACTCCCTGAGGTCCTACTACGCCTCCTGGTACCA
GCAGAAGCCCGGCCAGGCTCCTGTGCTGGTGATCTACGGCAAGAACAACAGG
CCCTCCGGCATCCCTGACAGGTTCTCCGGATCCTCCTCCGGCAACACCGCCTC
CCTGACCATCACAGGCGCTCAGGCCGAGGACGAGGCTGACTACTACTGCAAC
TCCAGGGACTCCTCCGGCAACCATGTGGTGTTCGGCGGCGGCACCAAGCTGA
CCGTGGGCCATGGCGGCGGCGGCTCCGGAGGCGGCGGCAGCGGCGGAGGAG
GATCCGAGGTGCAGCTGGTGGAGTCCGGAGGAGGAGTGGTGAGGCCTGGAG
GCTCCCTGAGGCTGAGCTGTGCTGCCTCCGGCTTCACCTTCGACGACTACGGC
ATGTCCTGGGTGAGGCAGGCTCCTGGAAAGGGCCTGGAGTGGGTGTCCGGCA
TCAACTGGAACGGCGGATCCACCGGCTACGCCGATTCCGTGAAGGGCAGGTT
CACCATCAGCAGGGACAACGCCAAGAACTCCCTGTACCTGCAGATGAACTCC
CTGAGGGCCGAGGACACCGCCGTGTACTACTGCGCCAGGGGCAGGTCCCTGC
TGTTCGACTACTGGGGACAGGGCACCCTGGTGACCGTGTCCAGGATTACATG
CCCCCCTCCCATGAGCGTGGAGCACGCCGACATCTGGGTGAAGAGCTATAGC
CTCTACAGCCGGGAGAGGTATATCTGTAACAGCGGCTTCAAGAGGAAGGCCG
GCACCAGCAGCCTCACCGAGTGCGTGCTGAATAAGGCTACCAACGTGGCTCA
CTGGACAACACCCTCTTTAAAGTGCATCCGGCAGGGCCAGGACAGGCACATG
ATCCGGATGAGGCAGCTCATCGACATCGTCGACCAGCTGAAGAACTACGTGA
ACGACCTGGTGCCCGAGTTTCTGCCTGCCCCCGAGGACGTGGAGACCAACTG
CGAGTGGTCCGCCTTCTCCTGCTTTCAGAAGGCCCAGCTGAAGTCCGCCAAC
ACCGGCAACAACGAGCGGATCATCAACGTGAGCATCAAGAAGCTGAAGCGG
AAGCCTCCCTCCACAAACGCCGGCAGGAGGCAGAAGCACAGGCTGACCTGC
CCCAGCTGTGACTCCTACGAGAAGAAGCCCCCCAAGGAGTTCCTGGAGAGGT
TCAAGTCCCTGCTGCAGAAGATGATCCATCAGCACCTGTCCTCCAGGACCCA
CGGCTCCGAGGACTCC (SEQ ID NO: 130).

In some embodiments, a second chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

MKWVTFISLLFLFSSAYSSELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQ
KPGQAPVLVIYGKNNRPSGIPDRFSGSSSGNTASLTITGAQAEDEADYYCNSRDSS
GNHVVFGGGTKLTVGHGGGGSGGGGSGGGGSEVQLVESGGGVVRPGGSLRLSC
AASGFTFDDYGMSWVRQAPGKGLEWVSGINWNGGSTGYADSVKGRFTISRDNA
KNSLYLQMNSLRAEDTAVYYCARGRSLLFDYWGQGTLVTVSRITCPPPMSVEH
ADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRQ
GQDRHMIRMRQLIDIVDQLKNYVNDLVPEFLPAPEDVETNCEWSAFSCFQKAQL
KSANTGNNERIINVSIKKLKRKPPSTNAGRRQKHRLTCPSCDSYEKKPPKEFLERF
KSLLQKMIHQHLSSRTHGSEDS (SEQ ID NO: 131).

In some embodiments, a second chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATGAAGTGGGTGACCTTCATCAGCCTGCTGTTCCTGTTCTCCAGCGCCTACTC
CTCCGAGCTGACCCAGGACCCTGCTGTGTCCGTGGCTCTGGGCCAGACCGTG
AGGATCACCTGCCAGGGCGACTCCCTGAGGTCCTACTACGCCTCCTGGTACC
AGCAGAAGCCCGGCCAGGCTCCTGTGCTGGTGATCTACGGCAAGAACAACAG
GCCCTCCGGCATCCCTGACAGGTTCTCCGGATCCTCCTCCGGCAACACCGCCT
CCCTGACCATCACAGGCGCTCAGGCCGAGGACGAGGCTGACTACTACTGCAA
CTCCAGGGACTCCTCCGGCAACCATGTGGTGTTCGGCGGCGGCACCAAGCTG
ACCGTGGGCCATGGCGGCGGCGGCTCCGGAGGCGGCGGCAGCGGCGGAGGA
GGATCCGAGGTGCAGCTGGTGGAGTCCGGAGGAGGAGTGGTGAGGCCTGGA
GGCTCCCTGAGGCTGAGCTGTGCTGCCTCCGGCTTCACCTTCGACGACTACGG
CATGTCCTGGGTGAGGCAGGCTCCTGGAAAGGGCCTGGAGTGGGTGTCCGGC
ATCAACTGGAACGGCGGATCCACCGGCTACGCCGATTCCGTGAAGGGCAGGT
TCACCATCAGCAGGGACAACGCCAAGAACTCCCTGTACCTGCAGATGAACTC
CCTGAGGGCCGAGGACACCGCCGTGTACTACTGCGCCAGGGGCAGGTCCCTG
CTGTTCGACTACTGGGGACAGGGCACCCTGGTGACCGTGTCCAGGATTACAT
GCCCCCCTCCCATGAGCGTGGAGCACGCCGACATCTGGGTGAAGAGCTATAG
CCTCTACAGCCGGGAGAGGTATATCTGTAACAGCGGCTTCAAGAGGAAGGCC
GGCACCAGCAGCCTCACCGAGTGCGTGCTGAATAAGGCTACCAACGTGGCTC
ACTGGACAACACCCTCTTTAAAGTGCATCCGGCAGGGCCAGGACAGGCACAT
GATCCGGATGAGGCAGCTCATCGACATCGTCGACCAGCTGAAGAACTACGTG
AACGACCTGGTGCCCGAGTTTCTGCCTGCCCCCGAGGACGTGGAGACCAACT
GCGAGTGGTCCGCCTTCTCCTGCTTTCAGAAGGCCCAGCTGAAGTCCGCCAA
CACCGGCAACAACGAGCGGATCATCAACGTGAGCATCAAGAAGCTGAAGCG
GAAGCCTCCCTCCACAAACGCCGGCAGGAGGCAGAAGCACAGGCTGACCTG
CCCCAGCTGTGACTCCTACGAGAAGAAGCCCCCCAAGGAGTTCCTGGAGAGG
TTCAAGTCCCTGCTGCAGAAGATGATCCATCAGCACCTGTCCTCCAGGACCC
ACGGCTCCGAGGACTCC (SEQ ID NO: 132).

Exemplary Multi-Chain Chimeric Polypeptides- Type G

In some embodiments of any of the multi-chain chimeric polypeptides described herein, the first target-binding domain and the second targeting-binding domain each independently bind specifically to TGFβ (e.g., a human TGFβRII receptor), CD16 (e.g., an anti-CD16 scFv), or a receptor for IL-21 (e.g., a soluble human IL-21). In some embodiments of these multi-chain chimeric polypeptides described herein, the first chimeric polypeptide further includes the additional target-binding domain. In some embodiments of these multi-chain chimeric polypeptides described herein, the second chimeric polypeptide further includes the additional target-binding domain. In some embodiments of these multi-chain chimeric polypeptides described herein, the additional target-binding domain binds specifically to CD16 or a receptor for IL-21.

In some examples of these multi-chain chimeric polypeptides, the first target-binding domain and the soluble tissue factor domain directly abut each other in the first chimeric polypeptide. In some examples of these multi-chain chimeric polypeptides, the first chimeric polypeptide further comprises a linker sequence (e.g., any of the exemplary linkers described herein) between the first target-binding domain and the soluble tissue factor domain in the first chimeric polypeptide.

In some embodiments of these multi-chain chimeric polypeptides, 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 embodiments of these multi-chain chimeric polypeptides, the first chimeric polypeptide further includes a linker sequence (e.g., any of the exemplary linkers described herein) between the soluble tissue factor domain and the first domain of the pair of affinity domains in the first chimeric polypeptide.

In some embodiments of these multi-chain chimeric polypeptides, 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 embodiments of these multi-chain chimeric polypeptides, the second chimeric polypeptide further includes a linker sequence (e.g., any of the exemplary linkers described herein) between the second domain of the pair of affinity domains and the second target-binding domain in the second chimeric polypeptide.

In some embodiments, the second chimeric polypeptide further comprises one or more additional target-binding domains at the N-terminal end or the C-terminal end of the second chimeric polypeptide.

In some embodiments of these multi-chain chimeric polypeptides, the additional target-binding domain and the second domain of the pair of affinity domains directly abut each other in the second chimeric polypeptide. In some embodiments of these multi-chain chimeric polypeptides, the second chimeric polypeptide further includes a linker sequence (e.g., any of the exemplary linkers described herein) between the second domain of the pair of affinity domains and the additional target-binding domain in the second chimeric polypeptide.

In some embodiments of these multi-chain chimeric polypeptides, the additional target-binding domain and the second target-binding domain directly abut each other in the second chimeric polypeptide. In some embodiments of these multi-chain chimeric polypeptides, the second chimeric polypeptide further includes a linker sequence (e.g., any of the exemplary linkers described herein) between the second target-binding domain and the additional target-binding domain in the second chimeric polypeptide.

In some embodiments of these multi-chain chimeric polypeptides, the soluble tissue factor domain can be any of the exemplary soluble tissue factor domains described herein. In some embodiments of these multi-chain chimeric polypeptides, the pair of affinity domains can be any of the exemplary pairs of affinity domains described herein.

In some embodiments of these multi-chain chimeric polypeptides, one or more of the first target-binding domain, the second target-binding domain and the additional antigen-binding domain is an agonistic antigen-binding domain. In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain, the second target-binding domain, and the additional antigen-binding domain are each agonistic antigen-binding domains. In some embodiments of these multi-chain chimeric polypeptides, the antigen-binding domain includes a scFv or single-domain antibody.

In some embodiments of any of the multi-chain chimeric polypeptides described herein, the first target-binding domain and the second targeting-binding domain each independently bind specifically to TGF-β, CD16, or a receptor for IL-21. In some embodiments of any of the multi-chain chimeric polypeptides described herein, the first

target-binding domain binds specifically to a TGF-β and the second target-binding domain binds specifically to CD16 or a receptor of IL-21. In some embodiments of any of the multi-chain chimeric polypeptides described herein, the first target-binding domain is a soluble TGF-β receptor. In some embodiments of any of the multi-chain chimeric polypeptides described herein, soluble TGF-β receptor is a soluble TGFβRII receptor. In some embodiments of any of the multi-chain chimeric polypeptides described herein, the second target-binding domain binds specifically to CD16. In some embodiments of any of the multi-chain chimeric polypeptides described herein, the second antigen-binding domain includes an antigen-binding domain that binds specifically to CD16. In some embodiments of any of the multi-chain chimeric polypeptides described herein, the second antigen-binding domain includes an scFv that binds specifically to CD16. In some embodiments of any of the multi-chain chimeric polypeptides described herein, the second target-binding domain binds specifically to a receptor for IL-21. In some embodiments of any of the multi-chain chimeric polypeptides described herein, the second target-binding domain includes a soluble IL-21. In some embodiments of any of the multi-chain chimeric polypeptides described herein, the second target-binding domain includes a soluble human IL-21. In some embodiments of any of the multi-chain chimeric polypeptides described herein, the second chimeric polypeptide further includes an additional target-binding domain that binds specifically to a receptor for IL-21. In some embodiments of any of the multi-chain chimeric polypeptides described herein, the additional target-binding domain includes a soluble IL-21. In some embodiments of any of the multi-chain chimeric polypeptides described herein, the soluble IL-21 is a soluble human IL-21. In some embodiments of any of the multi-chain chimeric polypeptides described herein, the second chimeric polypeptide further includes an additional target-binding domain that binds specifically to CD16.

In some embodiments of these multi-chain chimeric polypeptides, two or more of the first target-binding domain, the second target-binding domain, and the one or more additional target-binding domains bind specifically to the same antigen. In some embodiments, two or more of the first target-binding domain, the second target-binding domain, and the one or more additional target-binding domains bind specifically to the same epitope. In some embodiments, two or more of the first target-binding domain, the

second target-binding domain, and the one or more additional target-binding domains comprise the same amino acid sequence.

In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain includes a TGFβRII receptor (e.g., a soluble human TGFβRII receptor). In some embodiments of these multi-chain chimeric polypeptides, the soluble human TGFRβRII includes a first sequence of soluble human TGFRβRII and a second sequence of soluble human TGFRβRII. In some embodiments of these multi-chain chimeric polypeptides, the soluble human TGFRβRII includes a linker disposed between the first sequence of soluble human TGFRβRII and the second sequence of soluble human TGFRβRII. In some examples of these multi-chain chimeric polypeptides, the linker includes the sequence GGGGSGGGGSGGGGS (SEQ ID NO: 7).

In some embodiments of these multi-chain chimeric polypeptides, the first sequence of soluble human TGFRβRII receptor comprises a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

IPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICE KPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGET FFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 80).

In some embodiments of these multi-chain chimeric polypeptides, the second sequence of soluble human TGFRβRII receptor comprises a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

IPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICE KPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGET FFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 81).

In some embodiments of these multi-chain chimeric polypeptides, the first sequence of soluble human TGFRβRII receptor is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATCCCCCCCCCATGTGCAAAAGAGCGTGAACAACGATATGATCGTGACCGACA
ACAACGGCGCCGTGAAGTTTCCCCAGCTCTGCAAGTTCTGCGATGTCAGGTTC
AGCACCTGCGATAATCAGAAGTCCTGCATGTCCAACTGCAGCATCACCTCCA
TCTGCGAGAAGCCCCAAGAAGTGTGCGTGGCCGTGTGGCGGAAAAATGACG
AGAACATCACCCTGGAGACCGTGTGTCACGACCCCAAGCTCCCTTATCACGA
CTTCATTCTGGAGGACGCTGCCTCCCCCAAATGCATCATGAAGGAGAAGAAG
AAGCCCGGAGAGACCTTCTTTATGTGTTCCTGTAGCAGCGACGAGTGTAACG
ACAACATCATCTTCAGCGAAGAGTACAACACCAGCAACCCTGAT (SEQ ID NO: 82)

In some embodiments of these multi-chain chimeric polypeptides, the second sequence of soluble human TGFRβRII receptor is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATTCCTCCCCACGTGCAGAAGAGCGTGAATAATGACATGATCGTGACCGATA
ACAATGGCGCCGTGAAATTTCCCCAGCTGTGCAAATTCTGCGATGTGAGGTTT
TCCACCTGCGACAACCAGAAGTCCTGTATGAGCAACTGCTCCATCACCTCCAT
CTGTGAGAAGCCTCAGGAGGTGTGCGTGGCTGTCTGGCGGAAGAATGACGAG
AATATCACCCTGGAAACCGTCTGCCACGATCCCAAGCTGCCCTACCACGATTT
CATCCTGGAAGACGCCGCCAGCCCTAAGTGCATCATGAAAGAGAAAAAGAA
GCCTGGCGAGACCTTTTTCATGTGCTCCTGCAGCAGCGACGAATGCAACGAC
AATATCATCTTTAGCGAGGAATACAATACCAGCAACCCCGAC (SEQ ID NO: 83).

In some embodiments of these multi-chain chimeric polypeptides, the soluble TGF-β receptor includes a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

IPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICE
KPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGET
FFMCSCSSDECNDNIIFSEEYNTSNPDGGGGSGGGGSGGGGSIPPHVQKSVNNDM
IVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRK
NDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECND
NIIFSEEYNTSNPD (SEQ ID NO: 85).

In some embodiments of these multi-chain chimeric polypeptides, the soluble human TGFβRII receptor is encoded by a sequence that is at least 80% identical (e.g., at

least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATCCCCCCCCATGTGCAAAAGAGCGTGAACAACGATATGATCGTGACCGACA
ACAACGGCGCCGTGAAGTTTCCCCAGCTCTGCAAGTTCTGCGATGTCAGGTTC
AGCACCTGCGATAATCAGAAGTCCTGCATGTCCAACTGCAGCATCACCTCCA
TCTGCGAGAAGCCCCAAGAAGTGTGCGTGGCCGTGTGGCGGAAAAATGACG
AGAACATCACCCTGGAGACCGTGTGTCACGACCCCAAGCTCCCTTATCACGA
CTTCATTCTGGAGGACGCTGCCTCCCCCAAATGCATCATGAAGGAGAAGAAG
AAGCCCGGAGAGACCTTCTTTATGTGTTCCTGTAGCAGCGACGAGTGTAACG
ACAACATCATCTTCAGCGAAGAGTACAACACCAGCAACCCTGATGGAGGTGG
CGGATCCGGAGGTGGAGGTTCTGGTGGAGGTGGGAGTATTCCTCCCCACGTG
CAGAAGAGCGTGAATAATGACATGATCGTGACCGATAACAATGGCGCCGTGA
AATTTCCCCAGCTGTGCAAATTCTGCGATGTGAGGTTTTCCACCTGCGACAAC
CAGAAGTCCTGTATGAGCAACTGCTCCATCACCTCCATCTGTGAGAAGCCTC
AGGAGGTGTGCGTGGCTGTCTGGCGGAAGAATGACGAGAATATCACCCTGGA
AACCGTCTGCCACGATCCCAAGCTGCCCTACCACGATTTCATCCTGGAAGAC
GCCGCCAGCCCTAAGTGCATCATGAAAGAGAAAAAGAAGCCTGGCGAGACC
TTTTTCATGTGCTCCTGCAGCAGCGACGAATGCAACGACAATATCATCTTTAG
CGAGGAATACAATACCAGCAACCCCGAC (SEQ ID NO: 84).

In some embodiments of these multi-chain chimeric polypeptides, the sequence of soluble human IL-21 comprises a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

QGQDRHMIRMRQLIDIVDQLKNYVNDLVPEFLPAPEDVETNCEWSAFSCFQKAQ
LKSANTGNNERIINVSIKKLKRKPPSTNAGRRQKHRLTCPSCDSYEKKPPKEFLER
FKSLLQKMIHQHLSSRTHGSEDS (SEQ ID NO: 78).

In some embodiments of these multi-chain chimeric polypeptides, the soluble human IL-21 is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

CAAGGTCAAGATCGCCACATGATTAGAATGCGTCAACTTATAGATATTGTTG
ATCAGCTGAAAAATTATGTGAATGACTTGGTCCCTGAATTTCTGCCAGCTCCA
GAAGATGTAGAGACAAACTGTGAGTGGTCAGCTTTTTCCTGTTTTCAGAAGG
CCCAACTAAAGTCAGCAAATACAGGAAACAATGAAAGGATAATCAATGTATC

AATTAAAAAGCTGAAGAGGAAACCACCTTCCACAAATGCAGGGAGAAGACA
GAAACACAGACTAACATGCCCTTCATGTGATTCTTATGAGAAAAAACCACCC
AAAGAATTCCTAGAAAGATTCAAATCACTTCTCCAAAAGATGATTCATCAGC
ATCTGTCCTCTAGAACACACGGAAGTGAAGATTCC (SEQ ID NO: 94).

In some embodiments of these multi-chain chimeric polypeptides, the soluble human IL-21 is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

CAGGGCCAGGACAGGCACATGATCCGGATGAGGCAGCTCATCGACATCGTCG
ACCAGCTGAAGAACTACGTGAACGACCTGGTGCCCGAGTTTCTGCCTGCCCC
CGAGGACGTGGAGACCAACTGCGAGTGGTCCGCCTTCTCCTGCTTTCAGAAG
GCCCAGCTGAAGTCCGCCAACACCGGCAACAACGAGCGGATCATCAACGTG
AGCATCAAGAAGCTGAAGCGGAAGCCTCCCTCCACAAACGCCGGCAGGAGG
CAGAAGCACAGGCTGACCTGCCCCAGCTGTGACTCCTACGAGAAGAAGCCCC
CCAAGGAGTTCCTGGAGAGGTTCAAGTCCCTGCTGCAGAAGATGATCCATCA
GCACCTGTCCTCCAGGACCCACGGCTCCGAGGACTCC (SEQ ID NO: 79).

In some embodiments of these multi-chain chimeric polypeptides, the scFv that binds specifically to CD16 includes a light chain variable domain that includes a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

SELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVIYGKNNRPS
GIPDRFSGSSSGNTASLTITGAQAEDEADYYCNSRDSSGNHVVFGGGTKLTVGH
(SEQ ID NO: 112).

In some embodiments of these multi-chain chimeric polypeptides, the scFv that binds specifically to CD16 is encoded by a light chain variable domain sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

TCCGAGCTGACCCAGGACCCTGCTGTGTCCGTGGCTCTGGGCCAGACCGTGA
GGATCACCTGCCAGGGCGACTCCCTGAGGTCCTACTACGCCTCCTGGTACCA
GCAGAAGCCCGGCCAGGCTCCTGTGCTGGTGATCTACGGCAAGAACAACAGG

CCCTCCGGCATCCCTGACAGGTTCTCCGGATCCTCCTCCGGCAACACCGCCTC
CCTGACCATCACAGGCGCTCAGGCCGAGGACGAGGCTGACTACTACTGCAAC
TCCAGGGACTCCTCCGGCAACCATGTGGTGTTCGGCGGCGGCACCAAGCTGA
CCGTGGGCCAT (SEQ ID NO: 113).

In some embodiments of these multi-chain chimeric polypeptides, the scFv that binds specifically to CD16 includes a heavy chain variable domain that includes a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

EVQLVESGGGVVRPGGSLRLSCAASGFTFDDYGMSWVRQAPGKGLEWVSGINW
NGGSTGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGRSLLFDY
WGQGTLVTVSR (SEQ ID NO: 114).

In some embodiments of these multi-chain chimeric polypeptides, the scFv that binds specifically to CD16 is encoded by a heavy chain variable domain sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

GAGGTGCAGCTGGTGGAGTCCGGAGGAGGAGTGGTGAGGCCTGGAGGCTCC
CTGAGGCTGAGCTGTGCTGCCTCCGGCTTCACCTTCGACGACTACGGCATGTC
CTGGGTGAGGCAGGCTCCTGGAAAGGGCCTGGAGTGGGTGTCCGGCATCAAC
TGGAACGGCGGATCCACCGGCTACGCCGATTCCGTGAAGGGCAGGTTCACCA
TCAGCAGGGACAACGCCAAGAACTCCCTGTACCTGCAGATGAACTCCCTGAG
GGCCGAGGACACCGCCGTGTACTACTGCGCCAGGGGCAGGTCCCTGCTGTTC
GACTACTGGGGACAGGGCACCCTGGTGACCGTGTCCAGG (SEQ ID NO: 115).

In some embodiments, the first chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

IPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICE
KPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGET
FFMCSCSSDECNDNIIFSEEYNTSNPDGGGGSGGGGSGGGGSIPPHVQKSVNNDM
IVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRK

NDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECND
NIIFSEEYNTSNPDSGTTNTVAAYNLTWKSTNFKTILEWEPKPVNQVYTVQISTKS
GDWKSKCFYTTDTECDLTDEIVKDVKQTYLARVFSYPAGNVESTGSAGEPLYEN
SPEFTPYLETNLGQPTIQSFEQVGTKVNVTVEDERTLVRRNNTFLSLRDVFGKDLI
YTLYYWKSSSSGKKTAKTNTNEFLIDVDKGENYCFSVQAVIPSRTVNRKSTDSPV
ECMGQEKGEFRENWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKC
FLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFL
QSFVHIVQMFINTS (SEQ ID NO: 133).

In some embodiments, a first chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATCCCCCCCCCATGTGCAAAAGAGCGTGAACAACGATATGATCGTGACCGACA
ACAACGGCGCCGTGAAGTTTCCCCAGCTCTGCAAGTTCTGCGATGTCAGGTTC
AGCACCTGCGATAATCAGAAGTCCTGCATGTCCAACTGCAGCATCACCTCCA
TCTGCGAGAAGCCCCAAGAAGTGTGCGTGGCCGTGTGGCGGAAAAATGACG
AGAACATCACCCTGGAGACCGTGTGTCACGACCCCAAGCTCCCTTATCACGA
CTTCATTCTGGAGGACGCTGCCTCCCCCAAATGCATCATGAAGGAGAAGAAG
AAGCCCGGAGAGACCTTCTTTATGTGTTCCTGTAGCAGCGACGAGTGTAACG
ACAACATCATCTTCAGCGAAGAGTACAACACCAGCAACCCTGATGGAGGTGG
CGGATCCGGAGGTGGAGGTTCTGGTGGAGGTGGGAGTATTCCTCCCCACGTG
CAGAAGAGCGTGAATAATGACATGATCGTGACCGATAACAATGGCGCCGTGA
AATTTCCCCAGCTGTGCAAATTCTGCGATGTGAGGTTTTCCACCTGCGACAAC
CAGAAGTCCTGTATGAGCAACTGCTCCATCACCTCCATCTGTGAGAAGCCTC
AGGAGGTGTGCGTGGCTGTCTGGCGGAAGAATGACGAGAATATCACCCTGGA
AACCGTCTGCCACGATCCCAAGCTGCCCTACCACGATTTCATCCTGGAAGAC
GCCGCCAGCCCTAAGTGCATCATGAAAGAGAAAAAGAAGCCTGGCGAGACC
TTTTTCATGTGCTCCTGCAGCAGCGACGAATGCAACGACAATATCATCTTTAG
CGAGGAATACAATACCAGCAACCCCGACAGCGGCACAACCAACACAGTCGC
TGCCTATAACCTCACTTGGAAGAGCACCAACTTCAAAACCATCCTCGAATGG
GAACCCAAACCCGTTAACCAAGTTTACACCGTGCAGATCAGCACCAAGTCCG
GCGACTGGAAGTCCAAATGTTTCTATACCACCGACACCGAGTGCGATCTCAC
CGATGAGATCGTGAAAGATGTGAAACAGACCTACCTCGCCCGGGTGTTTAGC
TACCCCGCCGGCAATGTGGAGAGCACTGGTTCCGCTGGCGAGCCTTTATACG
AGAACAGCCCCGAATTTACCCCTTACCTCGAGACCAATTTAGGACAGCCCAC
CATCCAAAGCTTTGAGCAAGTTGGCACAAAGGTGAATGTGACAGTGGAGGAC
GAGCGGACTTTAGTGCGGCGGAACAACACCTTTCTCAGCCTCCGGGATGTGT
TCGGCAAAGATTTAATCTACACACTGTATTACTGGAAGTCCTCTTCCTCCGGC
AAGAAGACAGCTAAAACCAACACAAACGAGTTTTTAATCGACGTGGATAAA
GGCGAAAACTACTGTTTCAGCGTGCAAGCTGTGATCCCCTCCCGGACCGTGA

ATAGGAAAAGCACCGATAGCCCCGTTGAGTGCATGGGCCAAGAAAAGGGCG
AGTTCCGGGAGAACTGGGTGAACGTCATCAGCGATTTAAAGAAGATCGAAGA
TTTAATTCAGTCCATGCATATCGACGCCACTTTATACACAGAATCCGACGTGC
ACCCCTCTTGTAAGGTGACCGCCATGAAATGTTTTTTACTGGAGCTGCAAGTT
ATCTCTTTAGAGAGCGGAGACGCTAGCATCCACGACACCGTGGAGAATTTAA
TCATTTTAGCCAATAACTCTTTATCCAGCAACGGCAACGTGACAGAGTCCGGC
TGCAAGGAGTGCGAAGAGCTGGAGGAGAAGAACATCAAGGAGTTTCTGCAA
TCCTTTGTGCACATTGTCCAGATGTTCATCAATACCTCC (SEQ ID NO: 134).

In some embodiments, a first chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

MKWVTFISLLFLFSSAYSIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFST
CDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILED
AASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPDGGGGSGGGGSG
GGGSIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSI
TSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKK
PGETFFMCSCSSDECNDNIIFSEEYNTSNPDSGTTNTVAAYNLTWKSTNFKTILEW
EPKPVNQVYTVQISTKSGDWKSKCFYTTDTECDLTDEIVKDVKQTYLARVFSYP
AGNVESTGSAGEPLYENSPEFTPYLETNLGQPTIQSFEQVGTKVNVTVEDERTLV
RRNNTFLSLRDVFGKDLIYTLYYWKSSSSGKKTAKTNTNEFLIDVDKGENYCFSV
QAVIPSRTVNRKSTDSPVECMGQEKGEFRENWVNVISDLKKIEDLIQSMHIDATL
YTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVT
ESGCKECEELEEKNIKEFLQSFVHIVQMFINTS (SEQ ID NO: 135).

In some embodiments, a first chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATGAAGTGGGTGACCTTCATCAGCCTGCTGTTCCTGTTCTCCAGCGCCTACTC
CATCCCCCCCCCATGTGCAAAAGAGCGTGAACAACGATATGATCGTGACCGAC
AACAACGGCGCCGTGAAGTTTCCCCAGCTCTGCAAGTTCTGCGATGTCAGGTT
CAGCACCTGCGATAATCAGAAGTCCTGCATGTCCAACTGCAGCATCACCTCC
ATCTGCGAGAAGCCCCAAGAAGTGTGCGTGGCCGTGTGGCGGAAAAATGAC
GAGAACATCACCCTGGAGACCGTGTGTCACGACCCCAAGCTCCCTTATCACG
ACTTCATTCTGGAGGACGCTGCCTCCCCCAAATGCATCATGAAGGAGAAGAA
GAAGCCCGGAGAGACCTTCTTTATGTGTTCCTGTAGCAGCGACGAGTGTAAC

GACAACATCATCTTCAGCGAAGAGTACAACACCAGCAACCCTGATGGAGGTG
GCGGATCCGGAGGTGGAGGTTCTGGTGGAGGTGGGAGTATTCCTCCCCACGT
GCAGAAGAGCGTGAATAATGACATGATCGTGACCGATAACAATGGCGCCGTG
AAATTTCCCCAGCTGTGCAAATTCTGCGATGTGAGGTTTTCCACCTGCGACAA
CCAGAAGTCCTGTATGAGCAACTGCTCCATCACCTCCATCTGTGAGAAGCCTC
AGGAGGTGTGCGTGGCTGTCTGGCGGAAGAATGACGAGAATATCACCCTGGA
AACCGTCTGCCACGATCCCAAGCTGCCCTACCACGATTTCATCCTGGAAGAC
GCCGCCAGCCCTAAGTGCATCATGAAAGAGAAAAAGAAGCCTGGCGAGACC
TTTTTCATGTGCTCCTGCAGCAGCGACGAATGCAACGACAATATCATCTTTAG
CGAGGAATACAATACCAGCAACCCCGACAGCGGCACAACCAACACAGTCGC
TGCCTATAACCTCACTTGGAAGAGCACCAACTTCAAAACCATCCTCGAATGG
GAACCCAAACCCGTTAACCAAGTTTACACCGTGCAGATCAGCACCAAGTCCG
GCGACTGGAAGTCCAAATGTTTCTATACCACCGACACCGAGTGCGATCTCAC
CGATGAGATCGTGAAAGATGTGAAACAGACCTACCTCGCCCGGGTGTTTAGC
TACCCCGCCGGCAATGTGGAGAGCACTGGTTCCGCTGGCGAGCCTTTATACG
AGAACAGCCCCGAATTTACCCCTTACCTCGAGACCAATTTAGGACAGCCCAC
CATCCAAAGCTTTGAGCAAGTTGGCACAAAGGTGAATGTGACAGTGGAGGAC
GAGCGGACTTTAGTGCGGCGGAACAACACCTTTCTCAGCCTCCGGGATGTGT
TCGGCAAAGATTTAATCTACACACTGTATTACTGGAAGTCCTCTTCCTCCGGC
AAGAAGACAGCTAAAACCAACACAAACGAGTTTTTAATCGACGTGGATAAA
GGCGAAAACTACTGTTTCAGCGTGCAAGCTGTGATCCCCTCCCGGACCGTGA
ATAGGAAAAGCACCGATAGCCCCGTTGAGTGCATGGGCCAAGAAAAGGGCG
AGTTCCGGGAGAACTGGGTGAACGTCATCAGCGATTTAAAGAAGATCGAAGA
TTTAATTCAGTCCATGCATATCGACGCCACTTTATACACAGAATCCGACGTGC
ACCCCTCTTGTAAGGTGACCGCCATGAAATGTTTTTTACTGGAGCTGCAAGTT
ATCTCTTTAGAGAGCGGAGACGCTAGCATCCACGACACCGTGGAGAATTTAA
TCATTTTAGCCAATAACTCTTTATCCAGCAACGGCAACGTGACAGAGTCCGGC
TGCAAGGAGTGCGAAGAGCTGGAGGAGAAGAACATCAAGGAGTTTCTGCAA
TCCTTTGTGCACATTGTCCAGATGTTCATCAATACCTCC (SEQ ID NO: 136).

In some embodiments, the second chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

SELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVIYGKNNRPS
GIPDRFSGSSSGNTASLTITGAQAEDEADYYCNSRDSSGNHVVFGGGTKLTVGHG
GGGSGGGGSGGGGSEVQLVESGGGVVRPGGSLRLSCAASGFTFDDYGMSWVRQ
APGKGLEWVSGINWNGGSTGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTA
VYYCARGRSLLFDYWGQGTLVTVSRITCPPPMSVEHADIWVKSYSLYSRERYIC
NSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRQGQDRHMIRMRQLIDIVD
QLKNYVNDLVPEFLPAPEDVETNCEWSAFSCFQKAQLKSANTGNNERIINVSIKK

LKRKPPSTNAGRRQKHRLTCPSCDSYEKKPPKEFLERFKSLLQKMIHQHLSSRTH GSEDS (SEQ ID NO: 137).

In some embodiments, a second chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

TCCGAGCTGACCCAGGACCCTGCTGTGTCCGTGGCTCTGGGCCAGACCGTGA
GGATCACCTGCCAGGGCGACTCCCTGAGGTCCTACTACGCCTCCTGGTACCA
GCAGAAGCCCGGCCAGGCTCCTGTGCTGGTGATCTACGGCAAGAACAACAGG
CCCTCCGGCATCCCTGACAGGTTCTCCGGATCCTCCTCCGGCAACACCGCCTC
CCTGACCATCACAGGCGCTCAGGCCGAGGACGAGGCTGACTACTACTGCAAC
TCCAGGGACTCCTCCGGCAACCATGTGGTGTTCGGCGGCGGCACCAAGCTGA
CCGTGGGCCATGGCGGCGGCGGCTCCGGAGGCGGCGGCAGCGGCGGAGGAG
GATCCGAGGTGCAGCTGGTGGAGTCCGGAGGAGGAGTGGTGAGGCCTGGAG
GCTCCCTGAGGCTGAGCTGTGCTGCCTCCGGCTTCACCTTCGACGACTACGGC
ATGTCCTGGGTGAGGCAGGCTCCTGGAAAGGGCCTGGAGTGGGTGTCCGGCA
TCAACTGGAACGGCGGATCCACCGGCTACGCCGATTCCGTGAAGGGCAGGTT
CACCATCAGCAGGGACAACGCCAAGAACTCCCTGTACCTGCAGATGAACTCC
CTGAGGGCCGAGGACACCGCCGTGTACTACTGCGCCAGGGGCAGGTCCCTGC
TGTTCGACTACTGGGGACAGGGCACCCTGGTGACCGTGTCCAGGATTACATG
CCCCCCTCCCATGAGCGTGGAGCACGCCGACATCTGGGTGAAGAGCTATAGC
CTCTACAGCCGGGAGAGGTATATCTGTAACAGCGGCTTCAAGAGGAAGGCCG
GCACCAGCAGCCTCACCGAGTGCGTGCTGAATAAGGCTACCAACGTGGCTCA
CTGGACAACACCCTCTTTAAAGTGCATCCGGCAGGGCCAGGACAGGCACATG
ATCCGGATGAGGCAGCTCATCGACATCGTCGACCAGCTGAAGAACTACGTGA
ACGACCTGGTGCCCGAGTTTCTGCCTGCCCCCGAGGACGTGGAGACCAACTG
CGAGTGGTCCGCCTTCTCCTGCTTTCAGAAGGCCCAGCTGAAGTCCGCCAAC
ACCGGCAACAACGAGCGGATCATCAACGTGAGCATCAAGAAGCTGAAGCGG
AAGCCTCCCTCCACAAACGCCGGCAGGAGGCAGAAGCACAGGCTGACCTGC
CCCAGCTGTGACTCCTACGAGAAGAAGCCCCCCAAGGAGTTCCTGGAGAGGT
TCAAGTCCCTGCTGCAGAAGATGATCCATCAGCACCTGTCCTCCAGGACCCA
CGGCTCCGAGGACTCC (SEQ ID NO: 138).

In some embodiments, a second chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

MKWVTFISLLFLFSSAYSSELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQ
KPGQAPVLVIYGKNNRPSGIPDRFSGSSSGNTASLTITGAQAEDEADYYCNSRDSS
GNHVVFGGGTKLTVGHGGGGSGGGGSGGGGSEVQLVESGGGVVRPGGSLRLSC
AASGFTFDDYGMSWVRQAPGKGLEWVSGINWNGGSTGYADSVKGRFTISRDNA
KNSLYLQMNSLRAEDTAVYYCARGRSLLFDYWGQGTLVTVSRITCPPPMSVEH
ADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRQ
GQDRHMIRMRQLIDIVDQLKNYVNDLVPEFLPAPEDVETNCEWSAFSCFQKAQL
KSANTGNNERIINVSIKKLKRKPPSTNAGRRQKHRLTCPSCDSYEKKPPKEFLERF
KSLLQKMIHQHLSSRTHGSEDS (SEQ ID NO: 139).

In some embodiments, a second chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATGAAGTGGGTGACCTTCATCAGCCTGCTGTTCCTGTTCTCCAGCGCCTACTC
CTCCGAGCTGACCCAGGACCCTGCTGTGTCCGTGGCTCTGGGCCAGACCGTG
AGGATCACCTGCCAGGGCGACTCCCTGAGGTCCTACTACGCCTCCTGGTACC
AGCAGAAGCCCGGCCAGGCTCCTGTGCTGGTGATCTACGGCAAGAACAACAG
GCCCTCCGGCATCCCTGACAGGTTCTCCGGATCCTCCTCCGGCAACACCGCCT
CCCTGACCATCACAGGCGCTCAGGCCGAGGACGAGGCTGACTACTACTGCAA
CTCCAGGGACTCCTCCGGCAACCATGTGGTGTTCGGCGGCGGCACCAAGCTG
ACCGTGGGCCATGGCGGCGGCGGCTCCGGAGGCGGCGGCAGCGGCGGAGGA
GGATCCGAGGTGCAGCTGGTGGAGTCCGGAGGAGGAGTGGTGAGGCCTGGA
GGCTCCCTGAGGCTGAGCTGTGCTGCCTCCGGCTTCACCTTCGACGACTACGG
CATGTCCTGGGTGAGGCAGGCTCCTGGAAAGGGCCTGGAGTGGGTGTCCGGC
ATCAACTGGAACGGCGGATCCACCGGCTACGCCGATTCCGTGAAGGGCAGGT
TCACCATCAGCAGGGACAACGCCAAGAACTCCCTGTACCTGCAGATGAACTC
CCTGAGGGCCGAGGACACCGCCGTGTACTACTGCGCCAGGGGCAGGTCCCTG
CTGTTCGACTACTGGGGACAGGGCACCCTGGTGACCGTGTCCAGGATTACAT
GCCCCCCTCCCATGAGCGTGGAGCACGCCGACATCTGGGTGAAGAGCTATAG
CCTCTACAGCCGGGAGAGGTATATCTGTAACAGCGGCTTCAAGAGGAAGGCC
GGCACCAGCAGCCTCACCGAGTGCGTGCTGAATAAGGCTACCAACGTGGCTC
ACTGGACAACACCCTCTTTAAAGTGCATCCGGCAGGGCCAGGACAGGCACAT
GATCCGGATGAGGCAGCTCATCGACATCGTCGACCAGCTGAAGAACTACGTG
AACGACCTGGTGCCCGAGTTTCTGCCTGCCCCCGAGGACGTGGAGACCAACT
GCGAGTGGTCCGCCTTCTCCTGCTTTCAGAAGGCCCAGCTGAAGTCCGCCAA
CACCGGCAACAACGAGCGGATCATCAACGTGAGCATCAAGAAGCTGAAGCG
GAAGCCTCCCTCCACAAACGCCGGCAGGAGGCAGAAGCACAGGCTGACCTG
CCCCAGCTGTGACTCCTACGAGAAGAAGCCCCCCAAGGAGTTCCTGGAGAGG
TTCAAGTCCCTGCTGCAGAAGATGATCCATCAGCACCTGTCCTCCAGGACCC
ACGGCTCCGAGGACTCC (SEQ ID NO: 140).

Exemplary Multi-Chain Chimeric Polypeptides- Type H

In some embodiments of any of the multi-chain chimeric polypeptides described herein, the first target-binding domain and the second targeting-binding domain each independently bind specifically to a receptor of IL-7. In some examples of these multi-chain chimeric polypeptides, the first target-binding domain and the soluble tissue factor domain directly abut each other in the first chimeric polypeptide. In some examples of these multi-chain chimeric polypeptides, the first chimeric polypeptide further comprises a linker sequence (e.g., any of the exemplary linkers described herein) between the first target-binding domain and the soluble tissue factor domain in the first chimeric polypeptide.

In some embodiments of these multi-chain chimeric polypeptides, 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 embodiments of these multi-chain chimeric polypeptides, the first chimeric polypeptide further includes a linker sequence (e.g., any of the exemplary linkers described herein) between the soluble tissue factor domain and the first domain of the pair of affinity domains in the first chimeric polypeptide.

In some embodiments of these multi-chain chimeric polypeptides, 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 embodiments of these multi-chain chimeric polypeptides, the second chimeric polypeptide further includes a linker sequence (e.g., any of the exemplary linkers described herein) between the second domain of the pair of affinity domains and the second target-binding domain in the second chimeric polypeptide.

In some embodiments of these multi-chain chimeric polypeptides, the soluble tissue factor domain can be any of the exemplary soluble tissue factor domains described herein. In some embodiments of these multi-chain chimeric polypeptides, the pair of affinity domains can be any of the exemplary pairs of affinity domains described herein.

In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain and the second target-binding domain each independently bind specifically to a receptor for IL-7. In some embodiments of these multi-chain chimeric

polypeptides, the first target-binding domain and the second target-binding domain bind specifically to the same epitope. In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain and the second target-binding domain include the same amino acid sequence.

In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain and the second target-binding domain include a soluble IL-7 (e.g., a soluble human IL-7). In some embodiments of these multi-chain chimeric polypeptides, the soluble human IL-7 includes a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

DCDIEGKDGKQYESVLMVSIDQLLDSMKEIGSNCLNNEFNFFKRHICDANKEGM FLFRAARKLRQFLKMNSTGDFDLHLLKVSEGTTILLNCTGQVKGRKPAALGEAQ PTKSLEENKSLKEQKKLNDLCFLKRLLQEIKTCWNKILMGTKEH (SEQ ID NO: 11).

In some embodiments of these multi-chain chimeric polypeptides, the soluble human IL-7 is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

GATTGCGACATCGAGGGCAAGGACGGCAAGCAGTACGAGAGCGTGCTGATG GTGTCCATCGACCAGCTGCTGGACAGCATGAAGGAGATCGGCTCCAACTGCC TCAACAACGAGTTCAACTTCTTCAAGCGGCACATCTGCGACGCCAACAAGGA GGGCATGTTCCTGTTCAGGGCCGCCAGGAAACTGCGGCAGTTCCTGAAGATG AACTCCACCGGCGACTTCGACCTGCACCTGCTGAAGGTGTCCGAGGGCACCA CCATCCTGCTGAACTGCACCGGACAGGTGAAGGGCCGGAAACCTGCTGCTCT GGGAGAGGCCCAACCCACCAAGAGCCTGGAGGAGAACAAGTCCCTGAAGGA GCAGAAGAAGCTGAACGACCTGTGCTTCCTGAAGAGGCTGCTGCAGGAGATC AAGACCTGCTGGAACAAGATCCTGATGGGCACCAAGGAGCAT (SEQ ID NO: 95).

In some embodiments, the first chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least

94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

DCDIEGKDGKQYESVLMVSIDQLLDSMKEIGSNCLNNEFNFFKRHICDANKEGM
FLFRAARKLRQFLKMNSTGDFDLHLLKVSEGTTILLNCTGQVKGRKPAALGEAQ
PTKSLEENKSLKEQKKLNDLCFLKRLLQEIKTCWNKILMGTKEHSGTTNTVAAY
NLTWKSTNFKTILEWEPKPVNQVYTVQISTKSGDWKSKCFYTTDTECDLTDEIVK
DVKQTYLARVFSYPAGNVESTGSAGEPLYENSPEFTPYLETNLGQPTIQSFEQVG
TKVNVTVEDERTLVRRNNTFLSLRDVFGKDLIYTLYYWKSSSSGKKTAKTNTNE
FLIDVDKGENYCFSVQAVIPSRTVNRKSTDSPVECMGQEKGEFRENWVNVISDL
KKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVEN
LIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS (SEQ ID NO: 141).

In some embodiments, a first chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

GATTGCGACATCGAGGGCAAGGACGGCAAGCAGTACGAGAGCGTGCTGATG
GTGTCCATCGACCAGCTGCTGGACAGCATGAAGGAGATCGGCTCCAACTGCC
TCAACAACGAGTTCAACTTCTTCAAGCGGCACATCTGCGACGCCAACAAGGA
GGGCATGTTCCTGTTCAGGGCCGCCAGGAAACTGCGGCAGTTCCTGAAGATG
AACTCCACCGGCGACTTCGACCTGCACCTGCTGAAGGTGTCCGAGGGCACCA
CCATCCTGCTGAACTGCACCGGACAGGTGAAGGGCCGGAAACCTGCTGCTCT
GGGAGAGGCCCAACCCACCAAGAGCCTGGAGGAGAACAAGTCCCTGAAGGA
GCAGAAGAAGCTGAACGACCTGTGCTTCCTGAAGAGGCTGCTGCAGGAGATC
AAGACCTGCTGGAACAAGATCCTGATGGGCACCAAGGAGCATAGCGGCACA
ACCAACACAGTCGCTGCCTATAACCTCACTTGGAAGAGCACCAACTTCAAAA
CCATCCTCGAATGGGAACCCAAACCCGTTAACCAAGTTTACACCGTGCAGAT
CAGCACCAAGTCCGGCGACTGGAAGTCCAAATGTTTCTATACCACCGACACC
GAGTGCGATCTCACCGATGAGATCGTGAAAGATGTGAAACAGACCTACCTCG
CCCGGGTGTTTAGCTACCCCGCCGGCAATGTGGAGAGCACTGGTTCCGCTGG
CGAGCCTTTATACGAGAACAGCCCCGAATTTACCCCTTACCTCGAGACCAATT
TAGGACAGCCCACCATCCAAAGCTTTGAGCAAGTTGGCACAAAGGTGAATGT
GACAGTGGAGGACGAGCGGACTTTAGTGCGGCGGAACAACACCTTTCTCAGC
CTCCGGGATGTGTTCGGCAAAGATTTAATCTACACACTGTATTACTGGAAGTC
CTCTTCCTCCGGCAAGAAGACAGCTAAAACCAACACAAACGAGTTTTTAATC
GACGTGGATAAAGGCGAAAACTACTGTTTCAGCGTGCAAGCTGTGATCCCCT
CCCGGACCGTGAATAGGAAAAGCACCGATAGCCCCGTTGAGTGCATGGGCCA
AGAAAAGGGCGAGTTCCGGGAGAACTGGGTGAACGTCATCAGCGATTTAAA
GAAGATCGAAGATTTAATTCAGTCCATGCATATCGACGCCACTTTATACACA

GAATCCGACGTGCACCCCTCTTGTAAGGTGACCGCCATGAAATGTTTTTTACT
GGAGCTGCAAGTTATCTCTTTAGAGAGCGGAGACGCTAGCATCCACGACACC
GTGGAGAATTTAATCATTTTAGCCAATAACTCTTTATCCAGCAACGGCAACGT
GACAGAGTCCGGCTGCAAGGAGTGCGAAGAGCTGGAGGAGAAGAACATCAA
GGAGTTTCTGCAATCCTTTGTGCACATTGTCCAGATGTTCATCAATACCTCC
(SEQ ID NO: 142).

In some embodiments, a first chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

MKWVTFISLLFLFSSAYSDCDIEGKDGKQYESVLMVSIDQLLDSMKEIGSNCLNN
EFNFFKRHICDANKEGMFLFRAARKLRQFLKMNSTGDFDLHLLKVSEGTTILLNC
TGQVKGRKPAALGEAQPTKSLEENKSLKEQKKLNDLCFLKRLLQEIKTCWNKIL
MGTKEHSGTTNTVAAYNLTWKSTNFKTILEWEPKPVNQVYTVQISTKSGDWKS
KCFYTTDTECDLTDEIVKDVKQTYLARVFSYPAGNVESTGSAGEPLYENSPEFTP
YLETNLGQPTIQSFEQVGTKVNVTVEDERTLVRRNNTFLSLRDVFGKDLIYTLYY
WKSSSSGKKTAKTNTNEFLIDVDKGENYCFSVQAVIPSRTVNRKSTDSPVECMG
QEKGEFRENWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLEL
QVISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFV
HIVQMFINTS (SEQ ID NO: 143).

In some embodiments, a first chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATGAAGTGGGTGACCTTCATCAGCCTGCTGTTCCTGTTCTCCAGCGCCTACTC
CGATTGCGACATCGAGGGCAAGGACGGCAAGCAGTACGAGAGCGTGCTGAT
GGTGTCCATCGACCAGCTGCTGGACAGCATGAAGGAGATCGGCTCCAACTGC
CTCAACAACGAGTTCAACTTCTTCAAGCGGCACATCTGCGACGCCAACAAGG
AGGGCATGTTCCTGTTCAGGGCCGCCAGGAAACTGCGGCAGTTCCTGAAGAT
GAACTCCACCGGCGACTTCGACCTGCACCTGCTGAAGGTGTCCGAGGGCACC
ACCATCCTGCTGAACTGCACCGGACAGGTGAAGGGCCGGAAACCTGCTGCTC
TGGGAGAGGCCCAACCCACCAAGAGCCTGGAGGAGAACAAGTCCCTGAAGG
AGCAGAAGAAGCTGAACGACCTGTGCTTCCTGAAGAGGCTGCTGCAGGAGAT
CAAGACCTGCTGGAACAAGATCCTGATGGGCACCAAGGAGCATAGCGGCAC
AACCAACACAGTCGCTGCCTATAACCTCACTTGGAAGAGCACCAACTTCAAA
ACCATCCTCGAATGGGAACCCAAACCCGTTAACCAAGTTTACACCGTGCAGA

TCAGCACCAAGTCCGGCGACTGGAAGTCCAAATGTTTCTATACCACCGACAC
CGAGTGCGATCTCACCGATGAGATCGTGAAAGATGTGAAACAGACCTACCTC
GCCCGGGTGTTTAGCTACCCCGCCGGCAATGTGGAGAGCACTGGTTCCGCTG
GCGAGCCTTTATACGAGAACAGCCCCGAATTTACCCCTTACCTCGAGACCAA
TTTAGGACAGCCCACCATCCAAAGCTTTGAGCAAGTTGGCACAAAGGTGAAT
GTGACAGTGGAGGACGAGCGGACTTTAGTGCGGCGGAACAACACCTTTCTCA
GCCTCCGGGATGTGTTCGGCAAAGATTTAATCTACACACTGTATTACTGGAAG
TCCTCTTCCTCCGGCAAGAAGACAGCTAAAACCAACACAAACGAGTTTTTAA
TCGACGTGGATAAAGGCGAAAACTACTGTTTCAGCGTGCAAGCTGTGATCCC
CTCCCGGACCGTGAATAGGAAAAGCACCGATAGCCCCGTTGAGTGCATGGGC
CAAGAAAAGGGCGAGTTCCGGGAGAACTGGGTGAACGTCATCAGCGATTTA
AAGAAGATCGAAGATTTAATTCAGTCCATGCATATCGACGCCACTTTATACA
CAGAATCCGACGTGCACCCCTCTTGTAAGGTGACCGCCATGAAATGTTTTTTA
CTGGAGCTGCAAGTTATCTCTTTAGAGAGCGGAGACGCTAGCATCCACGACA
CCGTGGAGAATTTAATCATTTTAGCCAATAACTCTTTATCCAGCAACGGCAAC
GTGACAGAGTCCGGCTGCAAGGAGTGCGAAGAGCTGGAGGAGAAGAACATC
AAGGAGTTTCTGCAATCCTTTGTGCACATTGTCCAGATGTTCATCAATACCTC
C (SEQ ID NO: 144).

In some embodiments, the second chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

DCDIEGKDGKQYESVLMVSIDQLLDSMKEIGSNCLNNEFNFFKRHICDANKEGM
FLFRAARKLRQFLKMNSTGDFDLHLLKVSEGTTILLNCTGQVKGRKPAALGEAQ
PTKSLEENKSLKEQKKLNDLCFLKRLLQEIKTCWNKILMGTKEHITCPPPMSVEH
ADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR
(SEQ ID NO: 145).

In some embodiments, a second chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

GATTGTGATATTGAAGGTAAAGATGGCAAACAATATGAGAGTGTTCTAATGG
TCAGCATCGATCAATTATTGGACAGCATGAAAGAAATTGGTAGCAATTGCCT
GAATAATGAATTTAACTTTTTTAAAAGACATATCTGTGATGCTAATAAGGAA
GGTATGTTTTTATTCCGTGCTGCTCGCAAGTTGAGGCAATTTCTTAAAATGAA
TAGCACTGGTGATTTTGATCTCCACTTATTAAAAGTTTCAGAAGGCACAACAA

TACTGTTGAACTGCACTGGCCAGGTTAAAGGAAGAAAACCAGCTGCCCTGGG
TGAAGCCCAACCAACAAAGAGTTTGGAAGAAAATAAATCTTTAAAGGAACA
GAAAAAACTGAATGACTTGTGTTTCCTAAAGAGACTATTACAAGAGATAAAA
ACTTGTTGGAATAAAATTTTGATGGGCACTAAAGAACACATCACGTGCCCTC
CCCCCATGTCCGTGGAACACGCAGACATCTGGGTCAAGAGCTACAGCTTGTA
CTCCAGGGAGCGGTACATTTGTAACTCTGGTTTCAAGCGTAAAGCCGGCACG
TCCAGCCTGACGGAGTGCGTGTTGAACAAGGCCACGAATGTCGCCCACTGGA
CAACCCCCAGTCTCAAATGCATTAGA (SEQ ID NO: 146).

In some embodiments, a second chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

MKWVTFISLLFLFSSAYSDCDIEGKDGKQYESVLMVSIDQLLDSMKEIGSNCLNN
EFNFFKRHICDANKEGMFLFRAARKLRQFLKMNSTGDFDLHLLKVSEGTTILLNC
TGQVKGRKPAALGEAQPTKSLEENKSLKEQKKLNDLCFLKRLLQEIKTCWNKIL
MGTKEHITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNK
ATNVAHWTTPSLKCIR (SEQ ID NO: 147).

In some embodiments, a second chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATGAAGTGGGTGACCTTCATCAGCCTGCTGTTCCTGTTCTCCAGCGCCTACTC
CGATTGCGACATCGAGGGCAAGGACGGCAAGCAGTACGAGAGCGTGCTGAT
GGTGTCCATCGACCAGCTGCTGGACAGCATGAAGGAGATCGGCTCCAACTGC
CTCAACAACGAGTTCAACTTCTTCAAGCGGCACATCTGCGACGCCAACAAGG
AGGGCATGTTCCTGTTCAGGGCCGCCAGGAAACTGCGGCAGTTCCTGAAGAT
GAACTCCACCGGCGACTTCGACCTGCACCTGCTGAAGGTGTCCGAGGGCACC
ACCATCCTGCTGAACTGCACCGGACAGGTGAAGGGCCGGAAACCTGCTGCTC
TGGGAGAGGCCCAACCCACCAAGAGCCTGGAGGAGAACAAGTCCCTGAAGG
AGCAGAAGAAGCTGAACGACCTGTGCTTCCTGAAGAGGCTGCTGCAGGAGAT
CAAGACCTGCTGGAACAAGATCCTGATGGGCACCAAGGAGCATATTACATGC
CCCCCTCCCATGAGCGTGGAGCACGCCGACATCTGGGTGAAGAGCTATAGCC
TCTACAGCCGGGAGAGGTATATCTGTAACAGCGGCTTCAAGAGGAAGGCCGG
CACCAGCAGCCTCACCGAGTGCGTGCTGAATAAGGCTACCAACGTGGCTCAC
TGGACAACACCCTCTTTAAAGTGCATCCGG (SEQ ID NO: 148).

Exemplary Multi-Chain Chimeric Polypeptides- Type I

In some embodiments of any of the multi-chain chimeric polypeptides described herein, the first target-binding domain and the second targeting-binding domain each independently bind specifically to TGF-β. In some examples of these multi-chain chimeric polypeptides, the first target-binding domain and the soluble tissue factor domain directly abut each other in the first chimeric polypeptide. In some examples of these multi-chain chimeric polypeptides, the first chimeric polypeptide further comprises a linker sequence (e.g., any of the exemplary linkers described herein) between the first target-binding domain and the soluble tissue factor domain in the first chimeric polypeptide.

In some embodiments of these multi-chain chimeric polypeptides, 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 embodiments of these multi-chain chimeric polypeptides, the first chimeric polypeptide further includes a linker sequence (e.g., any of the exemplary linkers described herein) between the soluble tissue factor domain and the first domain of the pair of affinity domains in the first chimeric polypeptide.

In some embodiments of these multi-chain chimeric polypeptides, 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 embodiments of these multi-chain chimeric polypeptides, the second chimeric polypeptide further includes a linker sequence (e.g., any of the exemplary linkers described herein) between the second domain of the pair of affinity domains and the second target-binding domain in the second chimeric polypeptide.

In some embodiments of these multi-chain chimeric polypeptides, the soluble tissue factor domain can be any of the exemplary soluble tissue factor domains described herein. In some embodiments of these multi-chain chimeric polypeptides, the pair of affinity domains can be any of the exemplary pairs of affinity domains described herein.

In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain and the second target-binding domain each independently bind specifically to TGF-β. In some embodiments of these multi-chain chimeric polypeptides,

the first target-binding domain and the second target-binding domain bind specifically to the same epitope. In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain and the second target-binding domain include the same amino acid sequence.

In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain and the second target-binding domain is a soluble TGF-β receptor (e.g., a soluble TGFβRII receptor, e.g., a soluble human TGFβRII). In some embodiments of these multi-chain chimeric polypeptides, the soluble human TGFRβRII includes a first sequence of soluble human TGFRβRII and a second sequence of soluble human TGFRβRII. In some embodiments of these multi-chain chimeric polypeptides, the soluble human TGFRβRII includes a linker disposed between the first sequence of soluble human TGFRβRII and the second sequence of soluble human TGFRβRII. In some examples of these multi-chain chimeric polypeptides, the linker includes the sequence GGGGSGGGGSGGGGS (SEQ ID NO: 7).

In some embodiments of these multi-chain chimeric polypeptides, the first sequence of soluble human TGFRβRII receptor comprises a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

IPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICE KPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGET FFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 80).

In some embodiments of these multi-chain chimeric polypeptides, the second sequence of soluble human TGFRβRII receptor comprises a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to: c (SEQ ID NO: 81).

In some embodiments of these multi-chain chimeric polypeptides, the first sequence of soluble human TGFRβRII receptor is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical,

at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATCCCCCCCCCATGTGCAAAAGAGCGTGAACAACGATATGATCGTGACCGACAA
CAACGGCGCCGTGAAGTTTCCCCAGCTCTGCAAGTTCTGCGATGTCAGGTTCA
GCACCTGCGATAATCAGAAGTCCTGCATGTCCAACTGCAGCATCACCTCCATCT
GCGAGAAGCCCCAAGAAGTGTGCGTGGCCGTGTGGCGGAAAAATGACGAGA
ACATCACCCTGGAGACCGTGTGTCACGACCCCAAGCTCCCTTATCACGACTTC
ATTCTGGAGGACGCTGCCTCCCCCAAATGCATCATGAAGGAGAAGAAGAAGC
CCGGAGAGACCTTCTTTATGTGTTCCTGTAGCAGCGACGAGTGTAACGACAAC
ATCATCTTCAGCGAAGAGTACAACACCAGCAACCCTGAT (SEQ ID NO: 82).

In some embodiments of these multi-chain chimeric polypeptides, the second sequence of soluble human TGFRβRII receptor is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATTCCTCCCCACGTGCAGAAGAGCGTGAATAATGACATGATCGTGACCGATA
ACAATGGCGCCGTGAAATTTCCCCAGCTGTGCAAATTCTGCGATGTGAGGTTT
TCCACCTGCGACAACCAGAAGTCCTGTATGAGCAACTGCTCCATCACCTCCAT
CTGTGAGAAGCCTCAGGAGGTGTGCGTGGCTGTCTGGCGGAAGAATGACGAG
AATATCACCCTGGAAACCGTCTGCCACGATCCCAAGCTGCCCTACCACGATTT
CATCCTGGAAGACGCCGCCAGCCCTAAGTGCATCATGAAAGAGAAAAAGAA
GCCTGGCGAGACCTTTTTCATGTGCTCCTGCAGCAGCGACGAATGCAACGAC
AATATCATCTTTAGCGAGGAATACAATACCAGCAACCCCGAC (SEQ ID NO: 83).

In some embodiments of these multi-chain chimeric polypeptides, the soluble TGF-β receptor includes a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

IPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICE
KPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGET
FFMCSCSSDECNDNIIFSEEYNTSNPDGGGGSGGGGSGGGGSIPPHVQKSVNNDM
IVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRK
NDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECND
NIIFSEEYNTSNPD (SEQ ID NO: 85).

In some embodiments of these multi-chain chimeric polypeptides, the soluble TGF-β receptor is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATCCCCCCCCATGTGCAAAAGAGCGTGAACAACGATATGATCGTGACCGACAA
CAACGGCGCCGTGAAGTTTCCCCAGCTCTGCAAGTTCTGCGATGTCAGGTTCA
GCACCTGCGATAATCAGAAGTCCTGCATGTCCAACTGCAGCATCACCTCCATCT
GCGAGAAGCCCCAAGAAGTGTGCGTGGCCGTGTGGCGGAAAAATGACGAGA
ACATCACCCTGGAGACCGTGTGTCACGACCCCAAGCTCCCTTATCACGACTTC
ATTCTGGAGGACGCTGCCTCCCCCAAATGCATCATGAAGGAGAAGAAGAAGC
CCGGAGAGACCTTCTTTATGTGTTCCTGTAGCAGCGACGAGTGTAACGACAAC
ATCATCTTCAGCGAAGAGTACAACACCAGCAACCCTGATGGAGGTGGCGGATC
CGGAGGTGGAGGTTCTGGTGGAGGTGGGAGTATTCCTCCCCACGTGCAGAAG
AGCGTGAATAATGACATGATCGTGACCGATAACAATGGCGCCGTGAAATTTCC
CCAGCTGTGCAAATTCTGCGATGTGAGGTTTTCCACCTGCGACAACCAGAAGT
CCTGTATGAGCAACTGCTCCATCACCTCCATCTGTGAGAAGCCTCAGGAGGTG
TGCGTGGCTGTCTGGCGGAAGAATGACGAGAATATCACCCTGGAAACCGTCTG
CCACGATCCCAAGCTGCCCTACCACGATTTCATCCTGGAAGACGCCGCCAGCC
CTAAGTGCATCATGAAAGAGAAAAAGAAGCCTGGCGAGACCTTTTTCATGTGC
TCCTGCAGCAGCGACGAATGCAACGACAATATCATCTTTAGCGAGGAATACAA
TACCAGCAACCCCGAC (SEQ ID NO: 84).

In some embodiments, the first chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

IPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICE
KPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGET
FFMCSCSSDECNDNIIFSEEYNTSNPDGGGGSGGGGSGGGGSIPPHVQKSVNNDM
IVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRK
NDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECND
NIIFSEEYNTSNPDSGTTNTVAAYNLTWKSTNFKTILEWEPKPVNQVYTVQISTKS
GDWKSKCFYTTDTECDLTDEIVKDVKQTYLARVFSYPAGNVESTGSAGEPLYEN
SPEFTPYLETNLGQPTIQSFEQVGTKVNVTVEDERTLVRRNNTFLSLRDVFGKDLI
YTLYYWKSSSSGKKTAKTNTNEFLIDVDKGENYCFSVQAVIPSRTVNRKSTDSPV
ECMGQEKGEFRENWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKC
FLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFL
QSFVHIVQMFINTS (SEQ ID NO: 149).

In some embodiments, a first chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATCCCCCCCCCATGTGCAAAAGAGCGTGAACAACGATATGATCGTGACCGACA
ACAACGGCGCCGTGAAGTTTCCCCAGCTCTGCAAGTTCTGCGATGTCAGGTTC
AGCACCTGCGATAATCAGAAGTCCTGCATGTCCAACTGCAGCATCACCTCCA
TCTGCGAGAAGCCCCAAGAAGTGTGCGTGGCCGTGTGGCGGAAAAATGACG
AGAACATCACCCTGGAGACCGTGTGTCACGACCCCAAGCTCCCTTATCACGA
CTTCATTCTGGAGGACGCTGCCTCCCCCAAATGCATCATGAAGGAGAAGAAG
AAGCCCGGAGAGACCTTCTTTATGTGTTCCTGTAGCAGCGACGAGTGTAACG
ACAACATCATCTTCAGCGAAGAGTACAACACCAGCAACCCTGATGGAGGTGG
CGGATCCGGAGGTGGAGGTTCTGGTGGAGGTGGGAGTATTCCTCCCCACGTG
CAGAAGAGCGTGAATAATGACATGATCGTGACCGATAACAATGGCGCCGTGA
AATTTCCCCAGCTGTGCAAATTCTGCGATGTGAGGTTTTCCACCTGCGACAAC
CAGAAGTCCTGTATGAGCAACTGCTCCATCACCTCCATCTGTGAGAAGCCTC
AGGAGGTGTGCGTGGCTGTCTGGCGGAAGAATGACGAGAATATCACCCTGGA
AACCGTCTGCCACGATCCCAAGCTGCCCTACCACGATTTCATCCTGGAAGAC
GCCGCCAGCCCTAAGTGCATCATGAAAGAGAAAAAGAAGCCTGGCGAGACC
TTTTTCATGTGCTCCTGCAGCAGCGACGAATGCAACGACAATATCATCTTTAG
CGAGGAATACAATACCAGCAACCCCGACAGCGGCACAACCAACACAGTCGC
TGCCTATAACCTCACTTGGAAGAGCACCAACTTCAAAACCATCCTCGAATGG
GAACCCAAACCCGTTAACCAAGTTTACACCGTGCAGATCAGCACCAAGTCCG
GCGACTGGAAGTCCAAATGTTTCTATACCACCGACACCGAGTGCGATCTCAC
CGATGAGATCGTGAAAGATGTGAAACAGACCTACCTCGCCCGGGTGTTTAGC
TACCCCGCCGGCAATGTGGAGAGCACTGGTTCCGCTGGCGAGCCTTTATACG
AGAACAGCCCCGAATTTACCCCTTACCTCGAGACCAATTTAGGACAGCCCAC
CATCCAAAGCTTTGAGCAAGTTGGCACAAAGGTGAATGTGACAGTGGAGGAC
GAGCGGACTTTAGTGCGGCGGAACAACACCTTTCTCAGCCTCCGGGATGTGT
TCGGCAAAGATTTAATCTACACACTGTATTACTGGAAGTCCTCTTCCTCCGGC
AAGAAGACAGCTAAAACCAACACAAACGAGTTTTTAATCGACGTGGATAAA
GGCGAAAACTACTGTTTCAGCGTGCAAGCTGTGATCCCCTCCCGGACCGTGA
ATAGGAAAAGCACCGATAGCCCCGTTGAGTGCATGGGCCAAGAAAAGGGCG
AGTTCCGGGAGAACTGGGTGAACGTCATCAGCGATTTAAAGAAGATCGAAGA
TTTAATTCAGTCCATGCATATCGACGCCACTTTATACACAGAATCCGACGTGC
ACCCCTCTTGTAAGGTGACCGCCATGAAATGTTTTTTACTGGAGCTGCAAGTT
ATCTCTTTAGAGAGCGGAGACGCTAGCATCCACGACACCGTGGAGAATTTAA
TCATTTTAGCCAATAACTCTTTATCCAGCAACGGCAACGTGACAGAGTCCGGC
TGCAAGGAGTGCGAAGAGCTGGAGGAGAAGAACATCAAGGAGTTTCTGCAA
TCCTTTGTGCACATTGTCCAGATGTTCATCAATACCTCC (SEQ ID NO: 150).

In some embodiments, a first chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

MKWVTFISLLFLFSSAYSIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFST
CDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILED
AASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPDGGGGSGGGGSG
GGGSIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSI
TSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKK
PGETFFMCSCSSDECNDNIIFSEEYNTSNPDSGTTNTVAAYNLTWKSTNFKTILEW
EPKPVNQVYTVQISTKSGDWKSKCFYTTDTECDLTDEIVKDVKQTYLARVFSYP
AGNVESTGSAGEPLYENSPEFTPYLETNLGQPTIQSFEQVGTKVNVTVEDERTLV
RRNNTFLSLRDVFGKDLIYTLYYWKSSSSGKKTAKTNTNEFLIDVDKGENYCFSV
QAVIPSRTVNRKSTDSPVECMGQEKGEFRENWVNVISDLKKIEDLIQSMHIDATL
YTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVT
ESGCKECEELEEKNIKEFLQSFVHIVQMFINTS (SEQ ID NO: 151).

In some embodiments, a first chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATGAAGTGGGTGACCTTCATCAGCCTGCTGTTCCTGTTCTCCAGCGCCTACTC
CATCCCCCCCCCATGTGCAAAAGAGCGTGAACAACGATATGATCGTGACCGAC
AACAACGGCGCCGTGAAGTTTCCCCAGCTCTGCAAGTTCTGCGATGTCAGGTT
CAGCACCTGCGATAATCAGAAGTCCTGCATGTCCAACTGCAGCATCACCTCC
ATCTGCGAGAAGCCCCAAGAAGTGTGCGTGGCCGTGTGGCGGAAAAATGAC
GAGAACATCACCCTGGAGACCGTGTGTCACGACCCCAAGCTCCCTTATCACG
ACTTCATTCTGGAGGACGCTGCCTCCCCCAAATGCATCATGAAGGAGAAGAA
GAAGCCCGGAGAGACCTTCTTTATGTGTTCCTGTAGCAGCGACGAGTGTAAC
GACAACATCATCTTCAGCGAAGAGTACAACACCAGCAACCCTGATGGAGGTG
GCGGATCCGGAGGTGGAGGTTCTGGTGGAGGTGGGAGTATTCCTCCCCACGT
GCAGAAGAGCGTGAATAATGACATGATCGTGACCGATAACAATGGCGCCGTG
AAATTTCCCCAGCTGTGCAAATTCTGCGATGTGAGGTTTTCCACCTGCGACAA
CCAGAAGTCCTGTATGAGCAACTGCTCCATCACCTCCATCTGTGAGAAGCCTC
AGGAGGTGTGCGTGGCTGTCTGGCGGAAGAATGACGAGAATATCACCCTGGA
AACCGTCTGCCACGATCCCAAGCTGCCCTACCACGATTTCATCCTGGAAGAC
GCCGCCAGCCCTAAGTGCATCATGAAAGAGAAAAAGAAGCCTGGCGAGACC
TTTTTCATGTGCTCCTGCAGCAGCGACGAATGCAACGACAATATCATCTTTAG

CGAGGAATACAATACCAGCAACCCCGACAGCGGCACAACCAACACAGTCGC
TGCCTATAACCTCACTTGGAAGAGCACCAACTTCAAAACCATCCTCGAATGG
GAACCCAAACCCGTTAACCAAGTTTACACCGTGCAGATCAGCACCAAGTCCG
GCGACTGGAAGTCCAAATGTTTCTATACCACCGACACCGAGTGCGATCTCAC
CGATGAGATCGTGAAAGATGTGAAACAGACCTACCTCGCCCGGGTGTTTAGC
TACCCCGCCGGCAATGTGGAGAGCACTGGTTCCGCTGGCGAGCCTTTATACG
AGAACAGCCCCGAATTTACCCCTTACCTCGAGACCAATTTAGGACAGCCCAC
CATCCAAAGCTTTGAGCAAGTTGGCACAAAGGTGAATGTGACAGTGGAGGAC
GAGCGGACTTTAGTGCGGCGGAACAACACCTTTCTCAGCCTCCGGGATGTGT
TCGGCAAAGATTTAATCTACACACTGTATTACTGGAAGTCCTCTTCCTCCGGC
AAGAAGACAGCTAAAACCAACACAAACGAGTTTTTAATCGACGTGGATAAA
GGCGAAAACTACTGTTTCAGCGTGCAAGCTGTGATCCCCTCCCGGACCGTGA
ATAGGAAAAGCACCGATAGCCCCGTTGAGTGCATGGGCCAAGAAAAGGGCG
AGTTCCGGGAGAACTGGGTGAACGTCATCAGCGATTTAAAGAAGATCGAAGA
TTTAATTCAGTCCATGCATATCGACGCCACTTTATACACAGAATCCGACGTGC
ACCCCTCTTGTAAGGTGACCGCCATGAAATGTTTTTTACTGGAGCTGCAAGTT
ATCTCTTTAGAGAGCGGAGACGCTAGCATCCACGACACCGTGGAGAATTTAA
TCATTTTAGCCAATAACTCTTTATCCAGCAACGGCAACGTGACAGAGTCCGGC
TGCAAGGAGTGCGAAGAGCTGGAGGAGAAGAACATCAAGGAGTTTCTGCAA
TCCTTTGTGCACATTGTCCAGATGTTCATCAATACCTCC (SEQ ID NO: 152).

In some embodiments, the second chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

IPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICE
KPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGET
FFMCSCSSDECNDNIIFSEEYNTSNPDGGGGSGGGGSGGGGSIPPHVQKSVNNDM
IVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRK
NDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECND
NIIFSEEYNTSNPDITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLT
ECVLNKATNVAHWTTPSLKCIR (SEQ ID NO: 153).

In some embodiments, a second chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATCCCCCCCCCATGTGCAAAAGAGCGTGAACAACGATATGATCGTGACCGACA
ACAACGGCGCCGTGAAGTTTCCCCAGCTCTGCAAGTTCTGCGATGTCAGGTTC
AGCACCTGCGATAATCAGAAGTCCTGCATGTCCAACTGCAGCATCACCTCCA
TCTGCGAGAAGCCCCAAGAAGTGTGCGTGGCCGTGTGGCGGAAAAATGACG
AGAACATCACCCTGGAGACCGTGTGTCACGACCCCAAGCTCCCTTATCACGA
CTTCATTCTGGAGGACGCTGCCTCCCCCAAATGCATCATGAAGGAGAAGAAG
AAGCCCGGAGAGACCTTCTTTATGTGTTCCTGTAGCAGCGACGAGTGTAACG
ACAACATCATCTTCAGCGAAGAGTACAACACCAGCAACCCTGATGGAGGTGG
CGGATCCGGAGGTGGAGGTTCTGGTGGAGGTGGGAGTATTCCTCCCCACGTG
CAGAAGAGCGTGAATAATGACATGATCGTGACCGATAACAATGGCGCCGTGA
AATTTCCCCAGCTGTGCAAATTCTGCGATGTGAGGTTTTCCACCTGCGACAAC
CAGAAGTCCTGTATGAGCAACTGCTCCATCACCTCCATCTGTGAGAAGCCTC
AGGAGGTGTGCGTGGCTGTCTGGCGGAAGAATGACGAGAATATCACCCTGGA
AACCGTCTGCCACGATCCCAAGCTGCCCTACCACGATTTCATCCTGGAAGAC
GCCGCCAGCCCTAAGTGCATCATGAAAGAGAAAAAGAAGCCTGGCGAGACC
TTTTTCATGTGCTCCTGCAGCAGCGACGAATGCAACGACAATATCATCTTTAG
CGAGGAATACAATACCAGCAACCCCGACATTACATGCCCCCCTCCCATGAGC
GTGGAGCACGCCGACATCTGGGTGAAGAGCTATAGCCTCTACAGCCGGGAGA
GGTATATCTGTAACAGCGGCTTCAAGAGGAAGGCCGGCACCAGCAGCCTCAC
CGAGTGCGTGCTGAATAAGGCTACCAACGTGGCTCACTGGACAACACCCTCT
TTAAAGTGCATCCGG (SEQ ID NO: 154).

In some embodiments, a second chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

MKWVTFISLLFLFSSAYSIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFST
CDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILED
AASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPDGGGGSGGGGSG
GGGSIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSI
TSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKK
PGETFFMCSCSSDECNDNIIFSEEYNTSNPDITCPPPMSVEHADIWVKSYSLYSRER
YICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR (SEQ ID NO: 155).

In some embodiments, a second chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATGAAGTGGGTGACCTTCATCAGCCTGCTGTTCCTGTTCTCCAGCGCCTACTC
CATCCCCCCCCCATGTGCAAAAGAGCGTGAACAACGATATGATCGTGACCGAC
AACAACGGCGCCGTGAAGTTTCCCCAGCTCTGCAAGTTCTGCGATGTCAGGTT
CAGCACCTGCGATAATCAGAAGTCCTGCATGTCCAACTGCAGCATCACCTCC
ATCTGCGAGAAGCCCCAAGAAGTGTGCGTGGCCGTGTGGCGGAAAAATGAC
GAGAACATCACCCTGGAGACCGTGTGTCACGACCCCAAGCTCCCTTATCACG
ACTTCATTCTGGAGGACGCTGCCTCCCCCAAATGCATCATGAAGGAGAAGAA
GAAGCCCGGAGAGACCTTCTTTATGTGTTCCTGTAGCAGCGACGAGTGTAAC
GACAACATCATCTTCAGCGAAGAGTACAACACCAGCAACCCTGATGGAGGTG
GCGGATCCGGAGGTGGAGGTTCTGGTGGAGGTGGGAGTATTCCTCCCCACGT
GCAGAAGAGCGTGAATAATGACATGATCGTGACCGATAACAATGGCGCCGTG
AAATTTCCCCAGCTGTGCAAATTCTGCGATGTGAGGTTTTCCACCTGCGACAA
CCAGAAGTCCTGTATGAGCAACTGCTCCATCACCTCCATCTGTGAGAAGCCTC
AGGAGGTGTGCGTGGCTGTCTGGCGGAAGAATGACGAGAATATCACCCTGGA
AACCGTCTGCCACGATCCCAAGCTGCCCTACCACGATTTCATCCTGGAAGAC
GCCGCCAGCCCTAAGTGCATCATGAAAGAGAAAAAGAAGCCTGGCGAGACC
TTTTTCATGTGCTCCTGCAGCAGCGACGAATGCAACGACAATATCATCTTTAG
CGAGGAATACAATACCAGCAACCCCGACATTACATGCCCCCCTCCCATGAGC
GTGGAGCACGCCGACATCTGGGTGAAGAGCTATAGCCTCTACAGCCGGGAGA
GGTATATCTGTAACAGCGGCTTCAAGAGGAAGGCCGGCACCAGCAGCCTCAC
CGAGTGCGTGCTGAATAAGGCTACCAACGTGGCTCACTGGACAACACCCTCT
TTAAAGTGCATCCGG (SEQ ID NO: 156).

Exemplary Multi-Chain Chimeric Polypeptides- Type J

In some embodiments of any of the multi-chain chimeric polypeptides described herein, the first target-binding domain and the second targeting-binding domain each independently bind specifically to a receptor of IL-7, a receptor of IL-21, or a receptor of CD137L. In some embodiments of these multi-chain chimeric polypeptides described herein, the second chimeric polypeptide further includes the additional target-binding domain. In some embodiments of these multi-chain chimeric polypeptides described herein, the additional target-binding domain binds specifically to a receptor for IL-21 (e.g., a soluble IL-21, e.g., a soluble human IL-21) or a receptor for CD137L (e.g., a soluble CD137L, e.g., a soluble human CD137L).

In some examples of these multi-chain chimeric polypeptides, the first target-binding domain and the soluble tissue factor domain directly abut each other in the first chimeric polypeptide. In some examples of these multi-chain chimeric polypeptides, the first chimeric polypeptide further comprises a linker sequence (e.g., any of the exemplary

linkers described herein) between the first target-binding domain and the soluble tissue factor domain in the first chimeric polypeptide.

In some embodiments of these multi-chain chimeric polypeptides, 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 embodiments of these multi-chain chimeric polypeptides, the first chimeric polypeptide further includes a linker sequence (e.g., any of the exemplary linkers described herein) between the soluble tissue factor domain and the first domain of the pair of affinity domains in the first chimeric polypeptide.

In some embodiments of these multi-chain chimeric polypeptides, 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 embodiments of these multi-chain chimeric polypeptides, the second chimeric polypeptide further includes a linker sequence (e.g., any of the exemplary linkers described herein) between the second domain of the pair of affinity domains and the second target-binding domain in the second chimeric polypeptide.

In some embodiments, the second chimeric polypeptide further comprises one or more additional target-binding domains at the N-terminal end or the C-terminal end of the second chimeric polypeptide.

In some embodiments of these multi-chain chimeric polypeptides, the additional target-binding domain and the second domain of the pair of affinity domains directly abut each other in the second chimeric polypeptide. In some embodiments of these multi-chain chimeric polypeptides, the second chimeric polypeptide further includes a linker sequence (e.g., any of the exemplary linkers described herein) between the second domain of the pair of affinity domains and the additional target-binding domain in the second chimeric polypeptide.

In some embodiments of these multi-chain chimeric polypeptides, the additional target-binding domain and the second target-binding domain directly abut each other in the second chimeric polypeptide. In some embodiments of these multi-chain chimeric polypeptides, the second chimeric polypeptide further includes a linker sequence (e.g.,

any of the exemplary linkers described herein) between the second target-binding domain and the additional target-binding domain in the second chimeric polypeptide.

In some embodiments of these multi-chain chimeric polypeptides, the soluble tissue factor domain can be any of the exemplary soluble tissue factor domains described herein. In some embodiments of these multi-chain chimeric polypeptides, the pair of affinity domains can be any of the exemplary pairs of affinity domains described herein.

In some embodiments, the second chimeric polypeptide can include an additional target-binding domain. In some embodiments, the additional target-binding domain and the

In some embodiments of these multi-chain chimeric polypeptides, one or more of the first target-binding domain, the second target-binding domain and the additional target-binding domain is an agonistic antigen-binding domain. In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain, the second target-binding domain, and the additional target-binding domain are each agonistic antigen-binding domains. In some embodiments of these multi-chain chimeric polypeptides, the antigen-binding domain includes a scFv or single-domain antibody.

In some embodiments of these multi-chain chimeric polypeptides, 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 a receptor for CD137L. In some embodiments, the additional target-binding domain binds specifically to a receptor for IL-21 or a receptor for CD137L.

In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain is a soluble IL-7 (e.g., a soluble human IL-7). In some embodiments of these multi-chain chimeric polypeptides, the soluble human IL-7 includes a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

DCDIEGKDGKQYESVLMVSIDQLLDSMKEIGSNCLNNEFNFFKRHICDANKEGM FLFRAARKLRQFLKMNSTGDFDLHLLKVSEGTTILLNCTGQVKGRKPAALGEAQ PTKSLEENKSLKEQKKLNDLCFLKRLLQEIKTCWNKILMGTKEH (SEQ ID NO: 11).

In some embodiments of these multi-chain chimeric polypeptides, the soluble human IL-7 is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

GATTGCGACATCGAGGGCAAGGACGGCAAGCAGTACGAGAGCGTGCTGATG
GTGTCCATCGACCAGCTGCTGGACAGCATGAAGGAGATCGGCTCCAACTGCC
TCAACAACGAGTTCAACTTCTTCAAGCGGCACATCTGCGACGCCAACAAGGA
GGGCATGTTCCTGTTCAGGGCCGCCAGGAAACTGCGGCAGTTCCTGAAGATG
AACTCCACCGGCGACTTCGACCTGCACCTGCTGAAGGTGTCCGAGGGCACCA
CCATCCTGCTGAACTGCACCGGACAGGTGAAGGGCCGGAAACCTGCTGCTCT
GGGAGAGGCCCAACCCACCAAGAGCCTGGAGGAGAACAAGTCCCTGAAGGA
GCAGAAGAAGCTGAACGACCTGTGCTTCCTGAAGAGGCTGCTGCAGGAGATC
AAGACCTGCTGGAACAAGATCCTGATGGGCACCAAGGAGCAT (SEQ ID NO: 124).

In some embodiments of these multi-chain chimeric polypeptides, the second target-binding domain or the additional target-binding domain binds specifically to a receptor for IL-21. In some embodiments of these multi-chain chimeric polypeptides, the second target-binding domain or the additional target-binding domain is a soluble IL-21 (e.g., a soluble human IL-21).

In some embodiments of these multi-chain chimeric polypeptides, a soluble human IL-21 includes a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

QGQDRHMIRMRQLIDIVDQLKNYVNDLVPEFLPAPEDVETNCEWSAFSCFQKAQ
LKSANTGNNERIINVSIKKLKRKPPSTNAGRRQKHRLTCPSCDSYEKKPPKEFLER
FKSLLQKMIHQHLSSRTHGSEDS (SEQ ID NO: 78).

In some embodiments of these multi-chain chimeric polypeptides, a soluble human IL-21 is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

CAGGGCCAGGACAGGCACATGATCCGGATGAGGCAGCTCATCGACATCGTCG
ACCAGCTGAAGAACTACGTGAACGACCTGGTGCCCGAGTTTCTGCCTGCCCC
CGAGGACGTGGAGACCAACTGCGAGTGGTCCGCCTTCTCCTGCTTTCAGAAG
GCCCAGCTGAAGTCCGCCAACACCGGCAACAACGAGCGGATCATCAACGTG
AGCATCAAGAAGCTGAAGCGGAAGCCTCCCTCCACAAACGCCGGCAGGAGG
CAGAAGCACAGGCTGACCTGCCCCAGCTGTGACTCCTACGAGAAGAAGCCCC
CCAAGGAGTTCCTGGAGAGGTTCAAGTCCCTGCTGCAGAAGATGATCCATCA
GCACCTGTCCTCCAGGACCCACGGCTCCGAGGACTCC (SEQ ID NO: 79).

In some embodiments of these multi-chain chimeric polypeptides, the second target-binding domain binds specifically to a receptor for CD137L. In some embodiments of these multi-chain chimeric polypeptides, the second chimeric polypeptide further comprises an additional target-binding domain that binds specifically to a receptor for CD137L. In some embodiments of these multi-chain chimeric polypeptides, the second target-binding domain and/or the additional target-binding domain is a soluble CD137L (e.g., a soluble human CD137L).

In some embodiments of these multi-chain chimeric polypeptides, a soluble human CD137L includes a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

REGPELSPDDPAGLLDLRQGMFAQLVAQNVLLIDGPLSWYSDPGLAGVSLTGGL
SYKEDTKELVVAKAGVYYVFFQLELRRVVAGEGSGSVSLALHLQPLRSAAGAA
ALALTVDLPPASSEARNSAFGFQGRLLHLSAGQRLGVHLHTEARARHAWQLTQ
GATVLGLFRVTPEIPAGLPSPRSE (SEQ ID NO: 157).

In some embodiments of these multi-chain chimeric polypeptides, a soluble human CD137L is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

CGCGAGGGTCCCGAGCTTTCGCCCGACGATCCCGCCGGCCTCTTGGACCTGC
GGCAGGGCATGTTTGCGCAGCTGGTGGCCCAAAATGTTCTGCTGATCGATGG
GCCCCTGAGCTGGTACAGTGACCCAGGCCTGGCAGGCGTGTCCCTGACGGGG
GGCCTGAGCTACAAAGAGGACACGAAGGAGCTGGTGGTGGCCAAGGCTGGA
GTCTACTATGTCTTCTTTCAACTAGAGCTGCGGCGCGTGGTGGCCGGCGAGGG
CTCAGGCTCCGTTTCACTTGCGCTGCACCTGCAGCCACTGCGCTCTGCTGCTG

GGGCCGCCGCCCTGGCTTTGACCGTGGACCTGCCACCCGCCTCCTCCGAGGCT
CGGAACTCGGCCTTCGGTTTCCAGGGCCGCTTGCTGCACCTGAGTGCCGGCC
AGCGCCTGGGCGTCCATCTTCACACTGAGGCCAGGGCACGCCATGCCTGGCA
GCTTACCCAGGGCGCCACAGTCTTGGGACTCTTCCGGGTGACCCCCGAAATC
CCAGCCGGACTCCCTTCACCGAGGTCGGAA (SEQ ID NO: 158).

In some embodiments of these multi-chain chimeric polypeptides, a soluble human CD137L includes a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

DPAGLLDLRQGMFAQLVAQNVLLIDGPLSWYSDPGLAGVSLTGGLSYKEDTKEL
VVAKAGVYYVFFQLELRRVVAGEGSGSVSLALHLQPLRSAAGAAALALTVDLP
PASSEARNSAFGFQGRLLHLSAGQRLGVHLHTEARARHAWQLTQGATVLGLFR
VTPEI (SEQ ID NO: 159).

In some embodiments of these multi-chain chimeric polypeptides, a soluble human CD137L is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

GATCCCGCCGGCCTCTTGGACCTGCGGCAGGGCATGTTTGCGCAGCTGGTGG
CCCAAAATGTTCTGCTGATCGATGGGCCCCTGAGCTGGTACAGTGACCCAGG
CCTGGCAGGCGTGTCCCTGACGGGGGGCCTGAGCTACAAAGAGGACACGAA
GGAGCTGGTGGTGGCCAAGGCTGGAGTCTACTATGTCTTCTTTCAACTAGAGC
TGCGGCGCGTGGTGGCCGGCGAGGGCTCAGGCTCCGTTTCACTTGCGCTGCA
CCTGCAGCCACTGCGCTCTGCTGCTGGGGCCGCCGCCCTGGCTTTGACCGTGG
ACCTGCCACCCGCCTCCTCCGAGGCTCGGAACTCGGCCTTCGGTTTCCAGGGC
CGCTTGCTGCACCTGAGTGCCGGCCAGCGCCTGGGCGTCCATCTTCACACTGA
GGCCAGGGCACGCCATGCCTGGCAGCTTACCCAGGGCGCCACAGTCTTGGGA
CTCTTCCGGGTGACCCCCGAAATC (SEQ ID NO: 160).

In some embodiments, the first chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

DCDIEGKDGKQYESVLMVSIDQLLDSMKEIGSNCLNNEFNFFKRHICDANKEGM
FLFRAARKLRQFLKMNSTGDFDLHLLKVSEGTTILLNCTGQVKGRKPAALGEAQ

PTKSLEENKSLKEQKKLNDLCFLKRLLQEIKTCWNKILMGTKEHSGTTNTVAAY
NLTWKSTNFKTILEWEPKPVNQVYTVQISTKSGDWKSKCFYTTDTECDLTDEIVK
DVKQTYLARVFSYPAGNVESTGSAGEPLYENSPEFTPYLETNLGQPTIQSFEQVG
TKVNVTVEDERTLVRRNNTFLSLRDVFGKDLIYTLYYWKSSSSGKKTAKTNTNE
FLIDVDKGENYCFSVQAVIPSRTVNRKSTDSPVECMGQEKGEFRENWVNVISDL
KKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVEN
LIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS (SEQ ID
NO: 161).

In some embodiments, a first chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

GATTGCGACATCGAGGGCAAGGACGGCAAGCAGTACGAGAGCGTGCTGATG
GTGTCCATCGACCAGCTGCTGGACAGCATGAAGGAGATCGGCTCCAACTGCC
TCAACAACGAGTTCAACTTCTTCAAGCGGCACATCTGCGACGCCAACAAGGA
GGGCATGTTCCTGTTCAGGGCCGCCAGGAAACTGCGGCAGTTCCTGAAGATG
AACTCCACCGGCGACTTCGACCTGCACCTGCTGAAGGTGTCCGAGGGCACCA
CCATCCTGCTGAACTGCACCGGACAGGTGAAGGGCCGGAAACCTGCTGCTCT
GGGAGAGGCCCAACCCACCAAGAGCCTGGAGGAGAACAAGTCCCTGAAGGA
GCAGAAGAAGCTGAACGACCTGTGCTTCCTGAAGAGGCTGCTGCAGGAGATC
AAGACCTGCTGGAACAAGATCCTGATGGGCACCAAGGAGCATAGCGGCACA
ACCAACACAGTCGCTGCCTATAACCTCACTTGGAAGAGCACCAACTTCAAAA
CCATCCTCGAATGGGAACCCAAACCCGTTAACCAAGTTTACACCGTGCAGAT
CAGCACCAAGTCCGGCGACTGGAAGTCCAAATGTTTCTATACCACCGACACC
GAGTGCGATCTCACCGATGAGATCGTGAAAGATGTGAAACAGACCTACCTCG
CCCGGGTGTTTAGCTACCCCGCCGGCAATGTGGAGAGCACTGGTTCCGCTGG
CGAGCCTTTATACGAGAACAGCCCCGAATTTACCCCTTACCTCGAGACCAATT
TAGGACAGCCCACCATCCAAAGCTTTGAGCAAGTTGGCACAAAGGTGAATGT
GACAGTGGAGGACGAGCGGACTTTAGTGCGGCGGAACAACACCTTTCTCAGC
CTCCGGGATGTGTTCGGCAAAGATTTAATCTACACACTGTATTACTGGAAGTC
CTCTTCCTCCGGCAAGAAGACAGCTAAAACCAACACAAACGAGTTTTTAATC
GACGTGGATAAAGGCGAAAACTACTGTTTCAGCGTGCAAGCTGTGATCCCCT
CCCGGACCGTGAATAGGAAAAGCACCGATAGCCCCGTTGAGTGCATGGGCCA
AGAAAAGGGCGAGTTCCGGGAGAACTGGGTGAACGTCATCAGCGATTTAAA
GAAGATCGAAGATTTAATTCAGTCCATGCATATCGACGCCACTTTATACACA
GAATCCGACGTGCACCCCTCTTGTAAGGTGACCGCCATGAAATGTTTTTTACT
GGAGCTGCAAGTTATCTCTTTAGAGAGCGGAGACGCTAGCATCCACGACACC
GTGGAGAATTTAATCATTTTAGCCAATAACTCTTTATCCAGCAACGGCAACGT
GACAGAGTCCGGCTGCAAGGAGTGCGAAGAGCTGGAGGAGAAGAACATCAA

GGAGTTTCTGCAATCCTTTGTGCACATTGTCCAGATGTTCATCAATACCTCC (SEQ ID NO: 162).

In some embodiments, the first chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

MKWVTFISLLFLFSSAYSDCDIEGKDGKQYESVLMVSIDQLLDSMKEIGSNCLNN
EFNFFKRHICDANKEGMFLFRAARKLRQFLKMNSTGDFDLHLLKVSEGTTILLNC
TGQVKGRKPAALGEAQPTKSLEENKSLKEQKKLNDLCFLKRLLQEIKTCWNKIL
MGTKEHSGTTNTVAAYNLTWKSTNFKTILEWEPKPVNQVYTVQISTKSGDWKS
KCFYTTDTECDLTDEIVKDVKQTYLARVFSYPAGNVESTGSAGEPLYENSPEFTP
YLETNLGQPTIQSFEQVGTKVNVTVEDERTLVRRNNTFLSLRDVFGKDLIYTLYY
WKSSSSGKKTAKTNTNEFLIDVDKGENYCFSVQAVIPSRTVNRKSTDSPVECMG
QEKGEFRENWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLEL
QVISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFV
HIVQMFINTS (SEQ ID NO: 163).

In some embodiments, a first chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATGAAGTGGGTGACCTTCATCAGCCTGCTGTTCCTGTTCTCCAGCGCCTACTC
CGATTGCGACATCGAGGGCAAGGACGGCAAGCAGTACGAGAGCGTGCTGAT
GGTGTCCATCGACCAGCTGCTGGACAGCATGAAGGAGATCGGCTCCAACTGC
CTCAACAACGAGTTCAACTTCTTCAAGCGGCACATCTGCGACGCCAACAAGG
AGGGCATGTTCCTGTTCAGGGCCGCCAGGAAACTGCGGCAGTTCCTGAAGAT
GAACTCCACCGGCGACTTCGACCTGCACCTGCTGAAGGTGTCCGAGGGCACC
ACCATCCTGCTGAACTGCACCGGACAGGTGAAGGGCCGGAAACCTGCTGCTC
TGGGAGAGGCCCAACCCACCAAGAGCCTGGAGGAGAACAAGTCCCTGAAGG
AGCAGAAGAAGCTGAACGACCTGTGCTTCCTGAAGAGGCTGCTGCAGGAGAT
CAAGACCTGCTGGAACAAGATCCTGATGGGCACCAAGGAGCATAGCGGCAC
AACCAACACAGTCGCTGCCTATAACCTCACTTGGAAGAGCACCAACTTCAAA
ACCATCCTCGAATGGGAACCCAAACCCGTTAACCAAGTTTACACCGTGCAGA
TCAGCACCAAGTCCGGCGACTGGAAGTCCAAATGTTTCTATACCACCGACAC
CGAGTGCGATCTCACCGATGAGATCGTGAAAGATGTGAAACAGACCTACCTC
GCCCGGGTGTTTAGCTACCCCGCCGGCAATGTGGAGAGCACTGGTTCCGCTG
GCGAGCCTTTATACGAGAACAGCCCCGAATTTACCCCTTACCTCGAGACCAA

TTTAGGACAGCCCACCATCCAAAGCTTTGAGCAAGTTGGCACAAAGGTGAAT
GTGACAGTGGAGGACGAGCGGACTTTAGTGCGGCGGAACAACACCTTTCTCA
GCCTCCGGGATGTGTTCGGCAAAGATTTAATCTACACACTGTATTACTGGAAG
TCCTCTTCCTCCGGCAAGAAGACAGCTAAAACCAACACAAACGAGTTTTTAA
TCGACGTGGATAAAGGCGAAAACTACTGTTTCAGCGTGCAAGCTGTGATCCC
CTCCCGGACCGTGAATAGGAAAAGCACCGATAGCCCCGTTGAGTGCATGGGC
CAAGAAAAGGGCGAGTTCCGGGAGAACTGGGTGAACGTCATCAGCGATTTA
AAGAAGATCGAAGATTTAATTCAGTCCATGCATATCGACGCCACTTTATACA
CAGAATCCGACGTGCACCCCTCTTGTAAGGTGACCGCCATGAAATGTTTTTTA
CTGGAGCTGCAAGTTATCTCTTTAGAGAGCGGAGACGCTAGCATCCACGACA
CCGTGGAGAATTTAATCATTTTAGCCAATAACTCTTTATCCAGCAACGGCAAC
GTGACAGAGTCCGGCTGCAAGGAGTGCGAAGAGCTGGAGGAGAAGAACATC
AAGGAGTTTCTGCAATCCTTTGTGCACATTGTCCAGATGTTCATCAATACCTC
C (SEQ ID NO: 164).

In some embodiments, the second chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

QGQDRHMIRMRQLIDIVDQLKNYVNDLVPEFLPAPEDVETNCEWSAFSCFQKAQ
LKSANTGNNERIINVSIKKLKRKPPSTNAGRRQKHRLTCPSCDSYEKKPPKEFLER
FKSLLQKMIHQHLSSRTHGSEDSITCPPPMSVEHADIWVKSYSLYSRERYICNSGF
KRKAGTSSLTECVLNKATNVAHWTTPSLKCIRGGGGSGGGGSGGGGSREGPELS
PDDPAGLLDLRQGMFAQLVAQNVLLIDGPLSWYSDPGLAGVSLTGGLSYKEDTK
ELVVAKAGVYYVFFQLELRRVVAGEGSGSVSLALHLQPLRSAAGAAALALTVD
LPPASSEARNSAFGFQGRLLHLSAGQRLGVHLHTEARARHAWQLTQGATVLGLF
RVTPEIPAGLPSPRSE (SEQ ID NO: 165).

In some embodiments, a second chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

CAGGGCCAGGACAGGCACATGATCCGGATGAGGCAGCTCATCGACATCGTCG
ACCAGCTGAAGAACTACGTGAACGACCTGGTGCCCGAGTTTCTGCCTGCCCC
CGAGGACGTGGAGACCAACTGCGAGTGGTCCGCCTTCTCCTGCTTTCAGAAG
GCCCAGCTGAAGTCCGCCAACACCGGCAACAACGAGCGGATCATCAACGTG
AGCATCAAGAAGCTGAAGCGGAAGCCTCCCTCCACAAACGCCGGCAGGAGG
CAGAAGCACAGGCTGACCTGCCCCAGCTGTGACTCCTACGAGAAGAAGCCCC

CCAAGGAGTTCCTGGAGAGGTTCAAGTCCCTGCTGCAGAAGATGATCCATCA
GCACCTGTCCTCCAGGACCCACGGCTCCGAGGACTCCATTACATGCCCCCCTC
CCATGAGCGTGGAGCACGCCGACATCTGGGTGAAGAGCTATAGCCTCTACAG
CCGGGAGAGGTATATCTGTAACAGCGGCTTCAAGAGGAAGGCCGGCACCAG
CAGCCTCACCGAGTGCGTGCTGAATAAGGCTACCAACGTGGCTCACTGGACA
ACACCCTCTTTAAAGTGCATCCGGGGCGGTGGAGGATCCGGAGGAGGTGGCT
CCGGCGGCGGAGGATCTCGCGAGGGTCCCGAGCTTTCGCCCGACGATCCCGC
CGGCCTCTTGGACCTGCGGCAGGGCATGTTTGCGCAGCTGGTGGCCCAAAAT
GTTCTGCTGATCGATGGGCCCCTGAGCTGGTACAGTGACCCAGGCCTGGCAG
GCGTGTCCCTGACGGGGGGCCTGAGCTACAAAGAGGACACGAAGGAGCTGG
TGGTGGCCAAGGCTGGAGTCTACTATGTCTTCTTTCAACTAGAGCTGCGGCGC
GTGGTGGCCGGCGAGGGCTCAGGCTCCGTTTCACTTGCGCTGCACCTGCAGC
CACTGCGCTCTGCTGCTGGGGCCGCCGCCCTGGCTTTGACCGTGGACCTGCCA
CCCGCCTCCTCCGAGGCTCGGAACTCGGCCTTCGGTTTCCAGGGCCGCTTGCT
GCACCTGAGTGCCGGCCAGCGCCTGGGCGTCCATCTTCACACTGAGGCCAGG
GCACGCCATGCCTGGCAGCTTACCCAGGGCGCCACAGTCTTGGGACTCTTCC
GGGTGACCCCCGAAATCCCAGCCGGACTCCCTTCACCGAGGTCGGAA (SEQ
ID NO: 166).

In some embodiments, the second chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

MKWVTFISLLFLFSSAYSQGQDRHMIRMRQLIDIVDQLKNYVNDLVPEFLPAPED
VETNCEWSAFSCFQKAQLKSANTGNNERIINVSIKKLKRKPPSTNAGRRQKHRLT
CPSCDSYEKKPPKEFLERFKSLLQKMIHQHLSSRTHGSEDSITCPPPMSVEHADIW
VKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRGGGGS
GGGGSGGGGSREGPELSPDDPAGLLDLRQGMFAQLVAQNVLLIDGPLSWYSDPG
LAGVSLTGGLSYKEDTKELVVAKAGVYYVFFQLELRRVVAGEGSGSVSLALHL
QPLRSAAGAAALALTVDLPPASSEARNSAFGFQGRLLHLSAGQRLGVHLHTEAR
ARHAWQLTQGATVLGLFRVTPEIPAGLPSPRSE (SEQ ID NO: 167).

In some embodiments, a second chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATGAAGTGGGTGACCTTCATCAGCCTGCTGTTCCTGTTCTCCAGCGCCTACTC
CCAGGGCCAGGACAGGCACATGATCCGGATGAGGCAGCTCATCGACATCGTC

GACCAGCTGAAGAACTACGTGAACGACCTGGTGCCCGAGTTTCTGCCTGCCC
CCGAGGACGTGGAGACCAACTGCGAGTGGTCCGCCTTCTCCTGCTTTCAGAA
GGCCCAGCTGAAGTCCGCCAACACCGGCAACAACGAGCGGATCATCAACGT
GAGCATCAAGAAGCTGAAGCGGAAGCCTCCCTCCACAAACGCCGGCAGGAG
GCAGAAGCACAGGCTGACCTGCCCCAGCTGTGACTCCTACGAGAAGAAGCCC
CCCAAGGAGTTCCTGGAGAGGTTCAAGTCCCTGCTGCAGAAGATGATCCATC
AGCACCTGTCCTCCAGGACCCACGGCTCCGAGGACTCCATTACATGCCCCCCT
CCCATGAGCGTGGAGCACGCCGACATCTGGGTGAAGAGCTATAGCCTCTACA
GCCGGGAGAGGTATATCTGTAACAGCGGCTTCAAGAGGAAGGCCGGCACCA
GCAGCCTCACCGAGTGCGTGCTGAATAAGGCTACCAACGTGGCTCACTGGAC
AACACCCTCTTTAAAGTGCATCCGGGGCGGTGGAGGATCCGGAGGAGGTGGC
TCCGGCGGCGGAGGATCTCGCGAGGGTCCCGAGCTTTCGCCCGACGATCCCG
CCGGCCTCTTGGACCTGCGGCAGGGCATGTTTGCGCAGCTGGTGGCCCAAAA
TGTTCTGCTGATCGATGGGCCCCTGAGCTGGTACAGTGACCCAGGCCTGGCA
GGCGTGTCCCTGACGGGGGGCCTGAGCTACAAAGAGGACACGAAGGAGCTG
GTGGTGGCCAAGGCTGGAGTCTACTATGTCTTCTTTCAACTAGAGCTGCGGCG
CGTGGTGGCCGGCGAGGGCTCAGGCTCCGTTTCACTTGCGCTGCACCTGCAG
CCACTGCGCTCTGCTGCTGGGGCCGCCGCCCTGGCTTTGACCGTGGACCTGCC
ACCCGCCTCCTCCGAGGCTCGGAACTCGGCCTTCGGTTTCCAGGGCCGCTTGC
TGCACCTGAGTGCCGGCCAGCGCCTGGGCGTCCATCTTCACACTGAGGCCAG
GGCACGCCATGCCTGGCAGCTTACCCAGGGCGCCACAGTCTTGGGACTCTTC
CGGGTGACCCCCGAAATCCCAGCCGGACTCCCTTCACCGAGGTCGGAA (SEQ ID NO: 168).

In some embodiments, the second chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

QGQDRHMIRMRQLIDIVDQLKNYVNDLVPEFLPAPEDVETNCEWSAFSCFQKAQ
LKSANTGNNERIINVSIKKLKRKPPSTNAGRRQKHRLTCPSCDSYEKKPPKEFLER
FKSLLQKMIHQHLSSRTHGSEDSITCPPPMSVEHADIWVKSYSLYSRERYICNSGF
KRKAGTSSLTECVLNKATNVAHWTTPSLKCIRGGGGSGGGGSGGGGSDPAGLL
DLRQGMFAQLVAQNVLLIDGPLSWYSDPGLAGVSLTGGLSYKEDTKELVVAKA
GVYYVFFQLELRRVVAGEGSGSVSLALHLQPLRSAAGAAALALTVDLPPASSEA
RNSAFGFQGRLLHLSAGQRLGVHLHTEARARHAWQLTQGATVLGLFRVTPEI (SEQ ID NO: 169).

In some embodiments, a second chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at

least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

CAGGGCCAGGACAGGCACATGATCCGGATGAGGCAGCTCATCGACATCGTCG
ACCAGCTGAAGAACTACGTGAACGACCTGGTGCCCGAGTTTCTGCCTGCCCC
CGAGGACGTGGAGACCAACTGCGAGTGGTCCGCCTTCTCCTGCTTTCAGAAG
GCCCAGCTGAAGTCCGCCAACACCGGCAACAACGAGCGGATCATCAACGTG
AGCATCAAGAAGCTGAAGCGGAAGCCTCCCTCCACAAACGCCGGCAGGAGG
CAGAAGCACAGGCTGACCTGCCCCAGCTGTGACTCCTACGAGAAGAAGCCCC
CCAAGGAGTTCCTGGAGAGGTTCAAGTCCCTGCTGCAGAAGATGATCCATCA
GCACCTGTCCTCCAGGACCCACGGCTCCGAGGACTCCATTACATGCCCCCCTC
CCATGAGCGTGGAGCACGCCGACATCTGGGTGAAGAGCTATAGCCTCTACAG
CCGGGAGAGGTATATCTGTAACAGCGGCTTCAAGAGGAAGGCCGGCACCAG
CAGCCTCACCGAGTGCGTGCTGAATAAGGCTACCAACGTGGCTCACTGGACA
ACACCCTCTTTAAAGTGCATCCGGGGCGGTGGAGGATCCGGAGGAGGTGGCT
CCGGCGGCGGAGGATCTGATCCCGCCGGCCTCTTGGACCTGCGGCAGGGCAT
GTTTGCGCAGCTGGTGGCCCAAAATGTTCTGCTGATCGATGGGCCCCTGAGCT
GGTACAGTGACCCAGGCCTGGCAGGCGTGTCCCTGACGGGGGGCCTGAGCTA
CAAAGAGGACACGAAGGAGCTGGTGGTGGCCAAGGCTGGAGTCTACTATGTC
TTCTTTCAACTAGAGCTGCGGCGCGTGGTGGCCGGCGAGGGCTCAGGCTCCG
TTTCACTTGCGCTGCACCTGCAGCCACTGCGCTCTGCTGCTGGGGCCGCCGCC
CTGGCTTTGACCGTGGACCTGCCACCCGCCTCCTCCGAGGCTCGGAACTCGGC
CTTCGGTTTCCAGGGCCGCTTGCTGCACCTGAGTGCCGGCCAGCGCCTGGGC
GTCCATCTTCACACTGAGGCCAGGGCACGCCATGCCTGGCAGCTTACCCAGG
GCGCCACAGTCTTGGGACTCTTCCGGGTGACCCCCGAAATC (SEQ ID NO: 170).

In some embodiments, the second chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

MKWVTFISLLFLFSSAYSQGQDRHMIRMRQLIDIVDQLKNYVNDLVPEFLPAPED
VETNCEWSAFSCFQKAQLKSANTGNNERIINVSIKKLKRKPPSTNAGRRQKHRLT
CPSCDSYEKKPPKEFLERFKSLLQKMIHQHLSSRTHGSEDSITCPPPMSVEHADIW
VKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRGGGGS
GGGGSGGGGSDPAGLLDLRQGMFAQLVAQNVLLIDGPLSWYSDPGLAGVSLTG
GLSYKEDTKELVVAKAGVYYVFFQLELRRVVAGEGSGSVSLALHLQPLRSAAG
AAALALTVDLPPASSEARNSAFGFQGRLLHLSAGQRLGVHLHTEARARHAWQL
TQGATVLGLFRVTPEI (SEQ ID NO: 171).

In some embodiments, a second chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least

86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATGAAGTGGGTGACCTTCATCAGCCTGCTGTTCCTGTTCTCCAGCGCCTACTC
CCAGGGCCAGGACAGGCACATGATCCGGATGAGGCAGCTCATCGACATCGTC
GACCAGCTGAAGAACTACGTGAACGACCTGGTGCCCGAGTTTCTGCCTGCCC
CCGAGGACGTGGAGACCAACTGCGAGTGGTCCGCCTTCTCCTGCTTTCAGAA
GGCCCAGCTGAAGTCCGCCAACACCGGCAACAACGAGCGGATCATCAACGT
GAGCATCAAGAAGCTGAAGCGGAAGCCTCCCTCCACAAACGCCGGCAGGAG
GCAGAAGCACAGGCTGACCTGCCCCAGCTGTGACTCCTACGAGAAGAAGCCC
CCCAAGGAGTTCCTGGAGAGGTTCAAGTCCCTGCTGCAGAAGATGATCCATC
AGCACCTGTCCTCCAGGACCCACGGCTCCGAGGACTCCATTACATGCCCCCCT
CCCATGAGCGTGGAGCACGCCGACATCTGGGTGAAGAGCTATAGCCTCTACA
GCCGGGAGAGGTATATCTGTAACAGCGGCTTCAAGAGGAAGGCCGGCACCA
GCAGCCTCACCGAGTGCGTGCTGAATAAGGCTACCAACGTGGCTCACTGGAC
AACACCCTCTTTAAAGTGCATCCGGGGCGGTGGAGGATCCGGAGGAGGTGGC
TCCGGCGGCGGAGGATCTGATCCCGCCGGCCTCTTGGACCTGCGGCAGGGCA
TGTTTGCGCAGCTGGTGGCCCAAAATGTTCTGCTGATCGATGGGCCCCTGAGC
TGGTACAGTGACCCAGGCCTGGCAGGCGTGTCCCTGACGGGGGGCCTGAGCT
ACAAAGAGGACACGAAGGAGCTGGTGGTGGCCAAGGCTGGAGTCTACTATG
TCTTCTTTCAACTAGAGCTGCGGCGCGTGGTGGCCGGCGAGGGCTCAGGCTC
CGTTTCACTTGCGCTGCACCTGCAGCCACTGCGCTCTGCTGCTGGGGCCGCCG
CCCTGGCTTTGACCGTGGACCTGCCACCCGCCTCCTCCGAGGCTCGGAACTCG
GCCTTCGGTTTCCAGGGCCGCTTGCTGCACCTGAGTGCCGGCCAGCGCCTGG
GCGTCCATCTTCACACTGAGGCCAGGGCACGCCATGCCTGGCAGCTTACCCA
GGGCGCCACAGTCTTGGGACTCTTCCGGGTGACCCCCGAAATC (SEQ ID NO: 172).

Exemplary Multi-Chain Chimeric Polypeptides- Type K

In some embodiments of any of the multi-chain chimeric polypeptides described herein, the first target-binding domain and the second targeting-binding domain each independently bind specifically to a receptor of IL-7 or TGF-β. In some examples of these multi-chain chimeric polypeptides, the first target-binding domain and the soluble tissue factor domain directly abut each other in the first chimeric polypeptide. In some examples of these multi-chain chimeric polypeptides, the first chimeric polypeptide further comprises a linker sequence (e.g., any of the exemplary linkers described herein) between the first target-binding domain and the soluble tissue factor domain in the first chimeric polypeptide.

In some embodiments of these multi-chain chimeric polypeptides, 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 embodiments of these multi-chain chimeric polypeptides, the first chimeric polypeptide further includes a linker sequence (e.g., any of the exemplary linkers described herein) between the soluble tissue factor domain and the first domain of the pair of affinity domains in the first chimeric polypeptide.

In some embodiments of these multi-chain chimeric polypeptides, 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 embodiments of these multi-chain chimeric polypeptides, the second chimeric polypeptide further includes a linker sequence (e.g., any of the exemplary linkers described herein) between the second domain of the pair of affinity domains and the second target-binding domain in the second chimeric polypeptide.

In some embodiments of these multi-chain chimeric polypeptides, the soluble tissue factor domain can be any of the exemplary soluble tissue factor domains described herein. In some embodiments of these multi-chain chimeric polypeptides, the pair of affinity domains can be any of the exemplary pairs of affinity domains described herein.

In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain binds specifically to a receptor for IL-7, and the second target-binding domain binds specifically to TGF-β. In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain binds specifically to TGF-β, and the second target-binding domain binds specifically to a receptor for IL-7.

In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain includes a soluble IL-7 protein (e.g., a soluble human IL-7 protein). In some embodiments of these multi-chain chimeric polypeptides, the soluble human IL-7 protein includes a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

DCDIEGKDGKQYESVLMVSIDQLLDSMKEIGSNCLNNEFNFFKRHICDANKEGM FLFRAARKLRQFLKMNSTGDFDLHLLKVSEGTTILLNCTGQVKGRKPAALGEAQ PTKSLEENKSLKEQKKLNDLCFLKRLLQEIKTCWNKILMGTKEH (SEQ ID NO: 11).

In some embodiments of these multi-chain chimeric polypeptides, the soluble human IL-7 is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

GATTGCGACATCGAGGGCAAGGACGGCAAGCAGTACGAGAGCGTGCTGATG GTGTCCATCGACCAGCTGCTGGACAGCATGAAGGAGATCGGCTCCAACTGCC TCAACAACGAGTTCAACTTCTTCAAGCGGCACATCTGCGACGCCAACAAGGA GGGCATGTTCCTGTTCAGGGCCGCCAGGAAACTGCGGCAGTTCCTGAAGATG AACTCCACCGGCGACTTCGACCTGCACCTGCTGAAGGTGTCCGAGGGCACCA CCATCCTGCTGAACTGCACCGGACAGGTGAAGGGCCGGAAACCTGCTGCTCT GGGAGAGGCCCAACCCACCAAGAGCCTGGAGGAGAACAAGTCCCTGAAGGA GCAGAAGAAGCTGAACGACCTGTGCTTCCTGAAGAGGCTGCTGCAGGAGATC AAGACCTGCTGGAACAAGATCCTGATGGGCACCAAGGAGCAT (SEQ ID NO: 124).

In some embodiments of these multi-chain chimeric polypeptides, the second target-binding domain comprises a target-binding domain that binds specifically to TGF-β. In some embodiments of these multi-chain chimeric polypeptides, the second target-binding domain is a soluble TGF-β receptor (e.g., a soluble TGFβRII receptor, e.g., a soluble human TGFβRII receptor). In some embodiments of these multi-chain chimeric polypeptides, the soluble human TGFRβRII includes a first sequence of soluble human TGFRβRII and a second sequence of soluble human TGFRβRII. In some embodiments of these multi-chain chimeric polypeptides, the soluble human TGFRβRII includes a linker disposed between the first sequence of soluble human TGFRβRII and the second sequence of soluble human TGFRβRII. In some examples of these multi-chain chimeric polypeptides, the linker includes the sequence GGGGSGGGGSGGGGS (SEQ ID NO: 7).

In some embodiments of these multi-chain chimeric polypeptides, the first sequence of soluble human TGFRβRII receptor comprises a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at

least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

IPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICE KPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGET FFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 80).

In some embodiments of these multi-chain chimeric polypeptides, the second sequence of soluble human TGFRβRII receptor comprises a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

IPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICE KPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGET FFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 81).

In some embodiments of these multi-chain chimeric polypeptides, the first sequence of soluble human TGFRβRII receptor is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATCCCCCCCCATGTGCAAAAGAGCGTGAACAACGATATGATCGTGACCGACAA CAACGGCGCCGTGAAGTTTCCCCAGCTCTGCAAGTTCTGCGATGTCAGGTTCA GCACCTGCGATAATCAGAAGTCCTGCATGTCCAACTGCAGCATCACCTCCATCT GCGAGAAGCCCCAAGAAGTGTGCGTGGCCGTGTGGCGGAAAAATGACGAGA ACATCACCCTGGAGACCGTGTGTCACGACCCCAAGCTCCCTTATCACGACTTC ATTCTGGAGGACGCTGCCTCCCCCAAATGCATCATGAAGGAGAAGAAGAAGC CCGGAGAGACCTTCTTTATGTGTTCCTGTAGCAGCGACGAGTGTAACGACAAC ATCATCTTCAGCGAAGAGTACAACACCAGCAACCCTGAT (SEQ ID NO: 82).

In some embodiments of these multi-chain chimeric polypeptides, the second sequence of soluble human TGFRβRII receptor is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATTCCTCCCCACGTGCAGAAGAGCGTGAATAATGACATGATCGTGACCGATA
ACAATGGCGCCGTGAAATTTCCCCAGCTGTGCAAATTCTGCGATGTGAGGTTT
TCCACCTGCGACAACCAGAAGTCCTGTATGAGCAACTGCTCCATCACCTCCAT
CTGTGAGAAGCCTCAGGAGGTGTGCGTGGCTGTCTGGCGGAAGAATGACGAG
AATATCACCCTGGAAACCGTCTGCCACGATCCCAAGCTGCCCTACCACGATTT
CATCCTGGAAGACGCCGCCAGCCCTAAGTGCATCATGAAAGAGAAAAAGAA
GCCTGGCGAGACCTTTTTCATGTGCTCCTGCAGCAGCGACGAATGCAACGAC
AATATCATCTTTAGCGAGGAATACAATACCAGCAACCCCGAC (SEQ ID NO: 83).

In some embodiments of these multi-chain chimeric polypeptides, the soluble TGF-β receptor includes a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

IPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICE
KPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGET
FFMCSCSSDECNDNIIFSEEYNTSNPDGGGGSGGGGSGGGGSIPPHVQKSVNNDM
IVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRK
NDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECND
NIIFSEEYNTSNPD (SEQ ID NO: 85).

In some embodiments of these multi-chain chimeric polypeptides, the soluble TGF-β receptor is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATCCCCCCCCCATGTGCAAAAGAGCGTGAACAACGATATGATCGTGACCGACAA
CAACGGCGCCGTGAAGTTTCCCCAGCTCTGCAAGTTCTGCGATGTCAGGTTCA
GCACCTGCGATAATCAGAAGTCCTGCATGTCCAACTGCAGCATCACCTCCATCT
GCGAGAAGCCCCAAGAAGTGTGCGTGGCCGTGTGGCGGAAAAATGACGAGA
ACATCACCCTGGAGACCGTGTGTCACGACCCCAAGCTCCCTTATCACGACTTC
ATTCTGGAGGACGCTGCCTCCCCCAAATGCATCATGAAGGAGAAGAAGAAGC
CCGGAGAGACCTTCTTTATGTGTTCCTGTAGCAGCGACGAGTGTAACGACAAC
ATCATCTTCAGCGAAGAGTACAACACCAGCAACCCTGATGGAGGTGGCGGATC
CGGAGGTGGAGGTTCTGGTGGAGGTGGGAGTATTCCTCCCCACGTGCAGAAG
AGCGTGAATAATGACATGATCGTGACCGATAACAATGGCGCCGTGAAATTTCC
CCAGCTGTGCAAATTCTGCGATGTGAGGTTTTCCACCTGCGACAACCAGAAGT
CCTGTATGAGCAACTGCTCCATCACCTCCATCTGTGAGAAGCCTCAGGAGGTG
TGCGTGGCTGTCTGGCGGAAGAATGACGAGAATATCACCCTGGAAACCGTCTG

CCACGATCCCAAGCTGCCCTACCACGATTTCATCCTGGAAGACGCCGCCAGCC
CTAAGTGCATCATGAAAGAGAAAAAGAAGCCTGGCGAGACCTTTTTCATGTGC
TCCTGCAGCAGCGACGAATGCAACGACAATATCATCTTTAGCGAGGAATACAA
TACCAGCAACCCCGAC (SEQ ID NO: 84).

In some embodiments, the first chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

DCDIEGKDGKQYESVLMVSIDQLLDSMKEIGSNCLNNEFNFFKRHICDANKEGM
FLFRAARKLRQFLKMNSTGDFDLHLLKVSEGTTILLNCTGQVKGRKPAALGEAQ
PTKSLEENKSLKEQKKLNDLCFLKRLLQEIKTCWNKILMGTKEHSGTTNTVAAYN
LTWKSTNFKTILEWEPKPVNQVYTVQISTKSGDWKSKCFYTTDTECDLTDEIVKD
VKQTYLARVFSYPAGNVESTGSAGEPLYENSPEFTPYLETNLGQPTIQSFEQVGTK
VNVTVEDERTLVRRNNTFLSLRDVFGKDLIYTLYYWKSSSSGKKTAKTNTNEFLI
DVDKGENYCFSVQAVIPSRTVNRKSTDSPVECMGQEKGEFRENWVNVISDLKKIE
DLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILA
NNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS (SEQ ID NO: 173).

In some embodiments, a first chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

GATTGCGACATCGAGGGCAAGGACGGCAAGCAGTACGAGAGCGTGCTGATGG
TGTCCATCGACCAGCTGCTGGACAGCATGAAGGAGATCGGCTCCAACTGCCTC
AACAACGAGTTCAACTTCTTCAAGCGGCACATCTGCGACGCCAACAAGGAGG
GCATGTTCCTGTTCAGGGCCGCCAGGAAACTGCGGCAGTTCCTGAAGATGAA
CTCCACCGGCGACTTCGACCTGCACCTGCTGAAGGTGTCCGAGGGCACCACC
ATCCTGCTGAACTGCACCGGACAGGTGAAGGGCCGGAAACCTGCTGCTCTGG
GAGAGGCCCAACCCACCAAGAGCCTGGAGGAGAACAAGTCCCTGAAGGAGC
AGAAGAAGCTGAACGACCTGTGCTTCCTGAAGAGGCTGCTGCAGGAGATCAA
GACCTGCTGGAACAAGATCCTGATGGGCACCAAGGAGCATAGCGGCACAACC
AACACAGTCGCTGCCTATAACCTCACTTGGAAGAGCACCAACTTCAAAACCAT
CCTCGAATGGGAACCCAAACCCGTTAACCAAGTTTACACCGTGCAGATCAGCA
CCAAGTCCGGCGACTGGAAGTCCAAATGTTTCTATACCACCGACACCGAGTGC
GATCTCACCGATGAGATCGTGAAAGATGTGAAACAGACCTACCTCGCCCGGGT
GTTTAGCTACCCCGCCGGCAATGTGGAGAGCACTGGTTCCGCTGGCGAGCCTT
TATACGAGAACAGCCCCGAATTTACCCCTTACCTCGAGACCAATTTAGGACAG

CCCACCATCCAAAGCTTTGAGCAAGTTGGCACAAAGGTGAATGTGACAGTGG
AGGACGAGCGGACTTTAGTGCGGCGGAACAACACCTTTCTCAGCCTCCGGGA
TGTGTTCGGCAAAGATTTAATCTACACACTGTATTACTGGAAGTCCTCTTCCTC
CGGCAAGAAGACAGCTAAAACCAACACAAACGAGTTTTTAATCGACGTGGAT
AAAGGCGAAAACTACTGTTTCAGCGTGCAAGCTGTGATCCCCTCCCGGACCGT
GAATAGGAAAAGCACCGATAGCCCCGTTGAGTGCATGGGCCAAGAAAAGGGC
GAGTTCCGGGAGAACTGGGTGAACGTCATCAGCGATTTAAAGAAGATCGAAG
ATTTAATTCAGTCCATGCATATCGACGCCACTTTATACACAGAATCCGACGTGC
ACCCCTCTTGTAAGGTGACCGCCATGAAATGTTTTTTACTGGAGCTGCAAGTTA
TCTCTTTAGAGAGCGGAGACGCTAGCATCCACGACACCGTGGAGAATTTAATC
ATTTTAGCCAATAACTCTTTATCCAGCAACGGCAACGTGACAGAGTCCGGCTG
CAAGGAGTGCGAAGAGCTGGAGGAGAAGAACATCAAGGAGTTTCTGCAATCC
TTTGTGCACATTGTCCAGATGTTCATCAATACCTCC (SEQ ID NO: 174).

In some embodiments, a first chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

MKWVTFISLLFLFSSAYSDCDIEGKDGKQYESVLMVSIDQLLDSMKEIGSNCLNN
EFNFFKRHICDANKEGMFLFRAARKLRQFLKMNSTGDFDLHLLKVSEGTTILLNC
TGQVKGRKPAALGEAQPTKSLEENKSLKEQKKLNDLCFLKRLLQEIKTCWNKIL
MGTKEHSGTTNTVAAYNLTWKSTNFKTILEWEPKPVNQVYTVQISTKSGDWKSK
CFYTTDTECDLTDEIVKDVKQTYLARVFSYPAGNVESTGSAGEPLYENSPEFTPYL
ETNLGQPTIQSFEQVGTKVNVTVEDERTLVRRNNTFLSLRDVFGKDLIYTLYYWK
SSSSGKKTAKTNTNEFLIDVDKGENYCFSVQAVIPSRTVNRKSTDSPVECMGQEK
GEFRENWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVIS
LESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQ
MFINTS (SEQ ID NO: 175).

In some embodiments, a first chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATGAAGTGGGTGACCTTCATCAGCCTGCTGTTCCTGTTCTCCAGCGCCTACTCC
GATTGCGACATCGAGGGCAAGGACGGCAAGCAGTACGAGAGCGTGCTGATGG
TGTCCATCGACCAGCTGCTGGACAGCATGAAGGAGATCGGCTCCAACTGCCTC
AACAACGAGTTCAACTTCTTCAAGCGGCACATCTGCGACGCCAACAAGGAGG
GCATGTTCCTGTTCAGGGCCGCCAGGAAACTGCGGCAGTTCCTGAAGATGAA

CTCCACCGGCGACTTCGACCTGCACCTGCTGAAGGTGTCCGAGGGCACCACC
ATCCTGCTGAACTGCACCGGACAGGTGAAGGGCCGGAAACCTGCTGCTCTGG
GAGAGGCCCAACCCACCAAGAGCCTGGAGGAGAACAAGTCCCTGAAGGAGC
AGAAGAAGCTGAACGACCTGTGCTTCCTGAAGAGGCTGCTGCAGGAGATCAA
GACCTGCTGGAACAAGATCCTGATGGGCACCAAGGAGCATAGCGGCACAACC
AACACAGTCGCTGCCTATAACCTCACTTGGAAGAGCACCAACTTCAAAACCAT
CCTCGAATGGGAACCCAAACCCGTTAACCAAGTTTACACCGTGCAGATCAGCA
CCAAGTCCGGCGACTGGAAGTCCAAATGTTTCTATACCACCGACACCGAGTGC
GATCTCACCGATGAGATCGTGAAAGATGTGAAACAGACCTACCTCGCCCGGGT
GTTTAGCTACCCCGCCGGCAATGTGGAGAGCACTGGTTCCGCTGGCGAGCCTT
TATACGAGAACAGCCCCGAATTTACCCCTTACCTCGAGACCAATTTAGGACAG
CCCACCATCCAAAGCTTTGAGCAAGTTGGCACAAAGGTGAATGTGACAGTGG
AGGACGAGCGGACTTTAGTGCGGCGGAACAACACCTTTCTCAGCCTCCGGGA
TGTGTTCGGCAAAGATTTAATCTACACACTGTATTACTGGAAGTCCTCTTCCTC
CGGCAAGAAGACAGCTAAAACCAACACAAACGAGTTTTTAATCGACGTGGAT
AAAGGCGAAAACTACTGTTTCAGCGTGCAAGCTGTGATCCCCTCCCGGACCGT
GAATAGGAAAAGCACCGATAGCCCCGTTGAGTGCATGGGCCAAGAAAAGGGC
GAGTTCCGGGAGAACTGGGTGAACGTCATCAGCGATTTAAAGAAGATCGAAG
ATTTAATTCAGTCCATGCATATCGACGCCACTTTATACACAGAATCCGACGTGC
ACCCCTCTTGTAAGGTGACCGCCATGAAATGTTTTTTACTGGAGCTGCAAGTTA
TCTCTTTAGAGAGCGGAGACGCTAGCATCCACGACACCGTGGAGAATTTAATC
ATTTTAGCCAATAACTCTTTATCCAGCAACGGCAACGTGACAGAGTCCGGCTG
CAAGGAGTGCGAAGAGCTGGAGGAGAAGAACATCAAGGAGTTTCTGCAATCC
TTTGTGCACATTGTCCAGATGTTCATCAATACCTCC (SEQ ID NO: 176).

In some embodiments, the second chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

IPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICE
KPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETF
FMCSCSSDECNDNIIFSEEYNTSNPDGGGGSGGGGSGGGGSIPPHVQKSVNNDMI
VTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRKN
DENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNI
IFSEEYNTSNPDITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTEC
VLNKATNVAHWTTPSLKCIR (SEQ ID NO: 177).

In some embodiments, a second chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at

least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATCCCCCCCCATGTGCAAAAGAGCGTGAACAACGATATGATCGTGACCGACAA
CAACGGCGCCGTGAAGTTTCCCCAGCTCTGCAAGTTCTGCGATGTCAGGTTCA
GCACCTGCGATAATCAGAAGTCCTGCATGTCCAACTGCAGCATCACCTCCATCT
GCGAGAAGCCCCAAGAAGTGTGCGTGGCCGTGTGGCGGAAAAATGACGAGA
ACATCACCCTGGAGACCGTGTGTCACGACCCCAAGCTCCCTTATCACGACTTC
ATTCTGGAGGACGCTGCCTCCCCCAAATGCATCATGAAGGAGAAGAAGAAGC
CCGGAGAGACCTTCTTTATGTGTTCCTGTAGCAGCGACGAGTGTAACGACAAC
ATCATCTTCAGCGAAGAGTACAACACCAGCAACCCTGATGGAGGTGGCGGATC
CGGAGGTGGAGGTTCTGGTGGAGGTGGGAGTATTCCTCCCCACGTGCAGAAG
AGCGTGAATAATGACATGATCGTGACCGATAACAATGGCGCCGTGAAATTTCC
CCAGCTGTGCAAATTCTGCGATGTGAGGTTTTCCACCTGCGACAACCAGAAGT
CCTGTATGAGCAACTGCTCCATCACCTCCATCTGTGAGAAGCCTCAGGAGGTG
TGCGTGGCTGTCTGGCGGAAGAATGACGAGAATATCACCCTGGAAACCGTCTG
CCACGATCCCAAGCTGCCCTACCACGATTTCATCCTGGAAGACGCCGCCAGCC
CTAAGTGCATCATGAAAGAGAAAAAGAAGCCTGGCGAGACCTTTTTCATGTGC
TCCTGCAGCAGCGACGAATGCAACGACAATATCATCTTTAGCGAGGAATACAA
TACCAGCAACCCCGACATTACATGCCCCCCTCCCATGAGCGTGGAGCACGCCG
ACATCTGGGTGAAGAGCTATAGCCTCTACAGCCGGGAGAGGTATATCTGTAAC
AGCGGCTTCAAGAGGAAGGCCGGCACCAGCAGCCTCACCGAGTGCGTGCTG
AATAAGGCTACCAACGTGGCTCACTGGACAACACCCTCTTTAAAGTGCATCCG
G (SEQ ID NO: 178).

In some embodiments, a second chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

MKWVTFISLLFLFSSAYSIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFST
CDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILED
AASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPDGGGGSGGGGSG
GGGSIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSIT
SICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKP
GETFFMCSCSSDECNDNIIFSEEYNTSNPDITCPPPMSVEHADIWVKSYSLYSRERY
ICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR (SEQ ID NO: 179).

In some embodiments, a second chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at

least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATGAAGTGGGTGACCTTCATCAGCCTGCTGTTCCTGTTCTCCAGCGCCTACTCC
ATCCCCCCCCCATGTGCAAAAGAGCGTGAACAACGATATGATCGTGACCGACAA
CAACGGCGCCGTGAAGTTTCCCCAGCTCTGCAAGTTCTGCGATGTCAGGTTCA
GCACCTGCGATAATCAGAAGTCCTGCATGTCCAACTGCAGCATCACCTCCATCT
GCGAGAAGCCCCAAGAAGTGTGCGTGGCCGTGTGGCGGAAAAATGACGAGA
ACATCACCCTGGAGACCGTGTGTCACGACCCCAAGCTCCCTTATCACGACTTC
ATTCTGGAGGACGCTGCCTCCCCCAAATGCATCATGAAGGAGAAGAAGAAGC
CCGGAGAGACCTTCTTTATGTGTTCCTGTAGCAGCGACGAGTGTAACGACAAC
ATCATCTTCAGCGAAGAGTACAACACCAGCAACCCTGATGGAGGTGGCGGATC
CGGAGGTGGAGGTTCTGGTGGAGGTGGGAGTATTCCTCCCCACGTGCAGAAG
AGCGTGAATAATGACATGATCGTGACCGATAACAATGGCGCCGTGAAATTTCC
CCAGCTGTGCAAATTCTGCGATGTGAGGTTTTCCACCTGCGACAACCAGAAGT
CCTGTATGAGCAACTGCTCCATCACCTCCATCTGTGAGAAGCCTCAGGAGGTG
TGCGTGGCTGTCTGGCGGAAGAATGACGAGAATATCACCCTGGAAACCGTCTG
CCACGATCCCAAGCTGCCCTACCACGATTTCATCCTGGAAGACGCCGCCAGCC
CTAAGTGCATCATGAAAGAGAAAAAGAAGCCTGGCGAGACCTTTTTCATGTGC
TCCTGCAGCAGCGACGAATGCAACGACAATATCATCTTTAGCGAGGAATACAA
TACCAGCAACCCCGACATTACATGCCCCCCTCCCATGAGCGTGGAGCACGCCG
ACATCTGGGTGAAGAGCTATAGCCTCTACAGCCGGGAGAGGTATATCTGTAAC
AGCGGCTTCAAGAGGAAGGCCGGCACCAGCAGCCTCACCGAGTGCGTGCTG
AATAAGGCTACCAACGTGGCTCACTGGACAACACCCTCTTTAAAGTGCATCCG
G (SEQ ID NO: 180).

Exemplary Multi-Chain Chimeric Polypeptides- Type L

In some embodiments of any of the multi-chain chimeric polypeptides described herein, the first target-binding domain and the second targeting-binding domain each independently bind specifically to TGF-β, a receptor of IL-21, or a receptor of CD137L. In some embodiments of these multi-chain chimeric polypeptides described herein, the second chimeric polypeptide further includes the additional target-binding domain. In some embodiments of these multi-chain chimeric polypeptides described herein, the additional target-binding domain binds specifically to a receptor for IL-21 (e.g., a soluble IL-21, e.g., a soluble human IL-21) or a receptor for CD137L (e.g., a soluble CD137L, e.g., a soluble human CD137L).

In some examples of these multi-chain chimeric polypeptides, the first target-binding domain and the soluble tissue factor domain directly abut each other in the first chimeric polypeptide. In some examples of these multi-chain chimeric polypeptides, the

first chimeric polypeptide further comprises a linker sequence (e.g., any of the exemplary linkers described herein) between the first target-binding domain and the soluble tissue factor domain in the first chimeric polypeptide.

In some embodiments of these multi-chain chimeric polypeptides, 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 embodiments of these multi-chain chimeric polypeptides, the first chimeric polypeptide further includes a linker sequence (e.g., any of the exemplary linkers described herein) between the soluble tissue factor domain and the first domain of the pair of affinity domains in the first chimeric polypeptide.

In some embodiments of these multi-chain chimeric polypeptides, 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 embodiments of these multi-chain chimeric polypeptides, the second chimeric polypeptide further includes a linker sequence (e.g., any of the exemplary linkers described herein) between the second domain of the pair of affinity domains and the second target-binding domain in the second chimeric polypeptide.

In some embodiments, the second chimeric polypeptide further comprises one or more additional target-binding domains at the N-terminal end or the C-terminal end of the second chimeric polypeptide.

In some embodiments of these multi-chain chimeric polypeptides, the additional target-binding domain and the second domain of the pair of affinity domains directly abut each other in the second chimeric polypeptide. In some embodiments of these multi-chain chimeric polypeptides, the second chimeric polypeptide further includes a linker sequence (e.g., any of the exemplary linkers described herein) between the second domain of the pair of affinity domains and the additional target-binding domain in the second chimeric polypeptide.

In some embodiments of these multi-chain chimeric polypeptides, the additional target-binding domain and the second target-binding domain directly abut each other in the second chimeric polypeptide. In some embodiments of these multi-chain chimeric polypeptides, the second chimeric polypeptide further includes a linker sequence (e.g.,

any of the exemplary linkers described herein) between the second target-binding domain and the additional target-binding domain in the second chimeric polypeptide.

In some embodiments of these multi-chain chimeric polypeptides, the soluble tissue factor domain can be any of the exemplary soluble tissue factor domains described herein. In some embodiments of these multi-chain chimeric polypeptides, the pair of affinity domains can be any of the exemplary pairs of affinity domains described herein.

In some embodiments of these multi-chain chimeric polypeptides, one or more of the first target-binding domain, the second target-binding domain and the additional target-binding domain is an agonistic antigen-binding domain. In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain, the second target-binding domain, and the additional target-binding domain are each agonistic antigen-binding domains. In some embodiments of these multi-chain chimeric polypeptides, the antigen-binding domain includes a scFv or single-domain antibody.

In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain binds specifically to TGF-β and the second target-binding domain binds specifically to a receptor for IL-21 or a receptor for CD137L.

In some embodiments of these multi-chain chimeric polypeptides, the first target-binding domain is a soluble TGF-β receptor (e.g., a soluble TGFβRII receptor, e.g., a soluble human TGFβRII receptor). In some embodiments of these multi-chain chimeric polypeptides, the soluble human TGFRβRII includes a first sequence of soluble human TGFRβRII and a second sequence of soluble human TGFRβRII. In some embodiments of these multi-chain chimeric polypeptides, the soluble human TGFRβRII includes a linker disposed between the first sequence of soluble human TGFRβRII and the second sequence of soluble human TGFRβRII. In some examples of these multi-chain chimeric polypeptides, the linker includes the sequence GGGGSGGGGSGGGGS (SEQ ID NO: 7).

In some embodiments of these multi-chain chimeric polypeptides, the first sequence of soluble human TGFRβRII receptor comprises a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

IPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICE
KPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGET
FFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 80).

In some embodiments of these multi-chain chimeric polypeptides, the second sequence of soluble human TGFRβRII receptor comprises a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

IPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICE
KPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGET
FFMCSCSSDECNDNIIFSEEYNTSNPD (SEQ ID NO: 81).

In some embodiments of these multi-chain chimeric polypeptides, the first sequence of soluble human TGFRβRII receptor is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATCCCCCCCCCATGTGCAAAAGAGCGTGAACAACGATATGATCGTGACCGACAA
CAACGGCGCCGTGAAGTTTCCCCAGCTCTGCAAGTTCTGCGATGTCAGGTTCA
GCACCTGCGATAATCAGAAGTCCTGCATGTCCAACTGCAGCATCACCTCCATCT
GCGAGAAGCCCCAAGAAGTGTGCGTGGCCGTGTGGCGGAAAAATGACGAGA
ACATCACCCTGGAGACCGTGTGTCACGACCCCAAGCTCCCTTATCACGACTTC
ATTCTGGAGGACGCTGCCTCCCCCAAATGCATCATGAAGGAGAAGAAGAAGC
CCGGAGAGACCTTCTTTATGTGTTCCTGTAGCAGCGACGAGTGTAACGACAAC
ATCATCTTCAGCGAAGAGTACAACACCAGCAACCCTGAT (SEQ ID NO: 82)

In some embodiments of these multi-chain chimeric polypeptides, the second sequence of soluble human TGFRβRII receptor is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATTCCTCCCCACGTGCAGAAGAGCGTGAATAATGACATGATCGTGACCGATA
ACAATGGCGCCGTGAAATTTCCCCAGCTGTGCAAATTCTGCGATGTGAGGTTT
TCCACCTGCGACAACCAGAAGTCCTGTATGAGCAACTGCTCCATCACCTCCAT
CTGTGAGAAGCCTCAGGAGGTGTGCGTGGCTGTCTGGCGGAAGAATGACGAG

AATATCACCCTGGAAACCGTCTGCCACGATCCCAAGCTGCCCTACCACGATTT
CATCCTGGAAGACGCCGCCAGCCCTAAGTGCATCATGAAAGAGAAAAAGAA
GCCTGGCGAGACCTTTTTCATGTGCTCCTGCAGCAGCGACGAATGCAACGAC
AATATCATCTTTAGCGAGGAATACAATACCAGCAACCCCGAC (SEQ ID NO:
83).

In some embodiments of these multi-chain chimeric polypeptides, the soluble TGF-β receptor includes a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

IPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICE
KPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGET
FFMCSCSSDECNDNIIFSEEYNTSNPDGGGGSGGGGSGGGGSIPPHVQKSVNNDM
IVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRK
NDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECND
NIIFSEEYNTSNPD (SEQ ID NO: 85).

In some embodiments of these multi-chain chimeric polypeptides, the soluble TGF-β receptor is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATCCCCCCCCCATGTGCAAAAGAGCGTGAACAACGATATGATCGTGACCGACAA
CAACGGCGCCGTGAAGTTTCCCCAGCTCTGCAAGTTCTGCGATGTCAGGTTCA
GCACCTGCGATAATCAGAAGTCCTGCATGTCCAACTGCAGCATCACCTCCATCT
GCGAGAAGCCCCAAGAAGTGTGCGTGGCCGTGTGGCGGAAAAATGACGAGA
ACATCACCCTGGAGACCGTGTGTCACGACCCCAAGCTCCCTTATCACGACTTC
ATTCTGGAGGACGCTGCCTCCCCCAAATGCATCATGAAGGAGAAGAAGAAGC
CCGGAGAGACCTTCTTTATGTGTTCCTGTAGCAGCGACGAGTGTAACGACAAC
ATCATCTTCAGCGAAGAGTACAACACCAGCAACCCTGATGGAGGTGGCGGATC
CGGAGGTGGAGGTTCTGGTGGAGGTGGGAGTATTCCTCCCCACGTGCAGAAG
AGCGTGAATAATGACATGATCGTGACCGATAACAATGGCGCCGTGAAATTTCC
CCAGCTGTGCAAATTCTGCGATGTGAGGTTTTCCACCTGCGACAACCAGAAGT
CCTGTATGAGCAACTGCTCCATCACCTCCATCTGTGAGAAGCCTCAGGAGGTG
TGCGTGGCTGTCTGGCGGAAGAATGACGAGAATATCACCCTGGAAACCGTCTG
CCACGATCCCAAGCTGCCCTACCACGATTTCATCCTGGAAGACGCCGCCAGCC
CTAAGTGCATCATGAAAGAGAAAAAGAAGCCTGGCGAGACCTTTTTCATGTGC
TCCTGCAGCAGCGACGAATGCAACGACAATATCATCTTTAGCGAGGAATACAA
TACCAGCAACCCCGAC (SEQ ID NO: 84).

In some embodiments of these multi-chain chimeric polypeptides, the second target-binding domain or the additional target-binding domain binds specifically to a receptor for IL-21. In some embodiments of these multi-chain chimeric polypeptides, the second target-binding domain or the additional target-binding domain includes a soluble IL-21(e.g., a soluble human IL-21).

In some embodiments of these multi-chain chimeric polypeptides, a soluble human IL-21 includes a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

QGQDRHMIRMRQLIDIVDQLKNYVNDLVPEFLPAPEDVETNCEWSAFSCFQKAQ
LKSANTGNNERIINVSIKKLKRKPPSTNAGRRQKHRLTCPSCDSYEKKPPKEFLER
FKSLLQKMIHQHLSSRTHGSEDS (SEQ ID NO: 78).

In some embodiments of these multi-chain chimeric polypeptides, the soluble human IL-21 is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

CAGGGCCAGGACAGGCACATGATCCGGATGAGGCAGCTCATCGACATCGTCG
ACCAGCTGAAGAACTACGTGAACGACCTGGTGCCCGAGTTTCTGCCTGCCCC
CGAGGACGTGGAGACCAACTGCGAGTGGTCCGCCTTCTCCTGCTTTCAGAAG
GCCCAGCTGAAGTCCGCCAACACCGGCAACAACGAGCGGATCATCAACGTG
AGCATCAAGAAGCTGAAGCGGAAGCCTCCCTCCACAAACGCCGGCAGGAGG
CAGAAGCACAGGCTGACCTGCCCCAGCTGTGACTCCTACGAGAAGAAGCCCC
CCAAGGAGTTCCTGGAGAGGTTCAAGTCCCTGCTGCAGAAGATGATCCATCA
GCACCTGTCCTCCAGGACCCACGGCTCCGAGGACTCC (SEQ ID NO: 79).

In some embodiments of these multi-chain chimeric polypeptides, the second target-binding domain or the additional target-binding domain binds specifically to a receptor for CD137L. In some embodiments of these multi-chain chimeric polypeptides, the second target-binding domain and/or the additional target-binding domain includes a soluble CD137L (e.g., a soluble human CD137L).

In some embodiments of these multi-chain chimeric polypeptides, a soluble CD137L includes a sequence that is at least 80% identical (e.g., at least 82% identical, at

least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

REGPELSPDDPAGLLDLRQGMFAQLVAQNVLLIDGPLSWYSDPGLAGVSLTGGL
SYKEDTKELVVAKAGVYYVFFQLELRRVVAGEGSGSVSLALHLQPLRSAAGAA
ALALTVDLPPASSEARNSAFGFQGRLLHLSAGQRLGVHLHTEARARHAWQLTQ
GATVLGLFRVTPEIPAGLPSPRSE (SEQ ID NO: 157).

In some embodiments of these multi-chain chimeric polypeptides, a soluble CD137L is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

CGCGAGGGTCCCGAGCTTTCGCCCGACGATCCCGCCGGCCTCTTGGACCTGC
GGCAGGGCATGTTTGCGCAGCTGGTGGCCCAAAATGTTCTGCTGATCGATGG
GCCCCTGAGCTGGTACAGTGACCCAGGCCTGGCAGGCGTGTCCCTGACGGGG
GGCCTGAGCTACAAAGAGGACACGAAGGAGCTGGTGGTGGCCAAGGCTGGA
GTCTACTATGTCTTCTTTCAACTAGAGCTGCGGCGCGTGGTGGCCGGCGAGGG
CTCAGGCTCCGTTTCACTTGCGCTGCACCTGCAGCCACTGCGCTCTGCTGCTG
GGGCCGCCGCCCTGGCTTTGACCGTGGACCTGCCACCCGCCTCCTCCGAGGCT
CGGAACTCGGCCTTCGGTTTCCAGGGCCGCTTGCTGCACCTGAGTGCCGGCC
AGCGCCTGGGCGTCCATCTTCACACTGAGGCCAGGGCACGCCATGCCTGGCA
GCTTACCCAGGGCGCCACAGTCTTGGGACTCTTCCGGGTGACCCCCGAAATC
CCAGCCGGACTCCCTTCACCGAGGTCGGAA (SEQ ID NO: 158).

In some embodiments of these multi-chain chimeric polypeptides, a soluble human CD137L includes a sequence that is at least 80% identical (e.g., at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical) to:

DPAGLLDLRQGMFAQLVAQNVLLIDGPLSWYSDPGLAGVSLTGGLSYKEDTKEL
VVAKAGVYYVFFQLELRRVVAGEGSGSVSLALHLQPLRSAAGAAALALTVDLP
PASSEARNSAFGFQGRLLHLSAGQRLGVHLHTEARARHAWQLTQGATVLGLFR
VTPEI (SEQ ID NO: 159).

In some embodiments of these multi-chain chimeric polypeptides, a soluble human CD137L is encoded by a sequence that is at least 80% identical (e.g., at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical) to:

GATCCCGCCGGCCTCTTGGACCTGCGGCAGGGCATGTTTGCGCAGCTGGTGG
CCCAAAATGTTCTGCTGATCGATGGGCCCCTGAGCTGGTACAGTGACCCAGG
CCTGGCAGGCGTGTCCCTGACGGGGGGCCTGAGCTACAAAGAGGACACGAA
GGAGCTGGTGGTGGCCAAGGCTGGAGTCTACTATGTCTTCTTTCAACTAGAGC
TGCGGCGCGTGGTGGCCGGCGAGGGCTCAGGCTCCGTTTCACTTGCGCTGCA
CCTGCAGCCACTGCGCTCTGCTGCTGGGGCCGCCGCCCTGGCTTTGACCGTGG
ACCTGCCACCCGCCTCCTCCGAGGCTCGGAACTCGGCCTTCGGTTTCCAGGGC
CGCTTGCTGCACCTGAGTGCCGGCCAGCGCCTGGGCGTCCATCTTCACACTGA
GGCCAGGGCACGCCATGCCTGGCAGCTTACCCAGGGCGCCACAGTCTTGGGA
CTCTTCCGGGTGACCCCCGAAATC (SEQ ID NO: 160).

In some embodiments, the first chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

IPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICE
KPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETF
FMCSCSSDECNDNIIFSEEYNTSNPDGGGGSGGGGSGGGGSIPPHVQKSVNNDMI
VTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRKN
DENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNI
IFSEEYNTSNPDSGTTNTVAAYNLTWKSTNFKTILEWEPKPVNQVYTVQISTKSGD
WKSKCFYTTDTECDLTDEIVKDVKQTYLARVFSYPAGNVESTGSAGEPLYENSPE
FTPYLETNLGQPTIQSFEQVGTKVNVTVEDERTLVRRNNTFLSLRDVFGKDLIYTL
YYWKSSSSGKKTAKTNTNEFLIDVDKGENYCFSVQAVIPSRTVNRKSTDSPVECM
GQEKGEFRENWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLE
LQVISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSF
VHIVQMFINTS (SEQ ID NO: 181).

In some embodiments, a first chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATCCCCCCCCCATGTGCAAAAGAGCGTGAACAACGATATGATCGTGACCGACAA
CAACGGCGCCGTGAAGTTTCCCCAGCTCTGCAAGTTCTGCGATGTCAGGTTCA
GCACCTGCGATAATCAGAAGTCCTGCATGTCCAACTGCAGCATCACCTCCATCT
GCGAGAAGCCCCAAGAAGTGTGCGTGGCCGTGTGGCGGAAAAATGACGAGA
ACATCACCCTGGAGACCGTGTGTCACGACCCCAAGCTCCCTTATCACGACTTC
ATTCTGGAGGACGCTGCCTCCCCCAAATGCATCATGAAGGAGAAGAAGAAGC

CCGGAGAGACCTTCTTTATGTGTTCCTGTAGCAGCGACGAGTGTAACGACAAC
ATCATCTTCAGCGAAGAGTACAACACCAGCAACCCTGATGGAGGTGGCGGATC
CGGAGGTGGAGGTTCTGGTGGAGGTGGGAGTATTCCTCCCCACGTGCAGAAG
AGCGTGAATAATGACATGATCGTGACCGATAACAATGGCGCCGTGAAATTTCC
CCAGCTGTGCAAATTCTGCGATGTGAGGTTTTCCACCTGCGACAACCAGAAGT
CCTGTATGAGCAACTGCTCCATCACCTCCATCTGTGAGAAGCCTCAGGAGGTG
TGCGTGGCTGTCTGGCGGAAGAATGACGAGAATATCACCCTGGAAACCGTCTG
CCACGATCCCAAGCTGCCCTACCACGATTTCATCCTGGAAGACGCCGCCAGCC
CTAAGTGCATCATGAAAGAGAAAAAGAAGCCTGGCGAGACCTTTTTCATGTGC
TCCTGCAGCAGCGACGAATGCAACGACAATATCATCTTTAGCGAGGAATACAA
TACCAGCAACCCCGACAGCGGCACAACCAACACAGTCGCTGCCTATAACCTC
ACTTGGAAGAGCACCAACTTCAAAACCATCCTCGAATGGGAACCCAAACCCG
TTAACCAAGTTTACACCGTGCAGATCAGCACCAAGTCCGGCGACTGGAAGTC
CAAATGTTTCTATACCACCGACACCGAGTGCGATCTCACCGATGAGATCGTGA
AAGATGTGAAACAGACCTACCTCGCCCGGGTGTTTAGCTACCCCGCCGGCAAT
GTGGAGAGCACTGGTTCCGCTGGCGAGCCTTTATACGAGAACAGCCCCGAATT
TACCCCTTACCTCGAGACCAATTTAGGACAGCCCACCATCCAAAGCTTTGAGC
AAGTTGGCACAAAGGTGAATGTGACAGTGGAGGACGAGCGGACTTTAGTGCG
GCGGAACAACACCTTTCTCAGCCTCCGGGATGTGTTCGGCAAAGATTTAATCT
ACACACTGTATTACTGGAAGTCCTCTTCCTCCGGCAAGAAGACAGCTAAAACC
AACACAAACGAGTTTTTAATCGACGTGGATAAAGGCGAAAACTACTGTTTCAG
CGTGCAAGCTGTGATCCCCTCCCGGACCGTGAATAGGAAAAGCACCGATAGCC
CCGTTGAGTGCATGGGCCAAGAAAAGGGCGAGTTCCGGGAGAACTGGGTGA
ACGTCATCAGCGATTTAAAGAAGATCGAAGATTTAATTCAGTCCATGCATATCG
ACGCCACTTTATACACAGAATCCGACGTGCACCCCTCTTGTAAGGTGACCGCC
ATGAAATGTTTTTTACTGGAGCTGCAAGTTATCTCTTTAGAGAGCGGAGACGCT
AGCATCCACGACACCGTGGAGAATTTAATCATTTTAGCCAATAACTCTTTATCC
AGCAACGGCAACGTGACAGAGTCCGGCTGCAAGGAGTGCGAAGAGCTGGAG
GAGAAGAACATCAAGGAGTTTCTGCAATCCTTTGTGCACATTGTCCAGATGTT
CATCAATACCTCC (SEQ ID NO: 182).

In some embodiments, a first chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

MKWVTFISLLFLFSSAYSIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFST
CDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILED
AASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPDGGGGSGGGGSG
GGGSIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSIT
SICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKP
GETFFMCSCSSDECNDNIIFSEEYNTSNPDSGTTNTVAAYNLTWKSTNFKTILEWE

PKPVNQVYTVQISTKSGDWKSKCFYTTDTECDLTDEIVKDVKQTYLARVFSYPA
GNVESTGSAGEPLYENSPEFTPYLETNLGQPTIQSFEQVGTKVNVTVEDERTLVRR
NNTFLSLRDVFGKDLIYTLYYWKSSSSGKKTAKTNTNEFLIDVDKGENYCFSVQA
VIPSRTVNRKSTDSPVECMGQEKGEFRENWVNVISDLKKIEDLIQSMHIDATLYTE
SDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTESG
CKECEELEEKNIKEFLQSFVHIVQMFINTS (SEQ ID NO: 183).

In some embodiments, a first chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATGAAGTGGGTGACCTTCATCAGCCTGCTGTTCCTGTTCTCCAGCGCCTACTCC
ATCCCCCCCCCATGTGCAAAAGAGCGTGAACAACGATATGATCGTGACCGACAA
CAACGGCGCCGTGAAGTTTCCCCAGCTCTGCAAGTTCTGCGATGTCAGGTTCA
GCACCTGCGATAATCAGAAGTCCTGCATGTCCAACTGCAGCATCACCTCCATCT
GCGAGAAGCCCCAAGAAGTGTGCGTGGCCGTGTGGCGGAAAAATGACGAGA
ACATCACCCTGGAGACCGTGTGTCACGACCCCAAGCTCCCTTATCACGACTTC
ATTCTGGAGGACGCTGCCTCCCCCAAATGCATCATGAAGGAGAAGAAGAAGC
CCGGAGAGACCTTCTTTATGTGTTCCTGTAGCAGCGACGAGTGTAACGACAAC
ATCATCTTCAGCGAAGAGTACAACACCAGCAACCCTGATGGAGGTGGCGGATC
CGGAGGTGGAGGTTCTGGTGGAGGTGGGAGTATTCCTCCCCACGTGCAGAAG
AGCGTGAATAATGACATGATCGTGACCGATAACAATGGCGCCGTGAAATTTCC
CCAGCTGTGCAAATTCTGCGATGTGAGGTTTTCCACCTGCGACAACCAGAAGT
CCTGTATGAGCAACTGCTCCATCACCTCCATCTGTGAGAAGCCTCAGGAGGTG
TGCGTGGCTGTCTGGCGGAAGAATGACGAGAATATCACCCTGGAAACCGTCTG
CCACGATCCCAAGCTGCCCTACCACGATTTCATCCTGGAAGACGCCGCCAGCC
CTAAGTGCATCATGAAAGAGAAAAAGAAGCCTGGCGAGACCTTTTTCATGTGC
TCCTGCAGCAGCGACGAATGCAACGACAATATCATCTTTAGCGAGGAATACAA
TACCAGCAACCCCGACAGCGGCACAACCAACACAGTCGCTGCCTATAACCTC
ACTTGGAAGAGCACCAACTTCAAAACCATCCTCGAATGGGAACCCAAACCCG
TTAACCAAGTTTACACCGTGCAGATCAGCACCAAGTCCGGCGACTGGAAGTC
CAAATGTTTCTATACCACCGACACCGAGTGCGATCTCACCGATGAGATCGTGA
AAGATGTGAAACAGACCTACCTCGCCCGGGTGTTTAGCTACCCCGCCGGCAAT
GTGGAGAGCACTGGTTCCGCTGGCGAGCCTTTATACGAGAACAGCCCCGAATT
TACCCCTTACCTCGAGACCAATTTAGGACAGCCCACCATCCAAAGCTTTGAGC
AAGTTGGCACAAAGGTGAATGTGACAGTGGAGGACGAGCGGACTTTAGTGCG
GCGGAACAACACCTTTCTCAGCCTCCGGGATGTGTTCGGCAAAGATTTAATCT
ACACACTGTATTACTGGAAGTCCTCTTCCTCCGGCAAGAAGACAGCTAAAACC
AACACAAACGAGTTTTTAATCGACGTGGATAAAGGCGAAAACTACTGTTTCAG
CGTGCAAGCTGTGATCCCCTCCCGGACCGTGAATAGGAAAAGCACCGATAGCC
CCGTTGAGTGCATGGGCCAAGAAAAGGGCGAGTTCCGGGAGAACTGGGTGA

ACGTCATCAGCGATTTAAAGAAGATCGAAGATTTAATTCAGTCCATGCATATCG
ACGCCACTTTATACACAGAATCCGACGTGCACCCCTCTTGTAAGGTGACCGCC
ATGAAATGTTTTTTACTGGAGCTGCAAGTTATCTCTTTAGAGAGCGGAGACGCT
AGCATCCACGACACCGTGGAGAATTTAATCATTTTAGCCAATAACTCTTTATCC
AGCAACGGCAACGTGACAGAGTCCGGCTGCAAGGAGTGCGAAGAGCTGGAG
GAGAAGAACATCAAGGAGTTTCTGCAATCCTTTGTGCACATTGTCCAGATGTT
CATCAATACCTCC (SEQ ID NO: 184).

In some embodiments, the second chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

QGQDRHMIRMRQLIDIVDQLKNYVNDLVPEFLPAPEDVETNCEWSAFSCFQKAQ
LKSANTGNNERIINVSIKKLKRKPPSTNAGRRQKHRLTCPSCDSYEKKPPKEFLER
FKSLLQKMIHQHLSSRTHGSEDSITCPPPMSVEHADIWVKSYSLYSRERYICNSGF
KRKAGTSSLTECVLNKATNVAHWTTPSLKCIRGGGGSGGGGSGGGGSREGPELSP
DDPAGLLDLRQGMFAQLVAQNVLLIDGPLSWYSDPGLAGVSLTGGLSYKEDTKE
LVVAKAGVYYVFFQLELRRVVAGEGSGSVSLALHLQPLRSAAGAAALALTVDLPP
ASSEARNSAFGFQGRLLHLSAGQRLGVHLHTEARARHAWQLTQGATVLGLFRVT
PEIPAGLPSPRSE (SEQ ID NO: 185).

In some embodiments, a second chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

CAGGGCCAGGACAGGCACATGATCCGGATGAGGCAGCTCATCGACATCGTCG
ACCAGCTGAAGAACTACGTGAACGACCTGGTGCCCGAGTTTCTGCCTGCCCC
CGAGGACGTGGAGACCAACTGCGAGTGGTCCGCCTTCTCCTGCTTTCAGAAG
GCCCAGCTGAAGTCCGCCAACACCGGCAACAACGAGCGGATCATCAACGTGA
GCATCAAGAAGCTGAAGCGGAAGCCTCCCTCCACAAACGCCGGCAGGAGGC
AGAAGCACAGGCTGACCTGCCCCAGCTGTGACTCCTACGAGAAGAAGCCCCC
CAAGGAGTTCCTGGAGAGGTTCAAGTCCCTGCTGCAGAAGATGATCCATCAG
CACCTGTCCTCCAGGACCCACGGCTCCGAGGACTCCATTACATGCCCCCCTCC
CATGAGCGTGGAGCACGCCGACATCTGGGTGAAGAGCTATAGCCTCTACAGCC
GGGAGAGGTATATCTGTAACAGCGGCTTCAAGAGGAAGGCCGGCACCAGCAG
CCTCACCGAGTGCGTGCTGAATAAGGCTACCAACGTGGCTCACTGGACAACA
CCCTCTTTAAAGTGCATCCGGGGCGGTGGAGGATCCGGAGGAGGTGGCTCCG
GCGGCGGAGGATCTCGCGAGGGTCCCGAGCTTTCGCCCGACGATCCCGCCGG

CCTCTTGGACCTGCGGCAGGGCATGTTTGCGCAGCTGGTGGCCCAAAATGTTC
TGCTGATCGATGGGCCCCTGAGCTGGTACAGTGACCCAGGCCTGGCAGGCGT
GTCCCTGACGGGGGGCCTGAGCTACAAAGAGGACACGAAGGAGCTGGTGGT
GGCCAAGGCTGGAGTCTACTATGTCTTCTTTCAACTAGAGCTGCGGCGCGTGG
TGGCCGGCGAGGGCTCAGGCTCCGTTTCACTTGCGCTGCACCTGCAGCCACT
GCGCTCTGCTGCTGGGGCCGCCGCCCTGGCTTTGACCGTGGACCTGCCACCCG
CCTCCTCCGAGGCTCGGAACTCGGCCTTCGGTTTCCAGGGCCGCTTGCTGCAC
CTGAGTGCCGGCCAGCGCCTGGGCGTCCATCTTCACACTGAGGCCAGGGCAC
GCCATGCCTGGCAGCTTACCCAGGGCGCCACAGTCTTGGGACTCTTCCGGGTG
ACCCCCGAAATCCCAGCCGGACTCCCTTCACCGAGGTCGGAA (SEQ ID NO: 186).

In some embodiments, a second chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

MKWVTFISLLFLFSSAYSQGQDRHMIRMRQLIDIVDQLKNYVNDLVPEFLPAPED
VETNCEWSAFSCFQKAQLKSANTGNNERIINVSIKKLKRKPPSTNAGRRQKHRLT
CPSCDSYEKKPPKEFLERFKSLLQKMIHQHLSSRTHGSEDSITCPPPMSVEHADIW
VKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRGGGGS
GGGGSGGGGSREGPELSPDDPAGLLDLRQGMFAQLVAQNVLLIDGPLSWYSDPG
LAGVSLTGGLSYKEDTKELVVAKAGVYYVFFQLELRRVVAGEGSGSVSLALHLQ
PLRSAAGAAALALTVDLPPASSEARNSAFGFQGRLLHLSAGQRLGVHLHTEARA
RHAWQLTQGATVLGLFRVTPEIPAGLPSPRSE (SEQ ID NO: 187).

In some embodiments, a second chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATGAAGTGGGTGACCTTCATCAGCCTGCTGTTCCTGTTCTCCAGCGCCTACTCC
CAGGGCCAGGACAGGCACATGATCCGGATGAGGCAGCTCATCGACATCGTCG
ACCAGCTGAAGAACTACGTGAACGACCTGGTGCCCGAGTTTCTGCCTGCCCC
CGAGGACGTGGAGACCAACTGCGAGTGGTCCGCCTTCTCCTGCTTTCAGAAG
GCCCAGCTGAAGTCCGCCAACACCGGCAACAACGAGCGGATCATCAACGTGA
GCATCAAGAAGCTGAAGCGGAAGCCTCCCTCCACAAACGCCGGCAGGAGGC
AGAAGCACAGGCTGACCTGCCCCAGCTGTGACTCCTACGAGAAGAAGCCCCC
CAAGGAGTTCCTGGAGAGGTTCAAGTCCCTGCTGCAGAAGATGATCCATCAG
CACCTGTCCTCCAGGACCCACGGCTCCGAGGACTCCATTACATGCCCCCCTCC

CATGAGCGTGGAGCACGCCGACATCTGGGTGAAGAGCTATAGCCTCTACAGCC
GGGAGAGGTATATCTGTAACAGCGGCTTCAAGAGGAAGGCCGGCACCAGCAG
CCTCACCGAGTGCGTGCTGAATAAGGCTACCAACGTGGCTCACTGGACAACA
CCCTCTTTAAAGTGCATCCGGGGCGGTGGAGGATCCGGAGGAGGTGGCTCCG
GCGGCGGAGGATCTCGCGAGGGTCCCGAGCTTTCGCCCGACGATCCCGCCGG
CCTCTTGGACCTGCGGCAGGGCATGTTTGCGCAGCTGGTGGCCCAAAATGTTC
TGCTGATCGATGGGCCCCTGAGCTGGTACAGTGACCCAGGCCTGGCAGGCGT
GTCCCTGACGGGGGGCCTGAGCTACAAAGAGGACACGAAGGAGCTGGTGGT
GGCCAAGGCTGGAGTCTACTATGTCTTCTTTCAACTAGAGCTGCGGCGCGTGG
TGGCCGGCGAGGGCTCAGGCTCCGTTTCACTTGCGCTGCACCTGCAGCCACT
GCGCTCTGCTGCTGGGGCCGCCGCCCTGGCTTTGACCGTGGACCTGCCACCCG
CCTCCTCCGAGGCTCGGAACTCGGCCTTCGGTTTCCAGGGCCGCTTGCTGCAC
CTGAGTGCCGGCCAGCGCCTGGGCGTCCATCTTCACACTGAGGCCAGGGCAC
GCCATGCCTGGCAGCTTACCCAGGGCGCCACAGTCTTGGGACTCTTCCGGGTG
ACCCCCGAAATCCCAGCCGGACTCCCTTCACCGAGGTCGGAA (SEQ ID NO: 188).

In some embodiments, the second chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

QGQDRHMIRMRQLIDIVDQLKNYVNDLVPEFLPAPEDVETNCEWSAFSCFQKAQ
LKSANTGNNERIINVSIKKLKRKPPSTNAGRRQKHRLTCPSCDSYEKKPPKEFLER
FKSLLQKMIHQHLSSRTHGSEDSITCPPPMSVEHADIWVKSYSLYSRERYICNSGF
KRKAGTSSLTECVLNKATNVAHWTTPSLKCIRGGGGSGGGGSGGGGSDPAGLLD
LRQGMFAQLVAQNVLLIDGPLSWYSDPGLAGVSLTGGLSYKEDTKELVVAKAGV
YYVFFQLELRRVVAGEGSGSVSLALHLQPLRSAAGAAALALTVDLPPASSEARNS
AFGFQGRLLHLSAGQRLGVHLHTEARARHAWQLTQGATVLGLFRVTPEI (SEQ ID NO: 189).

In some embodiments, a second chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

CAGGGCCAGGACAGGCACATGATCCGGATGAGGCAGCTCATCGACATCGTCG
ACCAGCTGAAGAACTACGTGAACGACCTGGTGCCCGAGTTTCTGCCTGCCCC
CGAGGACGTGGAGACCAACTGCGAGTGGTCCGCCTTCTCCTGCTTTCAGAAG
GCCCAGCTGAAGTCCGCCAACACCGGCAACAACGAGCGGATCATCAACGTGA

GCATCAAGAAGCTGAAGCGGAAGCCTCCCTCCACAAACGCCGGCAGGAGGC
AGAAGCACAGGCTGACCTGCCCCAGCTGTGACTCCTACGAGAAGAAGCCCCC
CAAGGAGTTCCTGGAGAGGTTCAAGTCCCTGCTGCAGAAGATGATCCATCAG
CACCTGTCCTCCAGGACCCACGGCTCCGAGGACTCCATTACATGCCCCCCTCC
CATGAGCGTGGAGCACGCCGACATCTGGGTGAAGAGCTATAGCCTCTACAGCC
GGGAGAGGTATATCTGTAACAGCGGCTTCAAGAGGAAGGCCGGCACCAGCAG
CCTCACCGAGTGCGTGCTGAATAAGGCTACCAACGTGGCTCACTGGACAACA
CCCTCTTTAAAGTGCATCCGGGGCGGTGGAGGATCCGGAGGAGGTGGCTCCG
GCGGCGGAGGATCTGATCCCGCCGGCCTCTTGGACCTGCGGCAGGGCATGTTT
GCGCAGCTGGTGGCCCAAAATGTTCTGCTGATCGATGGGCCCCTGAGCTGGTA
CAGTGACCCAGGCCTGGCAGGCGTGTCCCTGACGGGGGGCCTGAGCTACAAA
GAGGACACGAAGGAGCTGGTGGTGGCCAAGGCTGGAGTCTACTATGTCTTCT
TTCAACTAGAGCTGCGGCGCGTGGTGGCCGGCGAGGGCTCAGGCTCCGTTTC
ACTTGCGCTGCACCTGCAGCCACTGCGCTCTGCTGCTGGGGCCGCCGCCCTGG
CTTTGACCGTGGACCTGCCACCCGCCTCCTCCGAGGCTCGGAACTCGGCCTTC
GGTTTCCAGGGCCGCTTGCTGCACCTGAGTGCCGGCCAGCGCCTGGGCGTCC
ATCTTCACACTGAGGCCAGGGCACGCCATGCCTGGCAGCTTACCCAGGGCGCC
ACAGTCTTGGGACTCTTCCGGGTGACCCCCGAAATC (SEQ ID NO: 190).

In some embodiments, the second chimeric polypeptide can include a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

MKWVTFISLLFLFSSAYSQGQDRHMIRMRQLIDIVDQLKNYVNDLVPEFLPAPED
VETNCEWSAFSCFQKAQLKSANTGNNERIINVSIKKLKRKPPSTNAGRRQKHRLT
CPSCDSYEKKPPKEFLERFKSLLQKMIHQHLSSRTHGSEDSITCPPPMSVEHADIW
VKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRGGGGS
GGGGSGGGGSDPAGLLDLRQGMFAQLVAQNVLLIDGPLSWYSDPGLAGVSLTGG
LSYKEDTKELVVAKAGVYYVFFQLELRRVVAGEGSGSVSLALHLQPLRSAAGAA
ALALTVDLPPASSEARNSAFGFQGRLLHLSAGQRLGVHLHTEARARHAWQLTQG
ATVLGLFRVTPEI (SEQ ID NO: 191).

In some embodiments, a second chimeric polypeptide is encoded by a sequence that is at least 80% identical (e.g., at least 82% identical, at least 84% identical, at least 86% identical, at least 88% identical, at least 90% identical, at least 92% identical, at least 94% identical, at least 96% identical, at least 98% identical, at least 99% identical, or 100% identical) to:

ATGAAGTGGGTGACCTTCATCAGCCTGCTGTTCCTGTTCTCCAGCGCCTACTCC
CAGGGCCAGGACAGGCACATGATCCGGATGAGGCAGCTCATCGACATCGTCG

ACCAGCTGAAGAACTACGTGAACGACCTGGTGCCCGAGTTTCTGCCTGCCCC
CGAGGACGTGGAGACCAACTGCGAGTGGTCCGCCTTCTCCTGCTTTCAGAAG
GCCCAGCTGAAGTCCGCCAACACCGGCAACAACGAGCGGATCATCAACGTGA
GCATCAAGAAGCTGAAGCGGAAGCCTCCCTCCACAAACGCCGGCAGGAGGC
AGAAGCACAGGCTGACCTGCCCCAGCTGTGACTCCTACGAGAAGAAGCCCCC
CAAGGAGTTCCTGGAGAGGTTCAAGTCCCTGCTGCAGAAGATGATCCATCAG
CACCTGTCCTCCAGGACCCACGGCTCCGAGGACTCCATTACATGCCCCCTCC
CATGAGCGTGGAGCACGCCGACATCTGGGTGAAGAGCTATAGCCTCTACAGCC
GGGAGAGGTATATCTGTAACAGCGGCTTCAAGAGGAAGGCCGGCACCAGCAG
CCTCACCGAGTGCGTGCTGAATAAGGCTACCAACGTGGCTCACTGGACAACA
CCCTCTTTAAAGTGCATCCGGGGCGGTGGAGGATCCGGAGGAGGTGGCTCCG
GCGGCGGAGGATCTGATCCCGCCGGCCTCTTGGACCTGCGGCAGGGCATGTTT
GCGCAGCTGGTGGCCCAAAATGTTCTGCTGATCGATGGGCCCCTGAGCTGGTA
CAGTGACCCAGGCCTGGCAGGCGTGTCCCTGACGGGGGGCCTGAGCTACAAA
GAGGACACGAAGGAGCTGGTGGTGGCCAAGGCTGGAGTCTACTATGTCTTCT
TTCAACTAGAGCTGCGGCGCGTGGTGGCCGGCGAGGGCTCAGGCTCCGTTTC
ACTTGCGCTGCACCTGCAGCCACTGCGCTCTGCTGCTGGGGCCGCCGCCCTGG
CTTTGACCGTGGACCTGCCACCCGCCTCCTCCGAGGCTCGGAACTCGGCCTTC
GGTTTCCAGGGCCGCTTGCTGCACCTGAGTGCCGGCCAGCGCCTGGGCGTCC
ATCTTCACACTGAGGCCAGGGCACGCCATGCCTGGCAGCTTACCCAGGGCGCC
ACAGTCTTGGGACTCTTCCGGGTGACCCCCGAAATC (SEQ ID NO: 192).

Exemplary Multi-Chain Chimeric Polypeptides- Type M

In some embodiments of any of the multi-chain chimeric polypeptides described herein, the first target-binding domain and the second targeting-binding domain each independently bind specifically to TGF-β or a receptor of IL-21. In some embodiments of these multi-chain chimeric polypeptides described herein, the second chimeric polypeptide further includes the additional target-binding domain. In some embodiments of these multi-chain chimeric polypeptides described herein, the additional target-binding domain binds specifically to a receptor for IL-21 (e.g., a soluble IL-21, e.g., a soluble human IL-21) or a TGF-β (e.g., a soluble TGF-β receptor, e.g., a soluble TGFβRII receptor).

In some examples of these multi-chain chimeric polypeptides, the first target-binding domain and the soluble tissue factor domain directly abut each other in the first chimeric polypeptide. In some examples of these multi-chain chimeric polypeptides, the first chimeric polypeptide further comprises a linker sequence (e.g., any of the exemplary linkers described herein) between the first target-binding domain and the soluble tissue factor domain in the first chimeric polypeptide.

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 3
CONTENANT LES PAGES 1 À 251

NOTE : Pour les tomes additionels, veuillez contacter le Bureau canadien des brevets

JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 3
CONTAINING PAGES 1 TO 251

NOTE: For additional volumes, please contact the Canadian Patent Office

NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

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.

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.

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. 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 of claims 1-22 or the composition of claim 23 or 24.

27. 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 of claims 1-22 or the composition of claim 23 or 24.

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

33. 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 of claims 1-22 or the composition of claim 23 or 24.

34. 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 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. The method of claim 35, 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. The method of claim 35, 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. The method of claim 35, 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. Nucleic acid encoding any of the multi-chain chimeric polypeptides of any one of claims 1-22.

40. A vector comprising the nucleic acid of claim 39.

41. A cell comprising the nucleic acid of claim 39 or the vector of claim 40.

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

culturing the cell of claim 41 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. The multi-chain chimeric polypeptide of claim 18, wherein the human soluble tissue factor domain does not initiate blood coagulation.

45. 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.

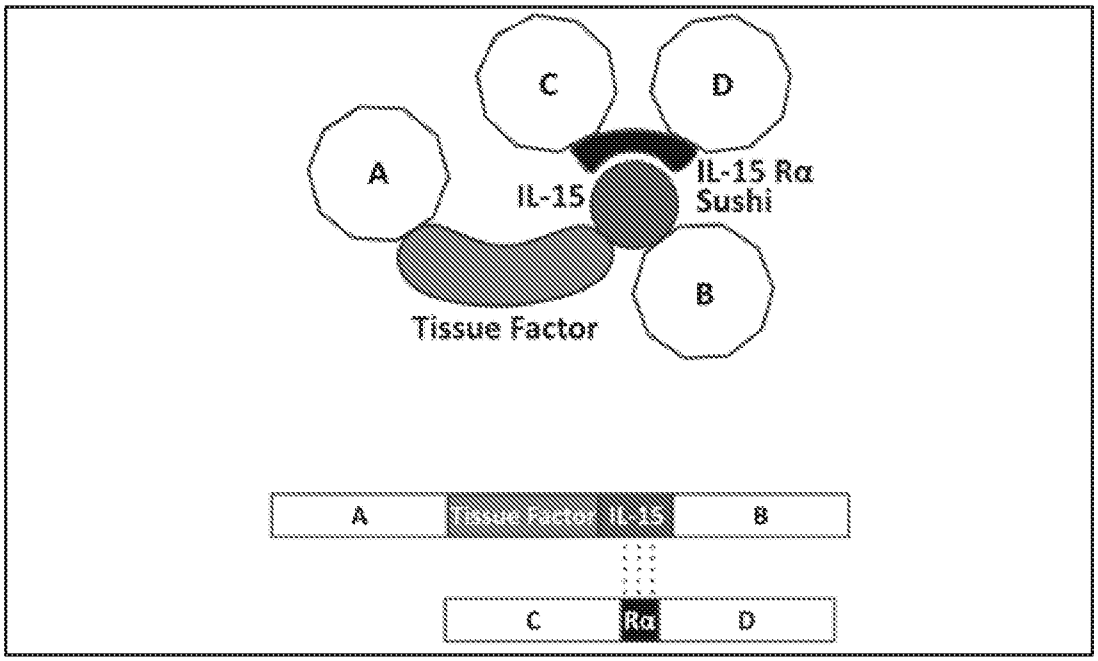


Figure 1

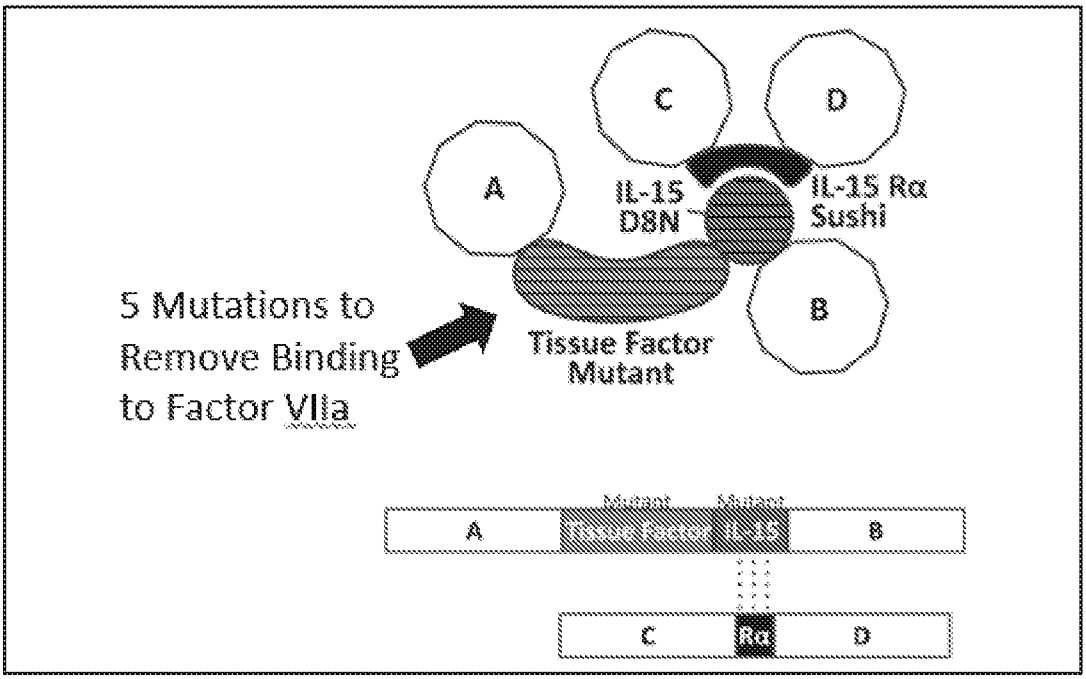


Figure 2

Figure 3

Figure 4

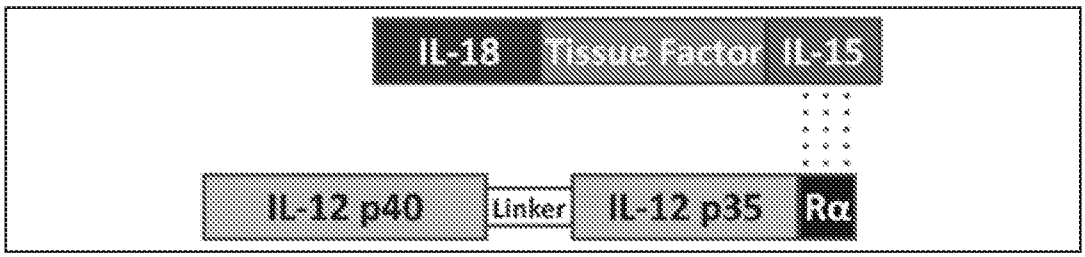


Figure 5

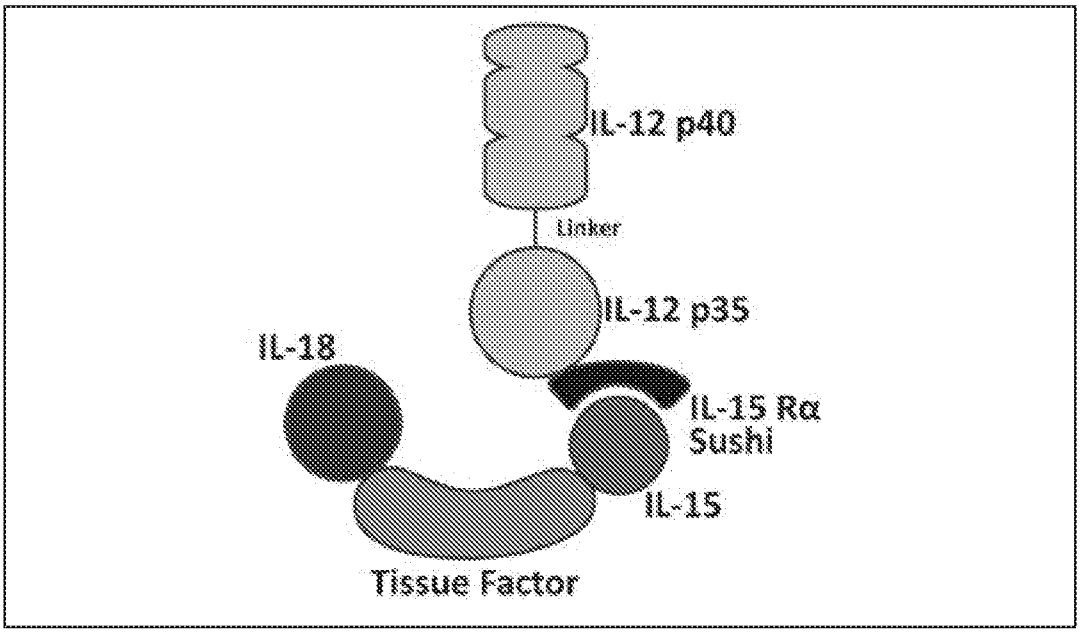


Figure 6

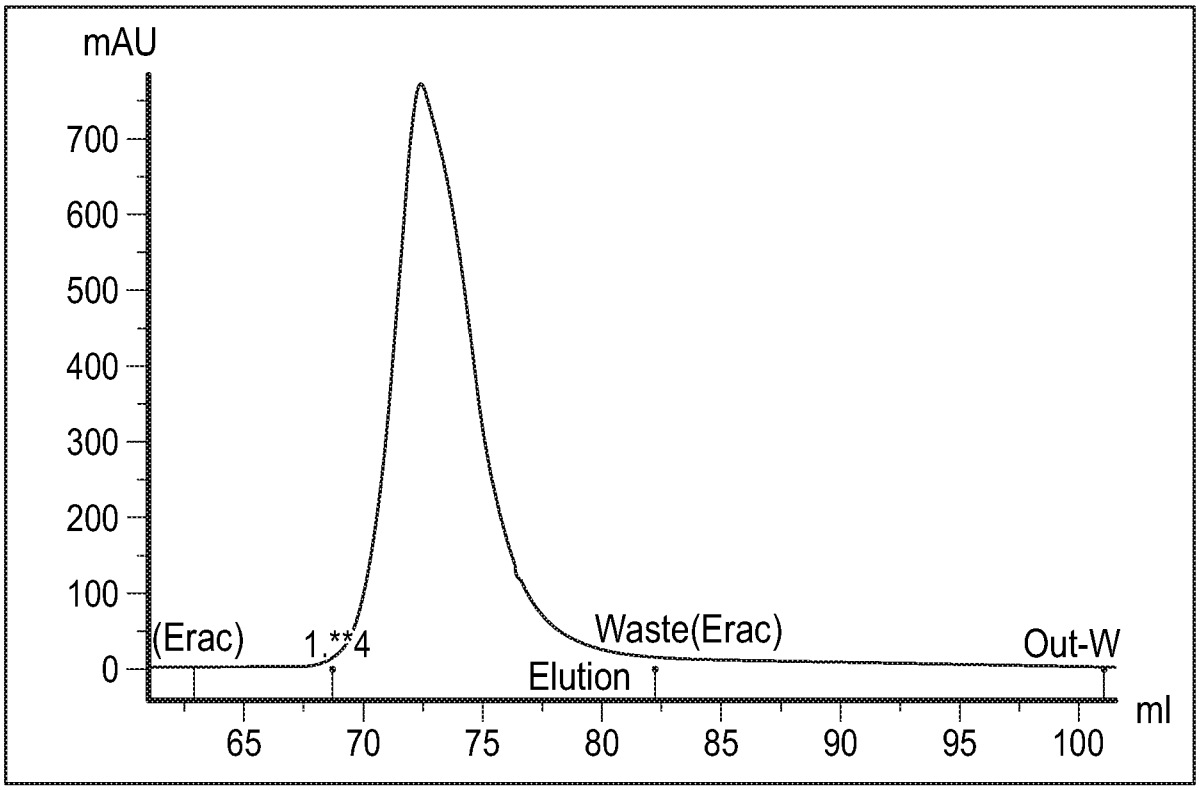


Figure 7

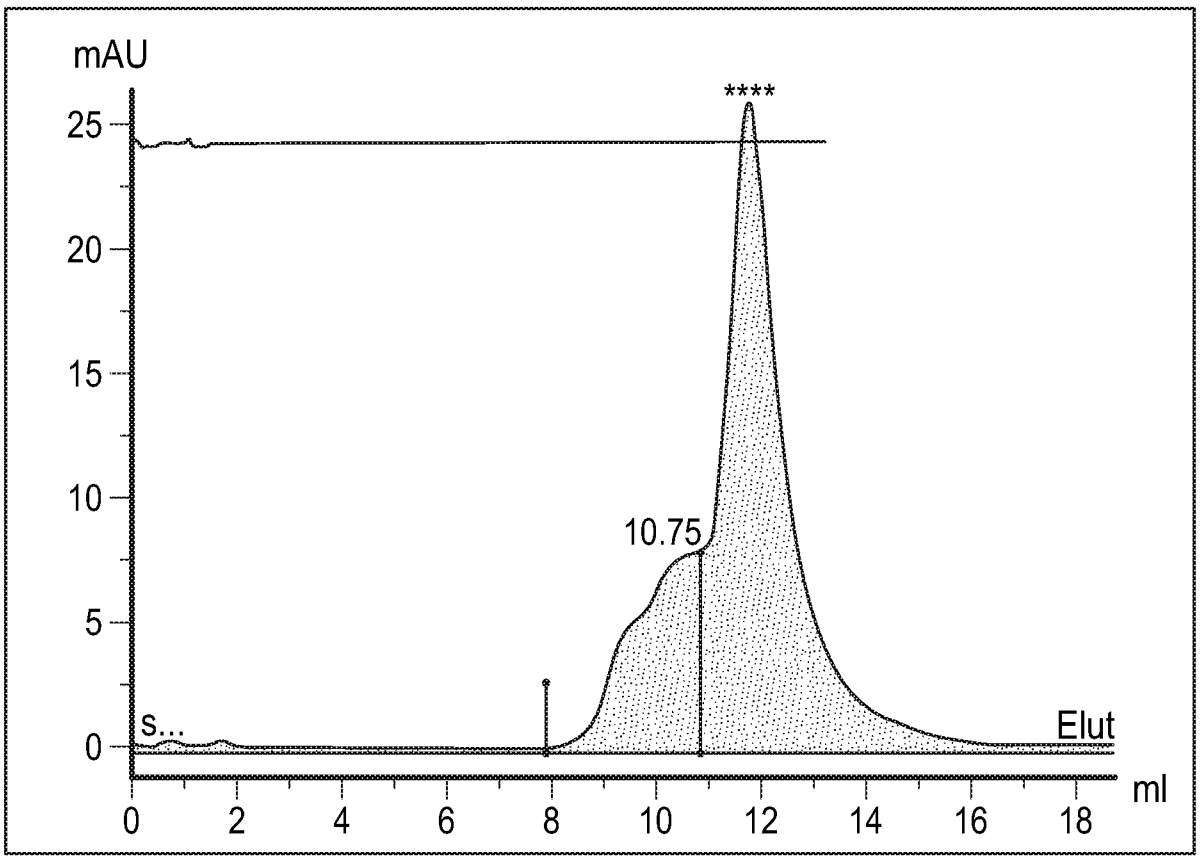


Figure 8

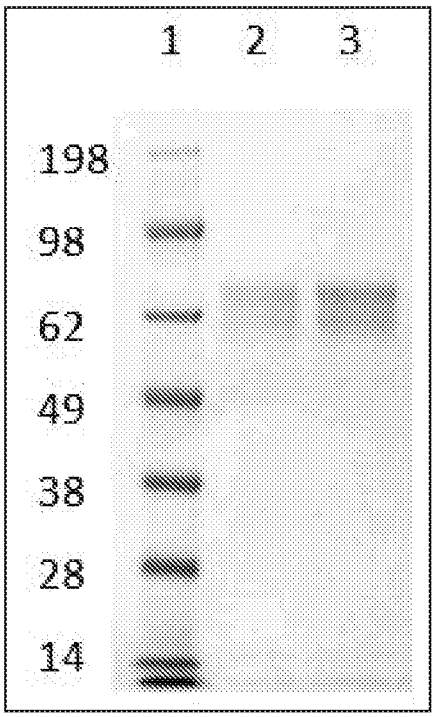


Figure 9

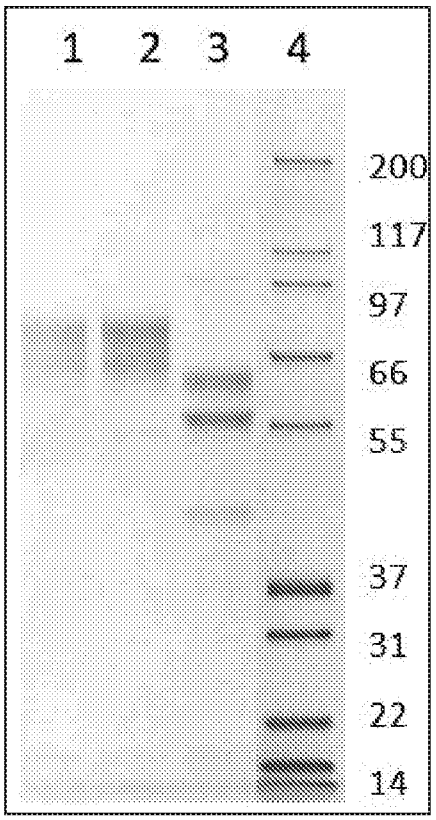


Figure 10

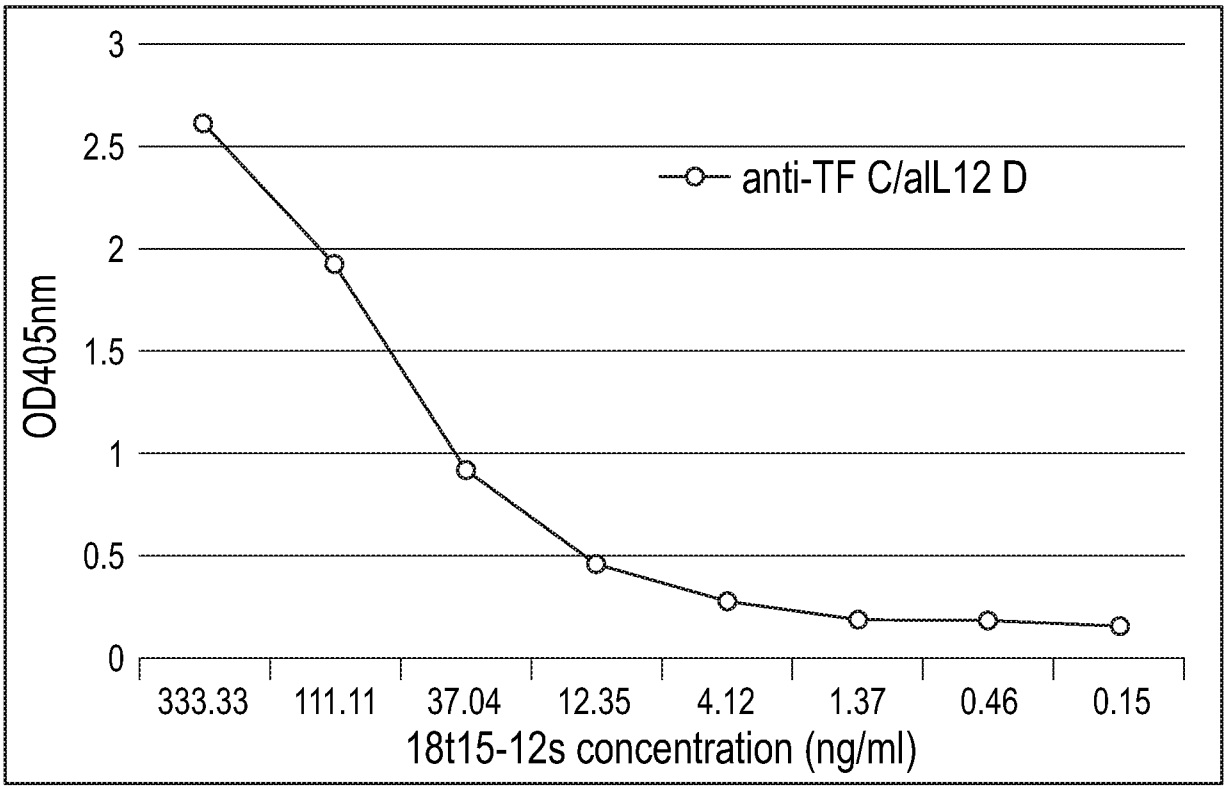


Figure 11

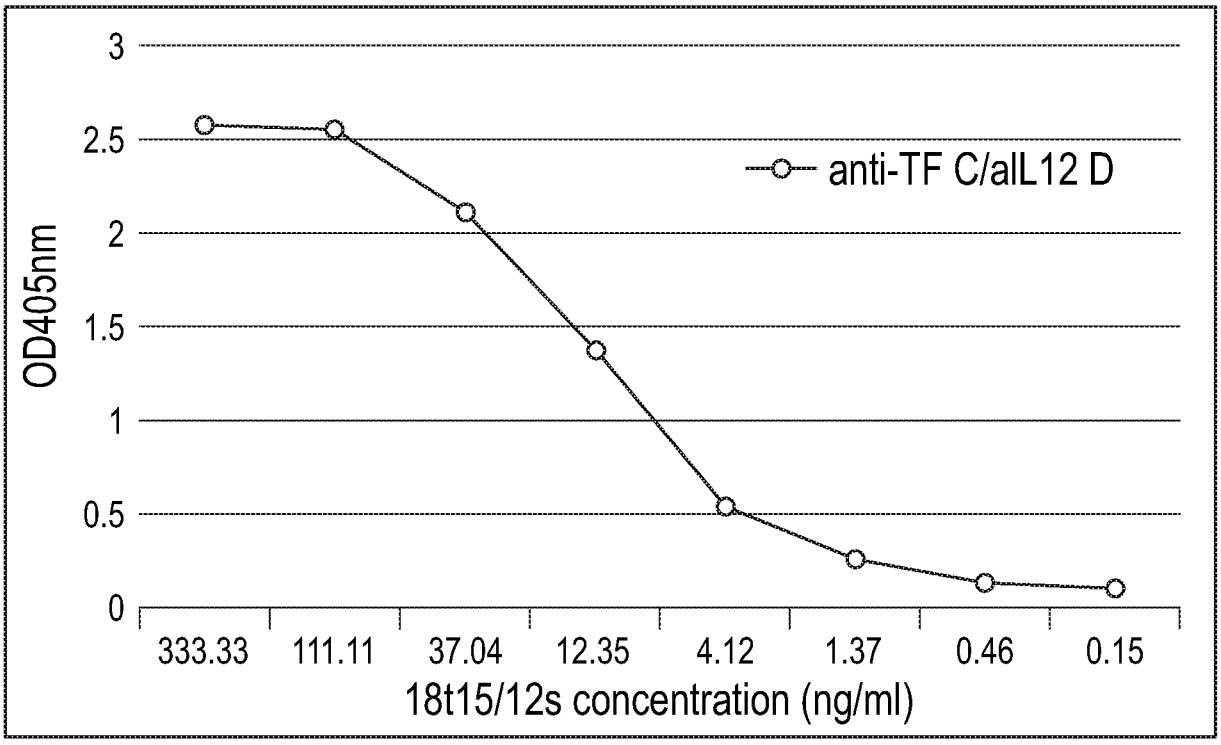


Figure 12

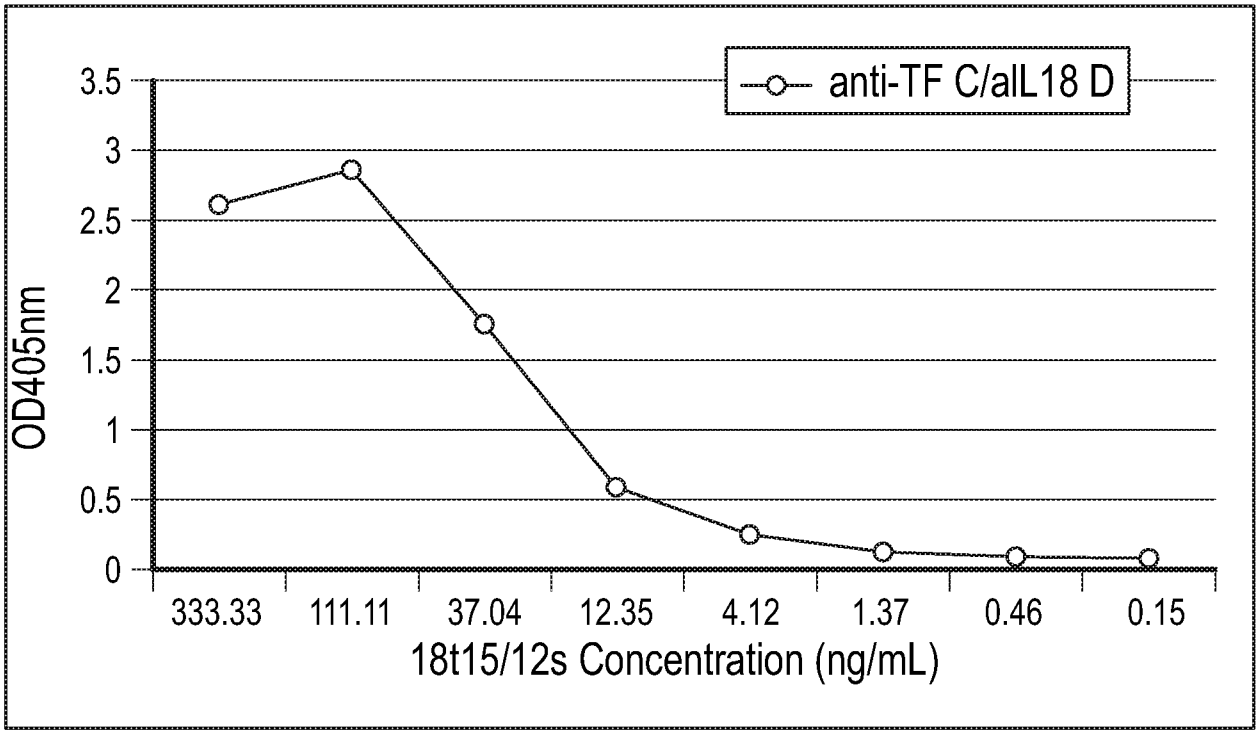


Figure 13

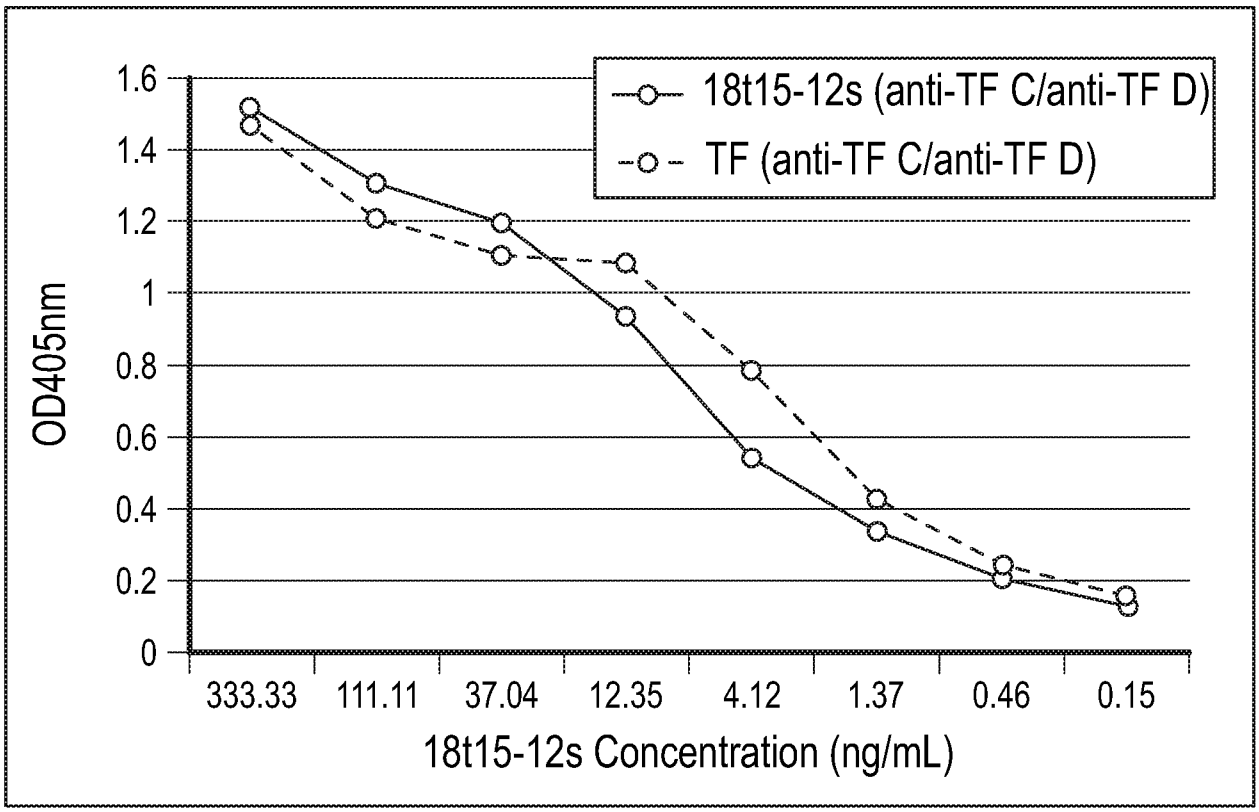


Figure 14

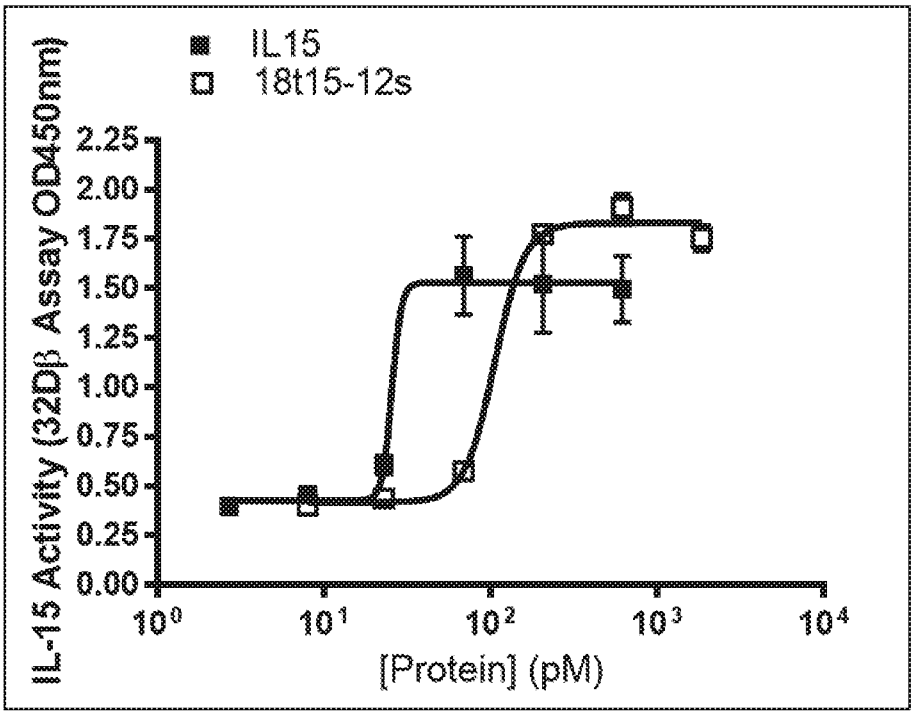


Figure 15

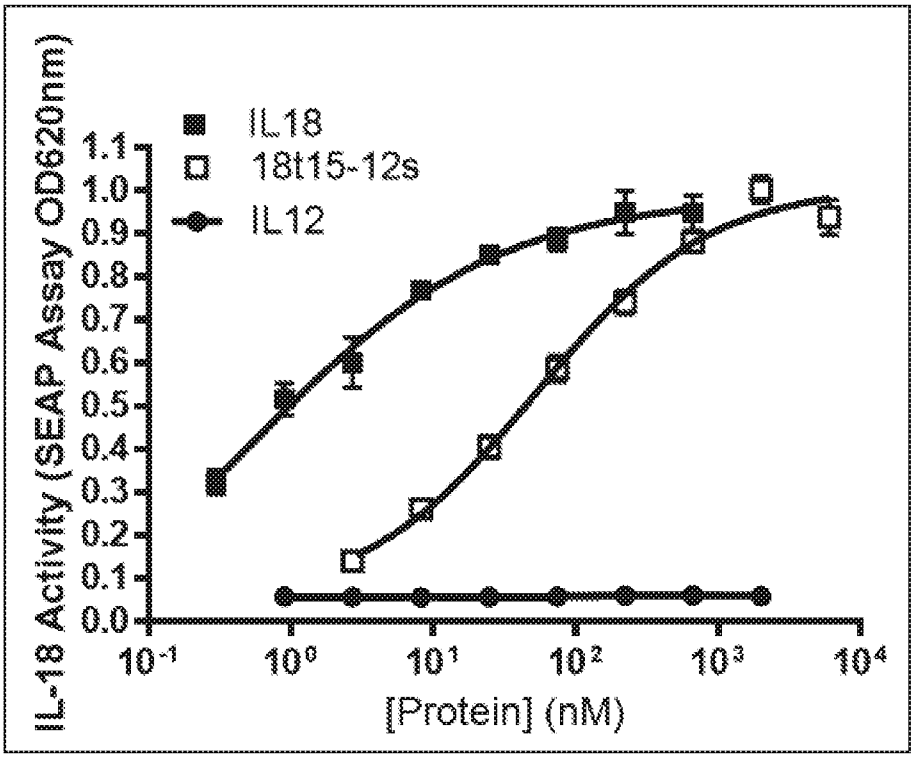


Figure 16

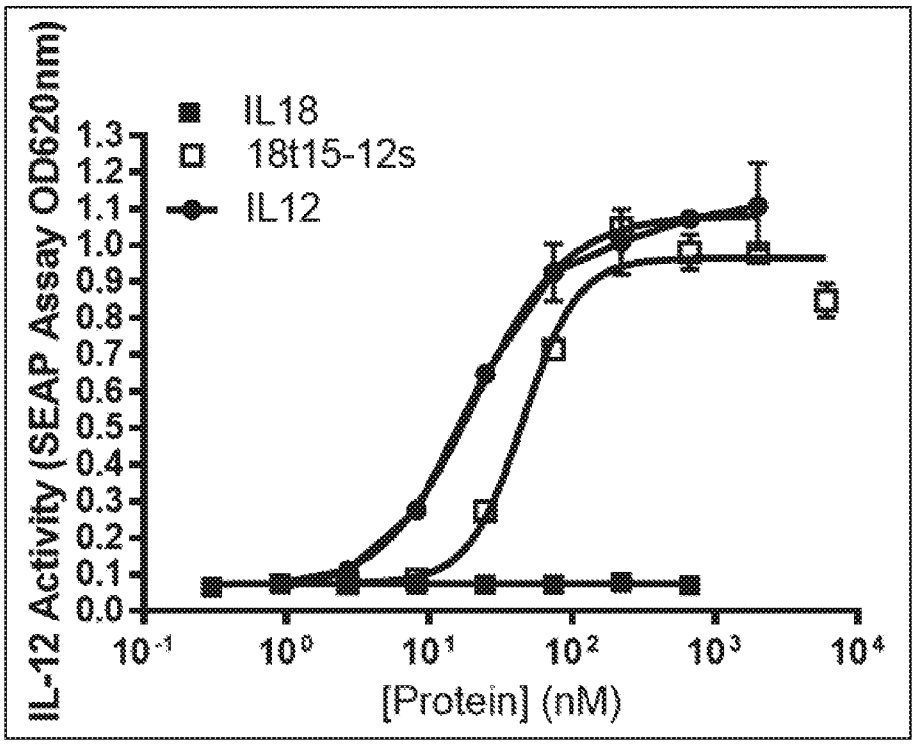


Figure 17

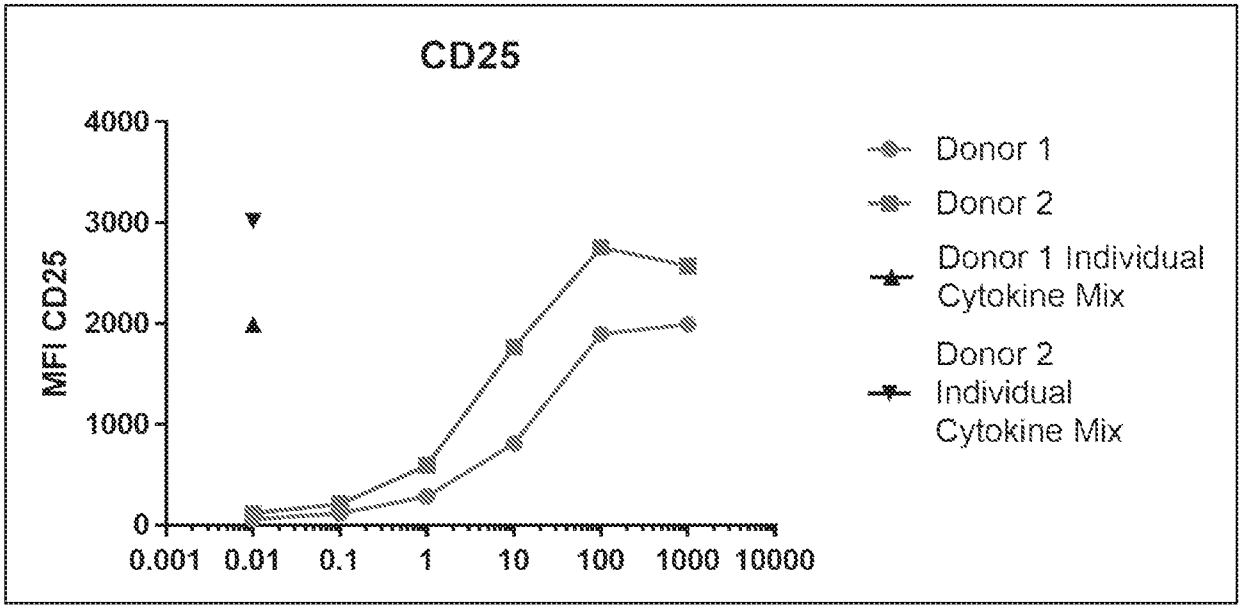


Figure 18A

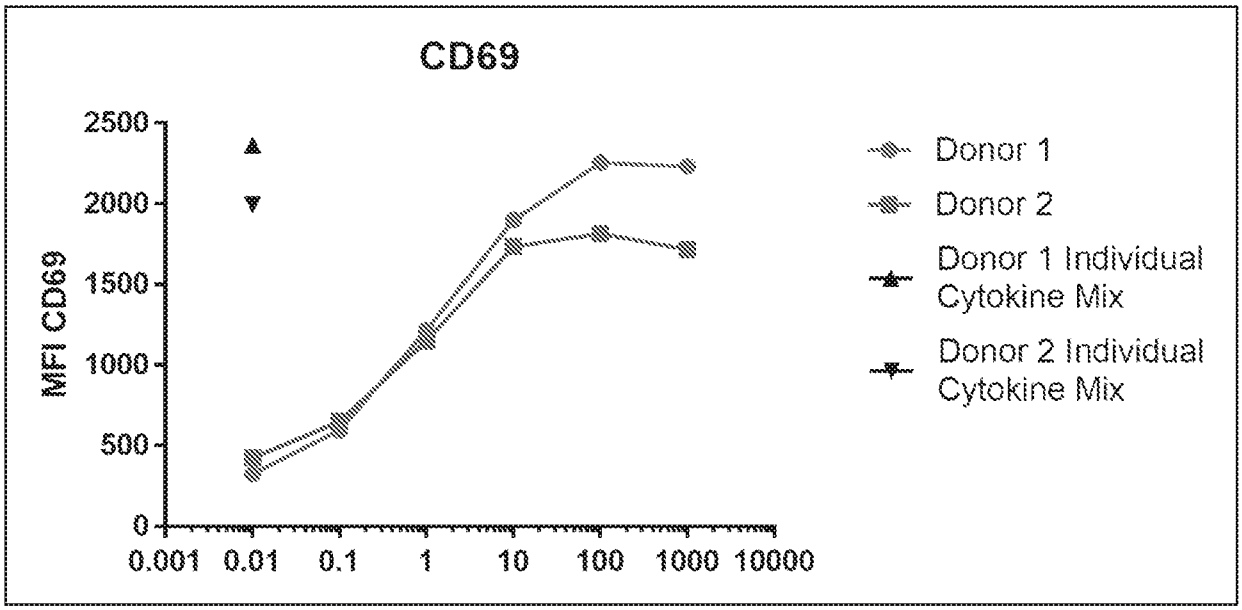


Figure 18B

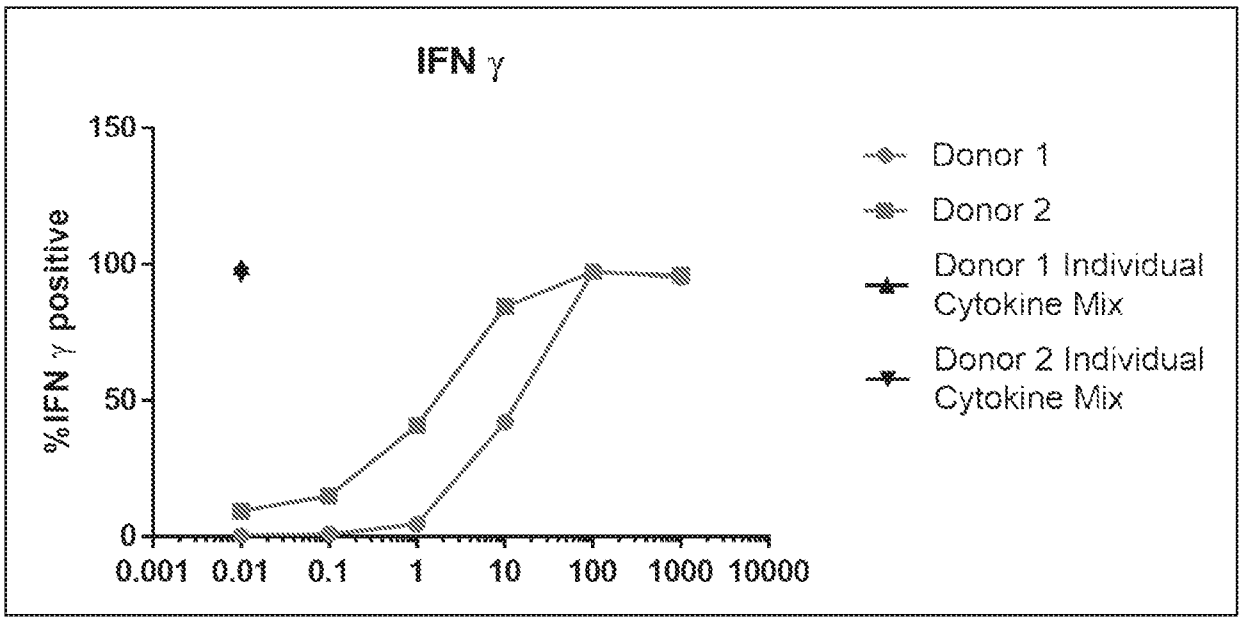


Figure 19

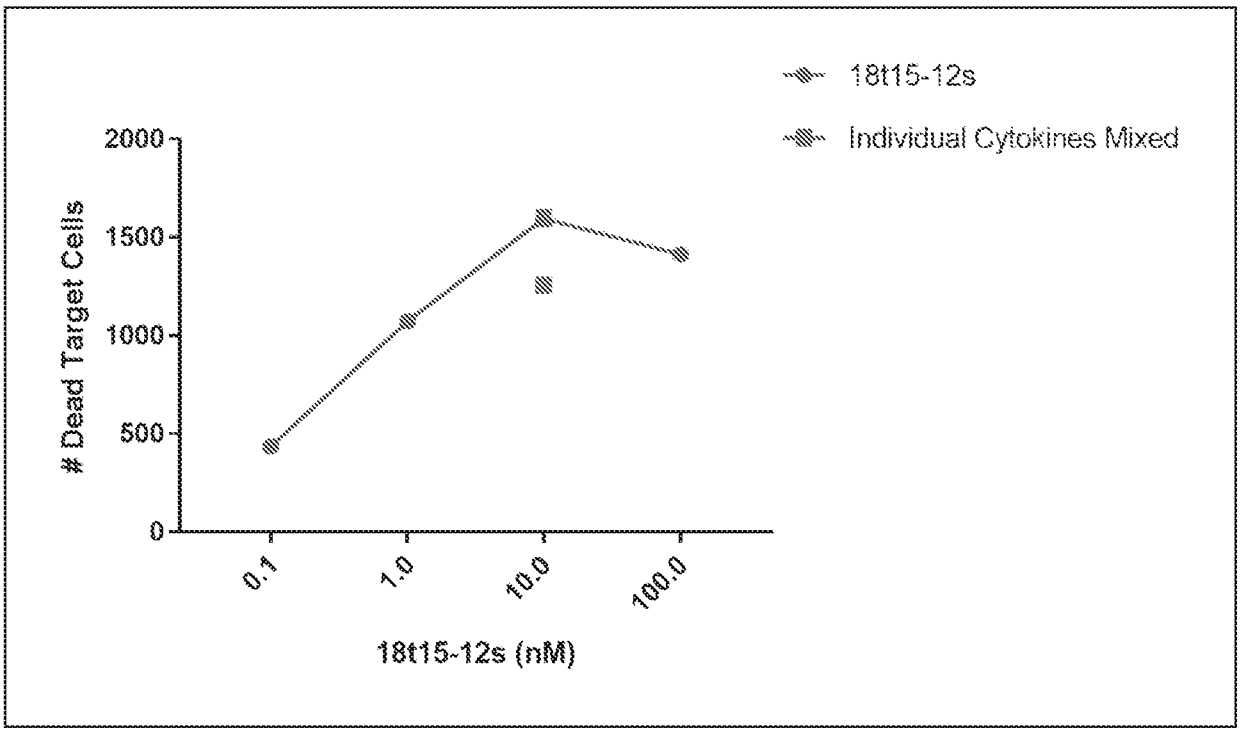

18t15-12s
Individual Cytokines Mixed
Dead Target Cells
2000
1500
1000
500
0
0.1
1.0
10.0
100.0
18t15-12s (nM)

Figure 20

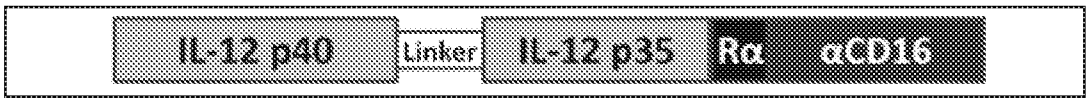


Figure 21

Figure 22

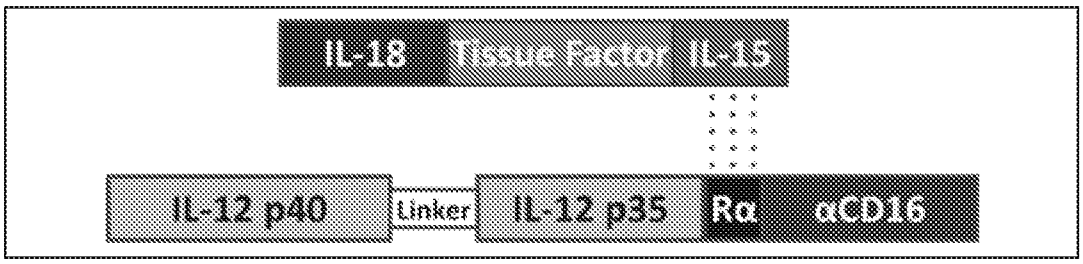


Figure 23

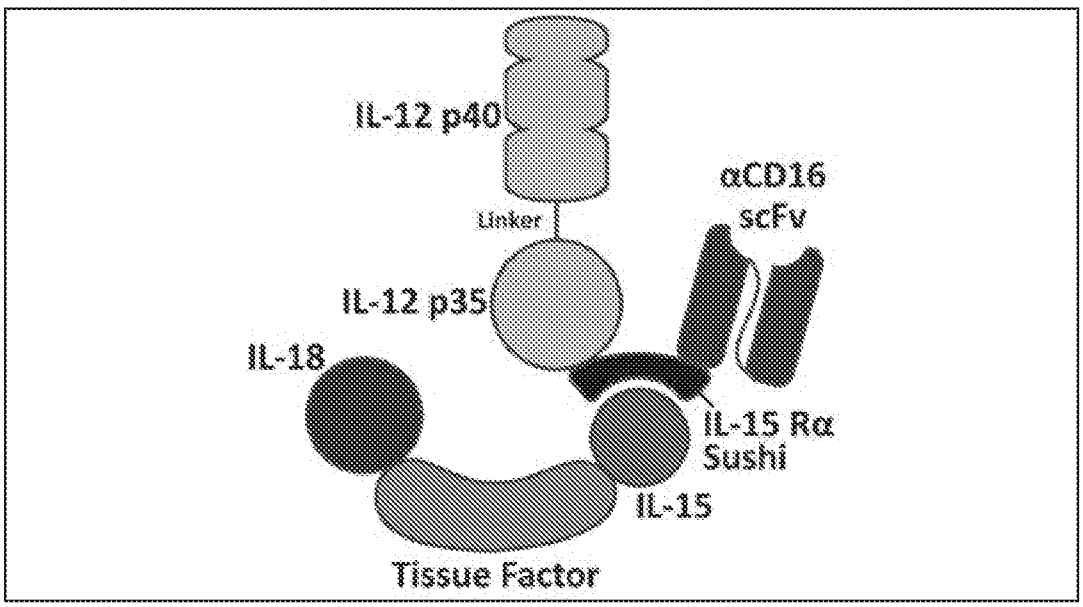


Figure 24

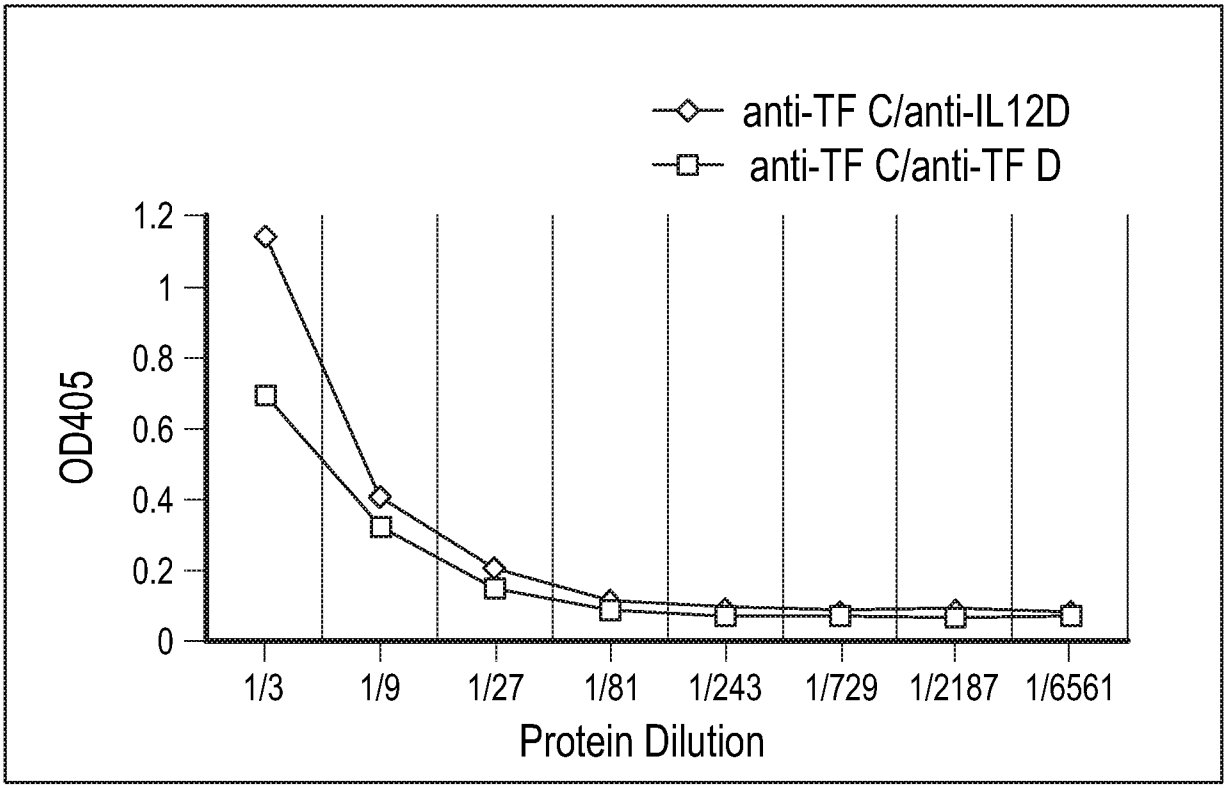

anti-TF C/anti-IL12D
anti-TF C/anti-TF D
OD405
1.2
1
0.8
0.6
0.4
0.2
0
1/3
1/9
1/27
1/81
1/243
1/729
1/2187
1/6561
Protein Dilution

Figure 25

Figure 26

Figure 27

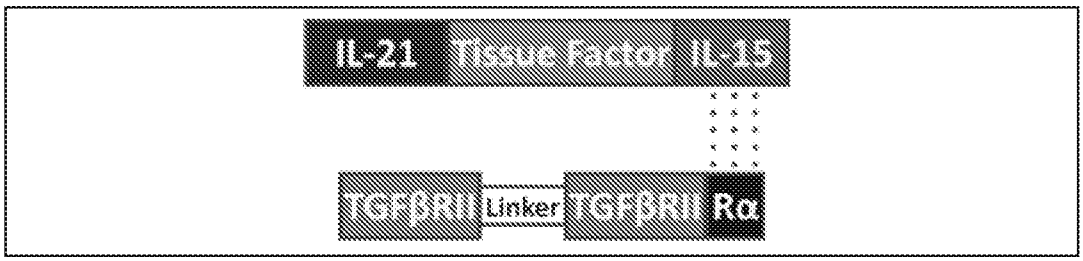


Figure 28

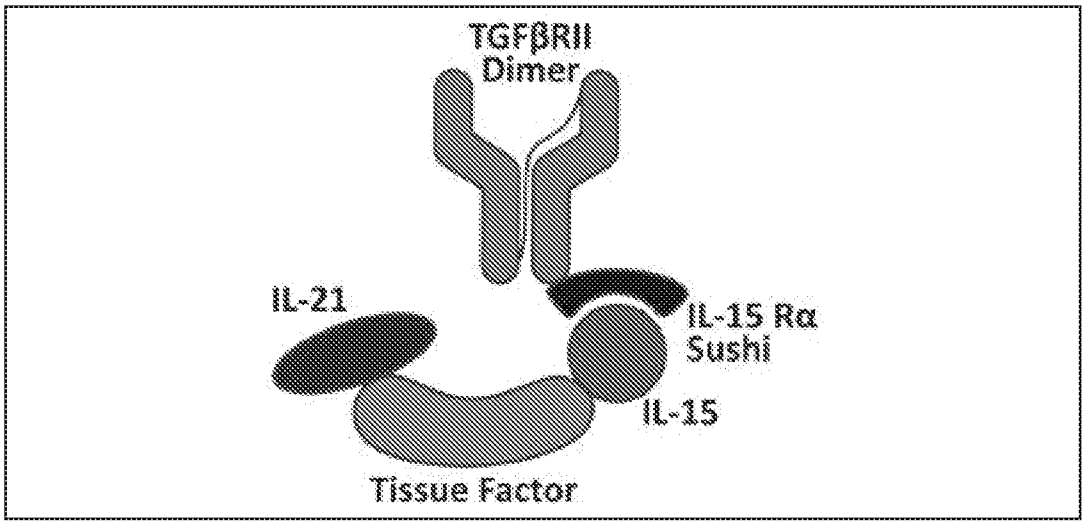


Figure 29

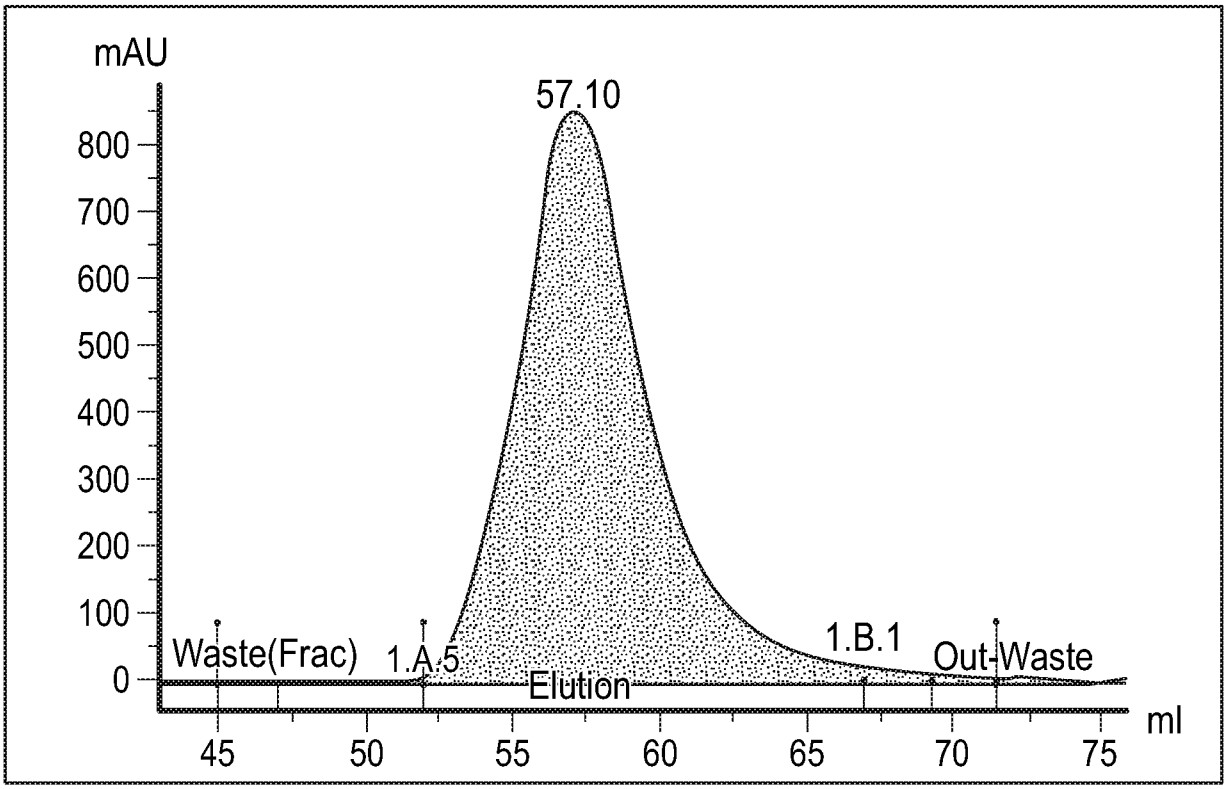


Figure 30

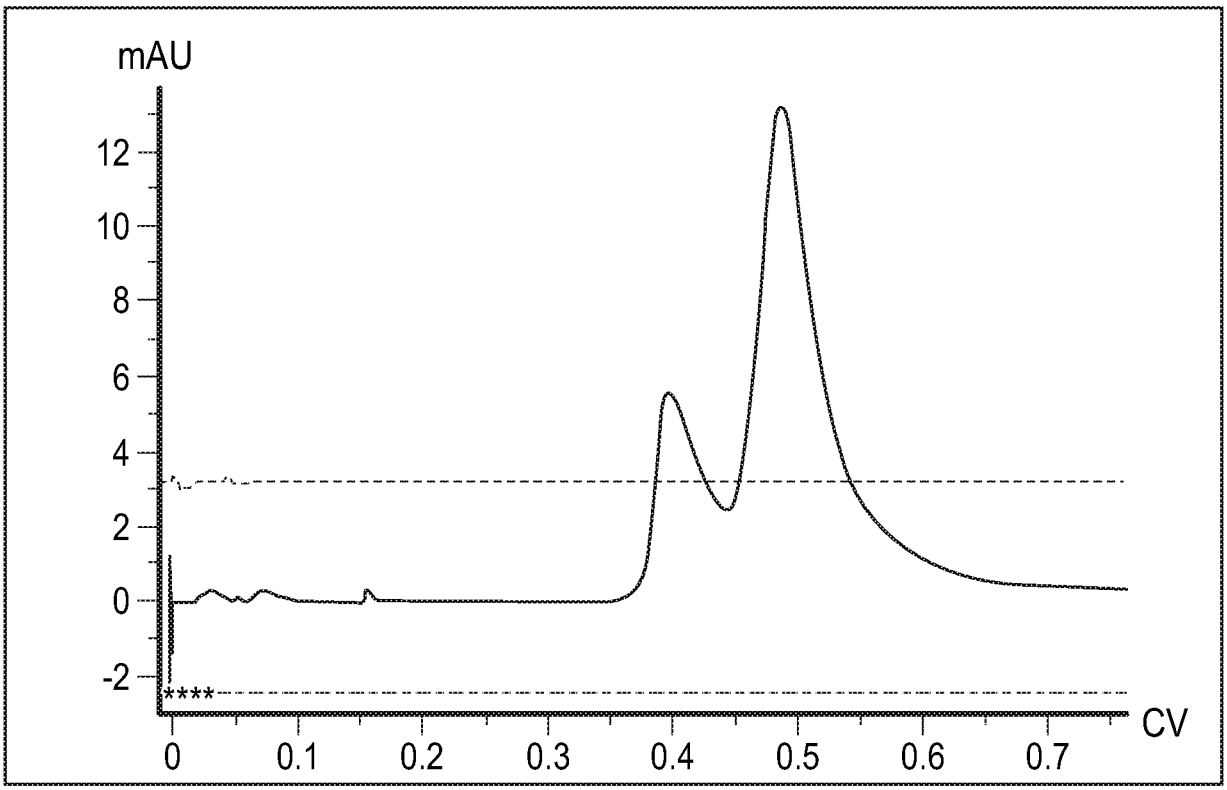


Figure 31

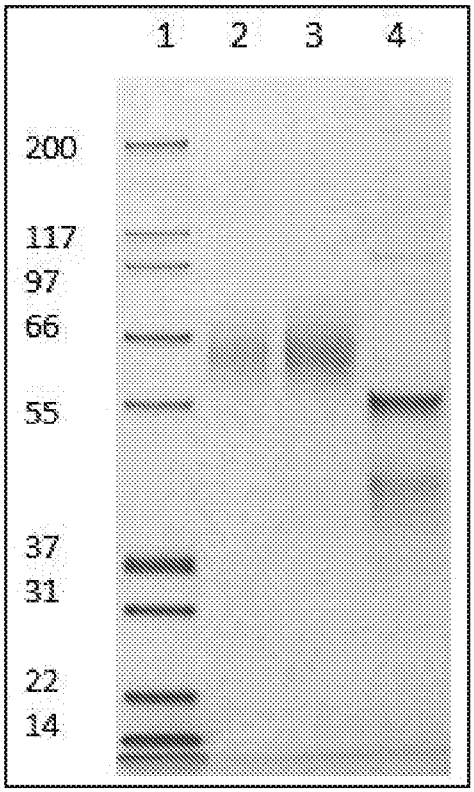


Figure 32

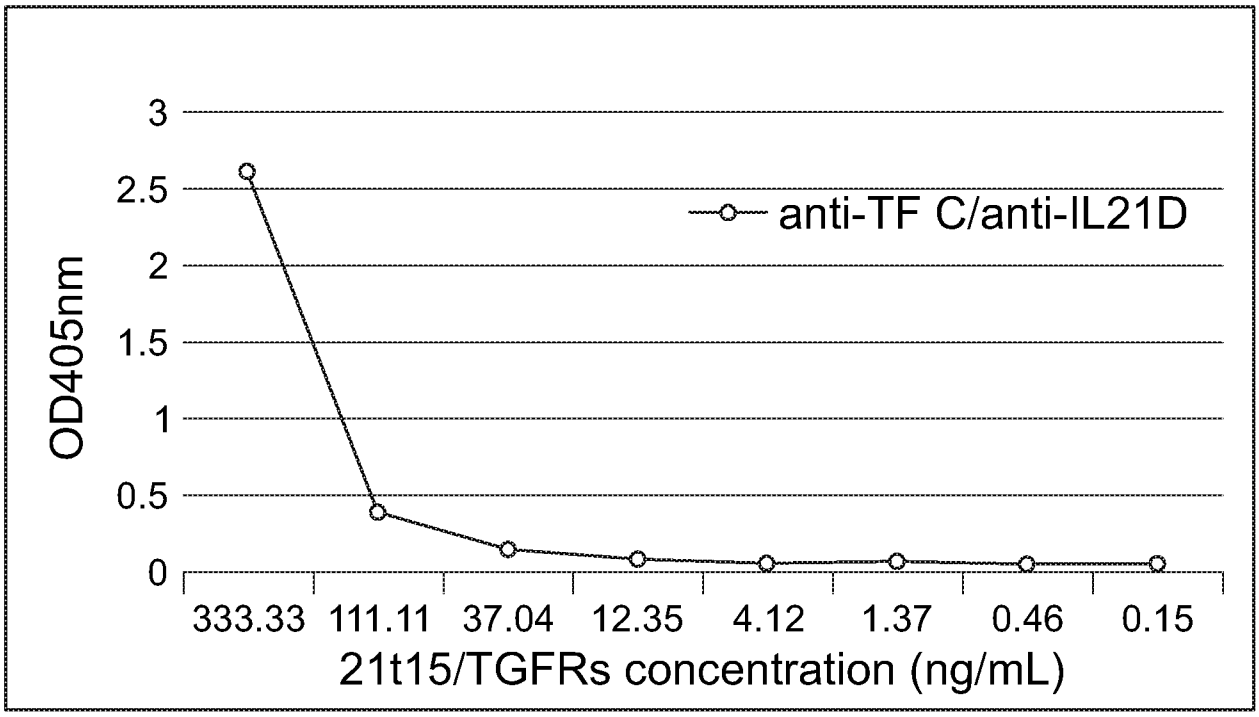


Figure 33

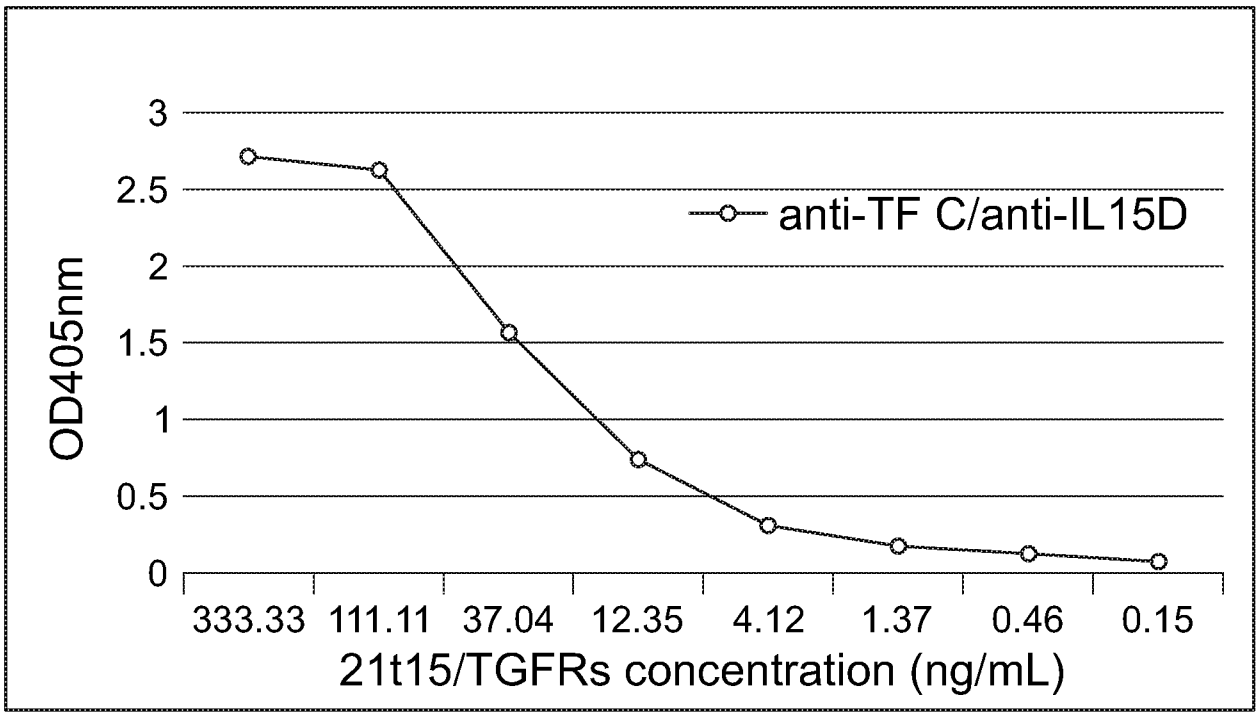


Figure 34

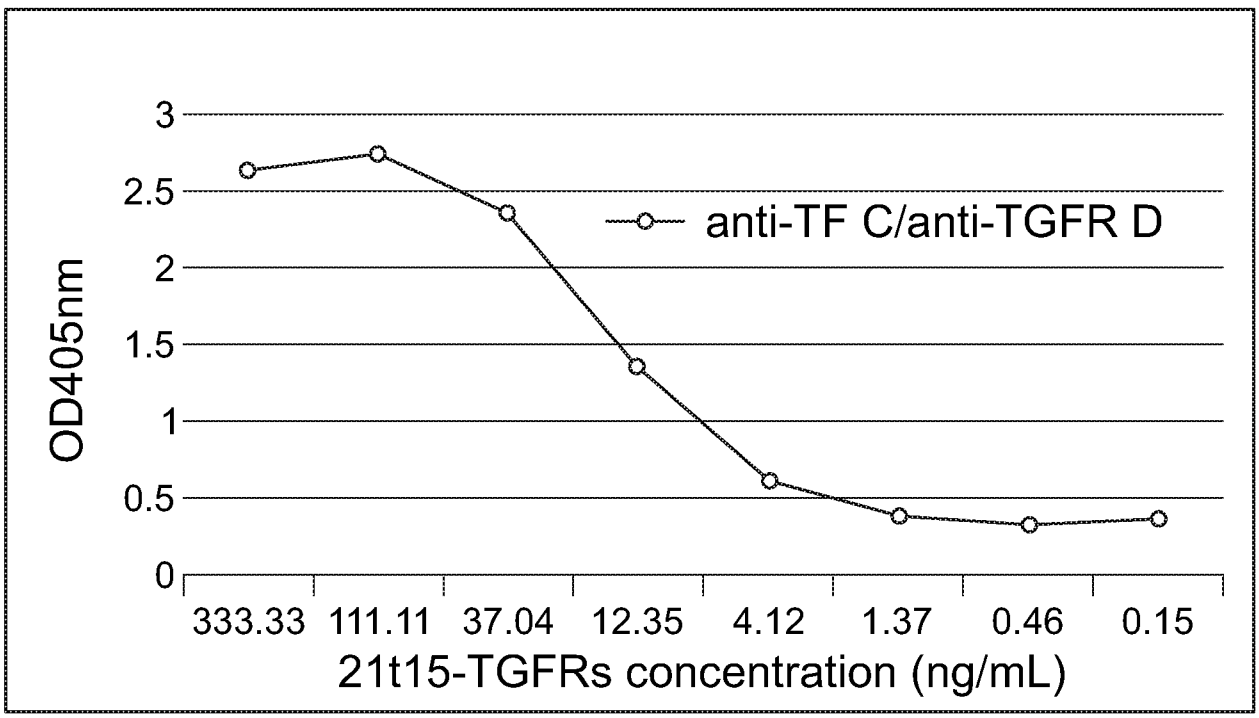


Figure 35

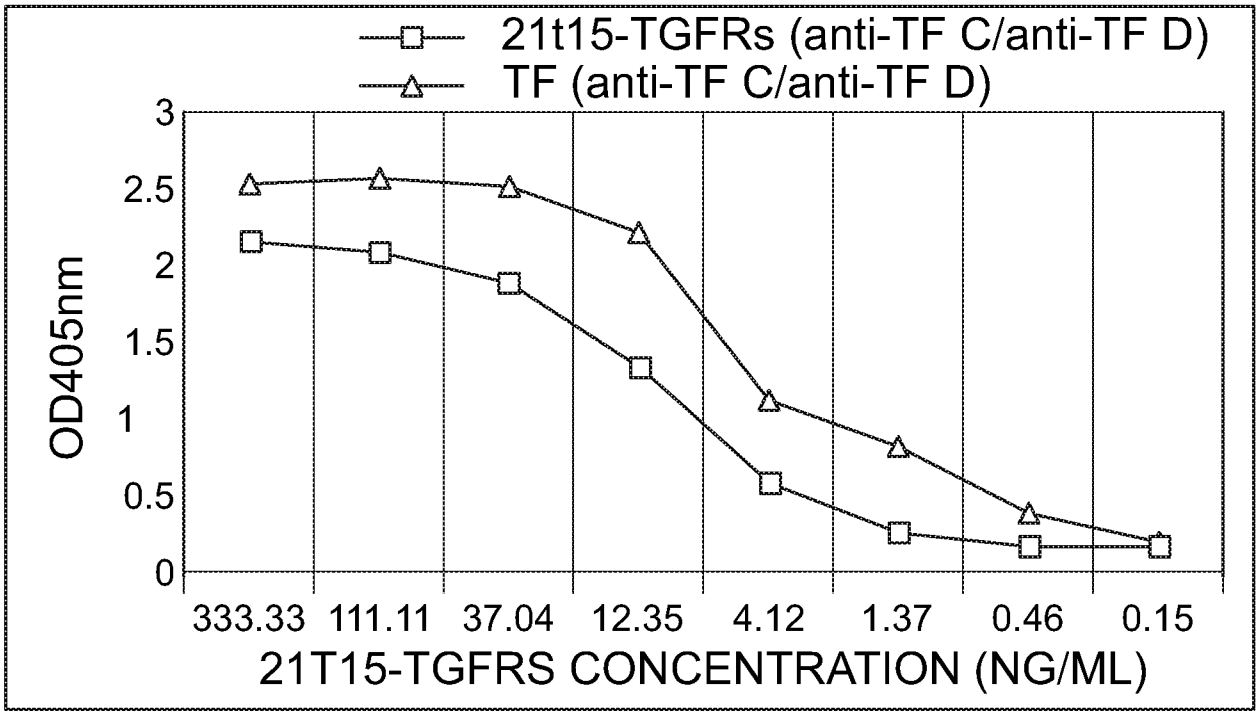


Figure 36

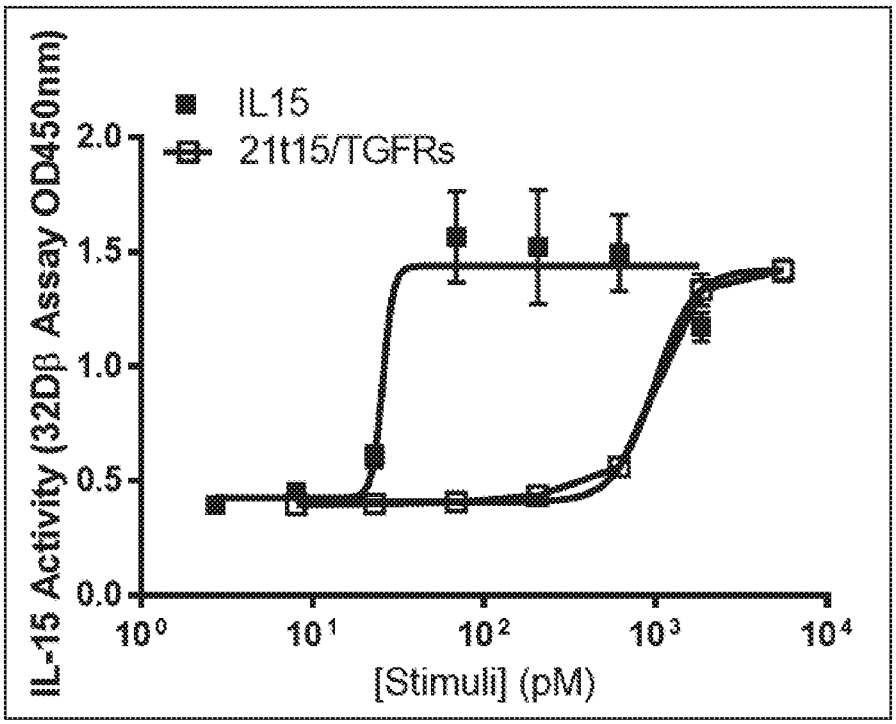


Figure 37

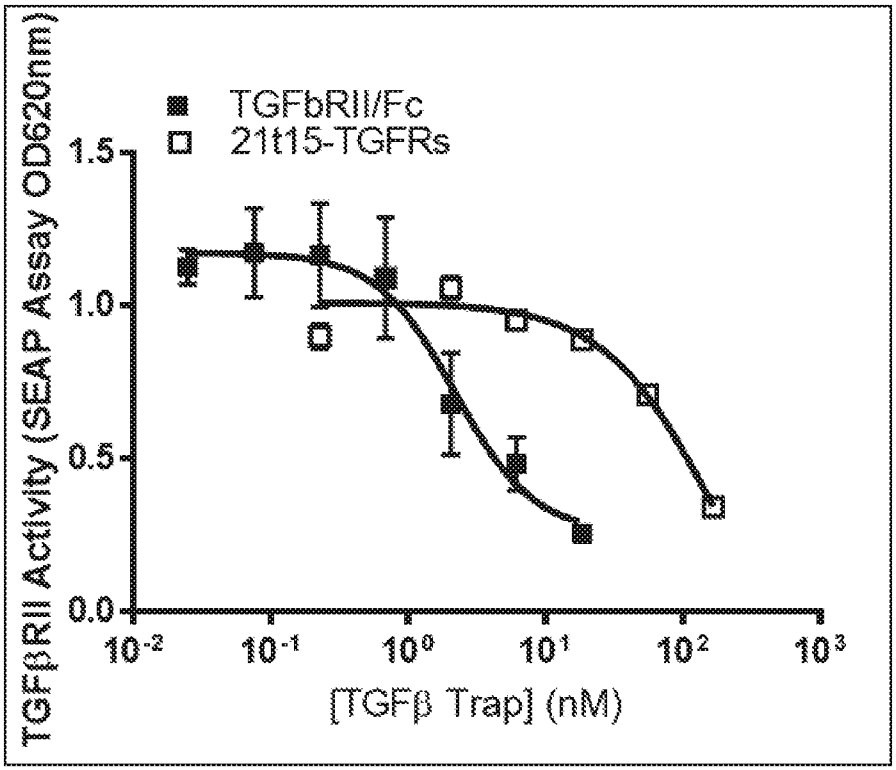


Figure 38

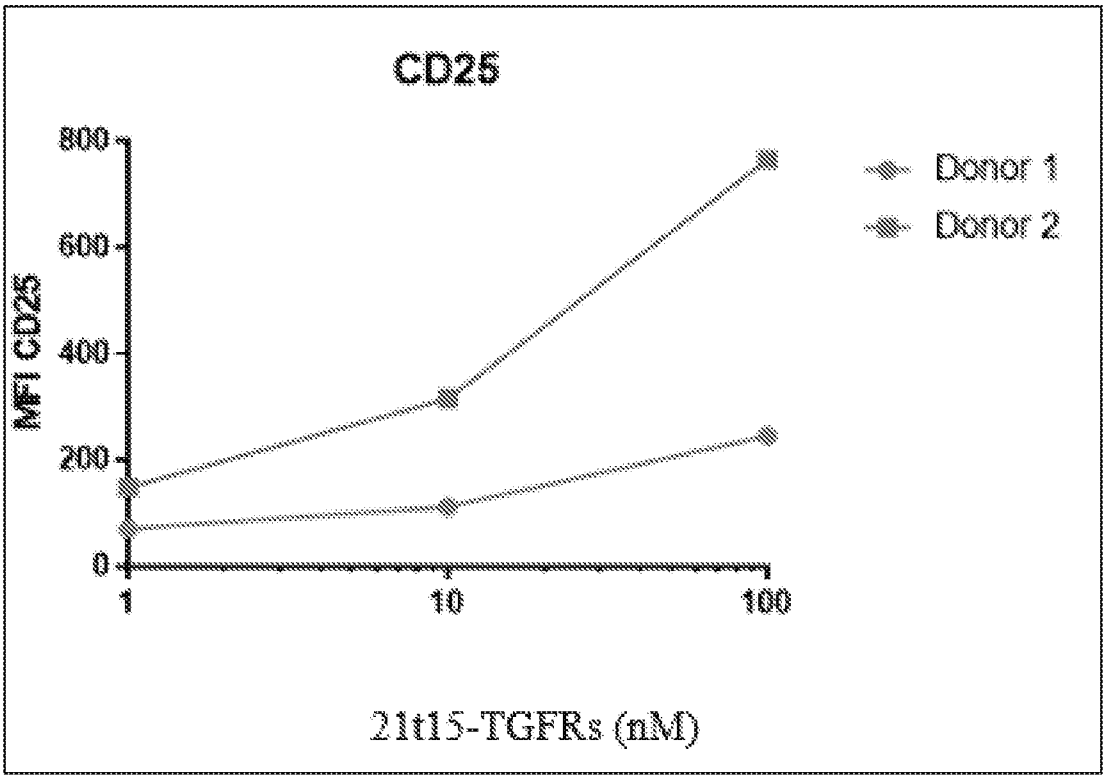


Figure 39

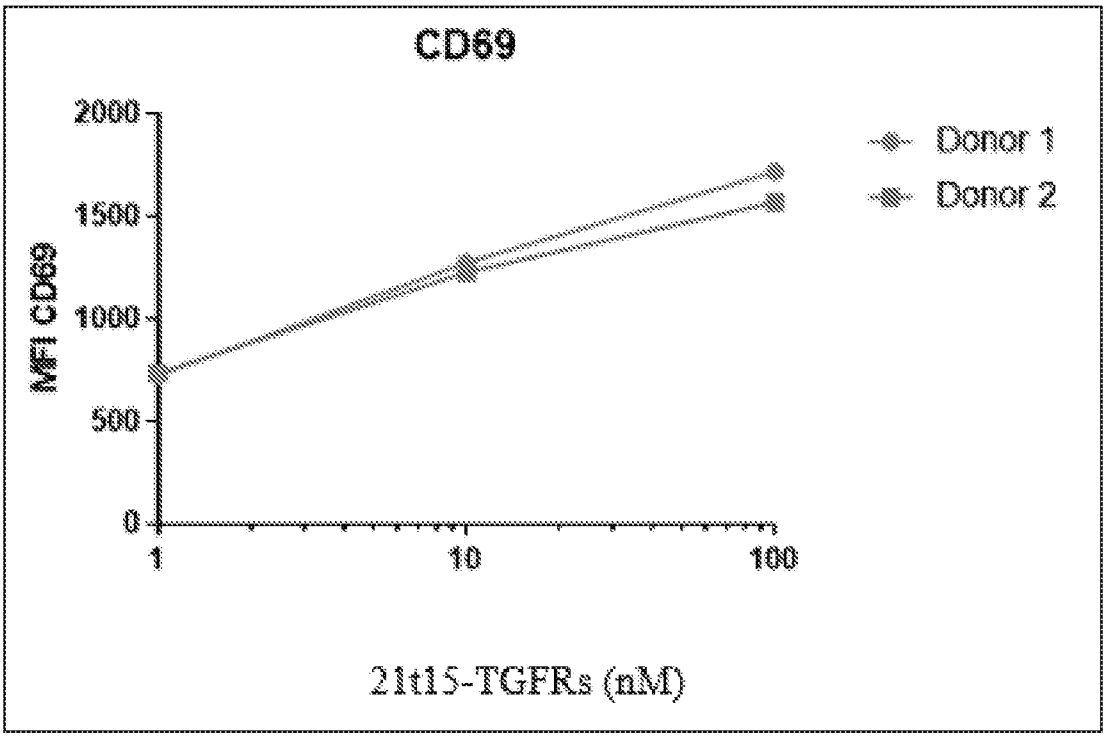


Figure 40

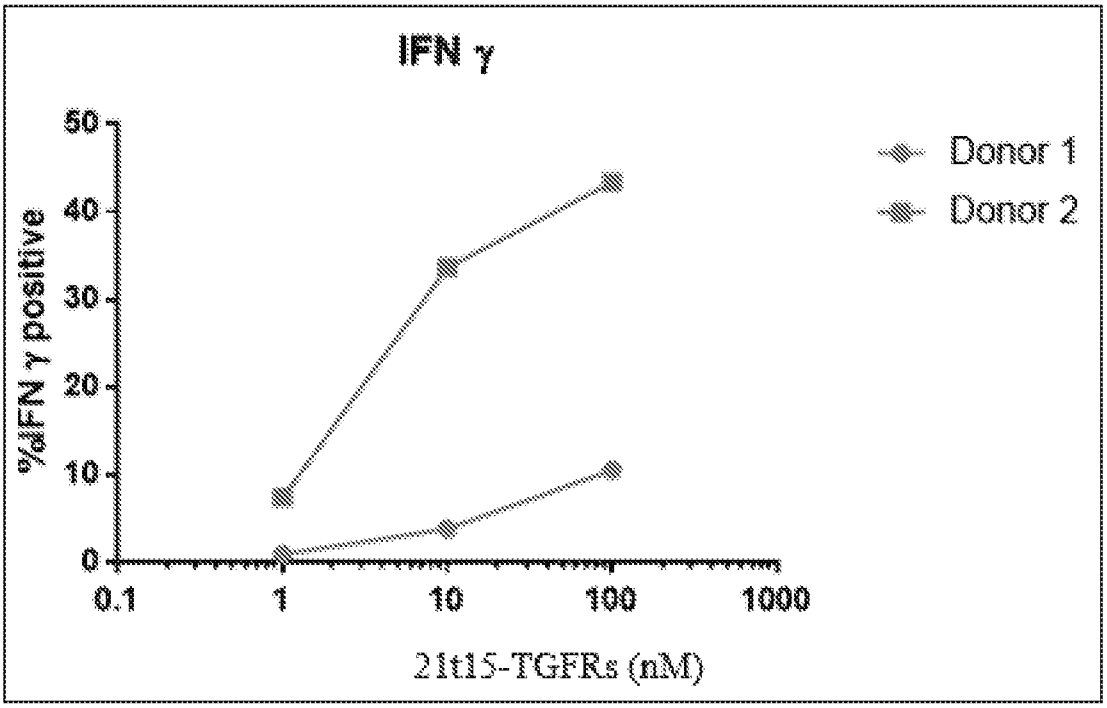


Figure 41

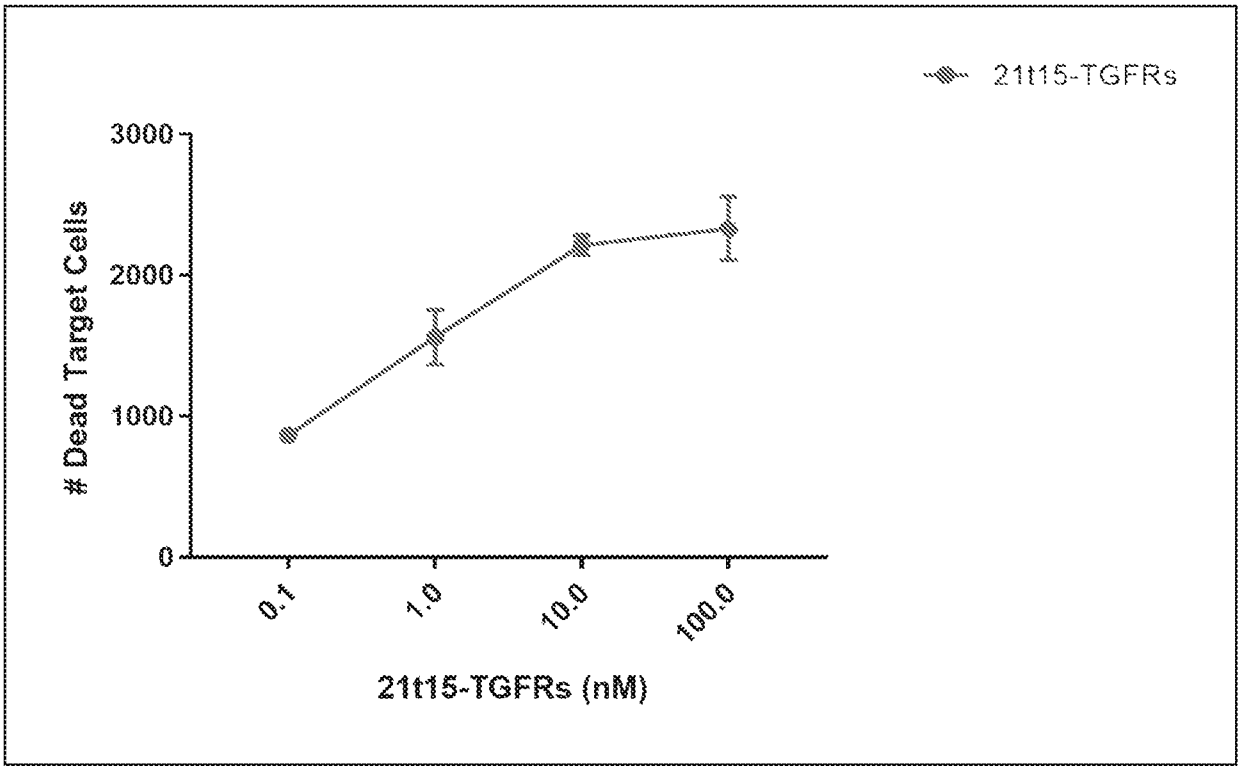

21t15-TGFRs
3000
2000
1000
0
Dead Target Cells
0.1
1.0
10.0
100.0
21t15-TGFRs (nM)

Figure 42

Figure 43

Figure 44

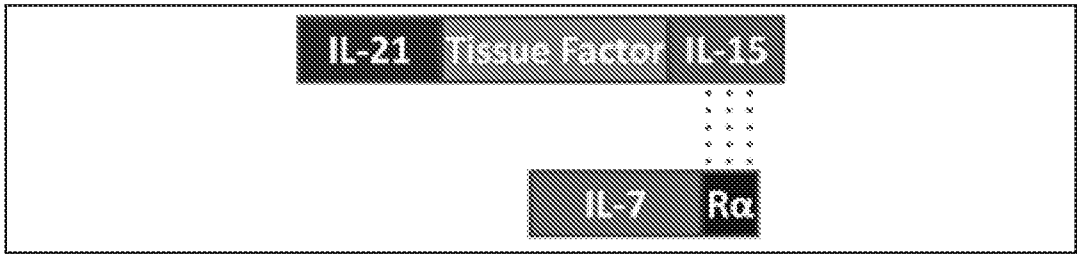


Figure 45

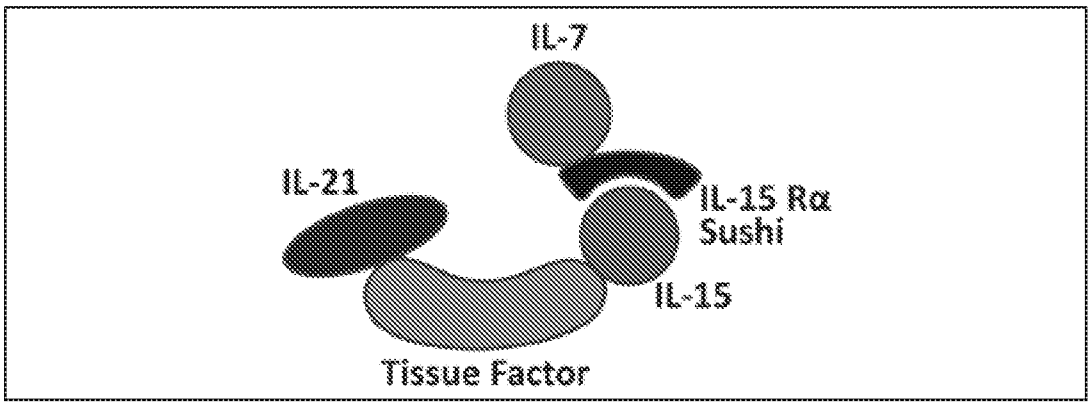


Figure 46

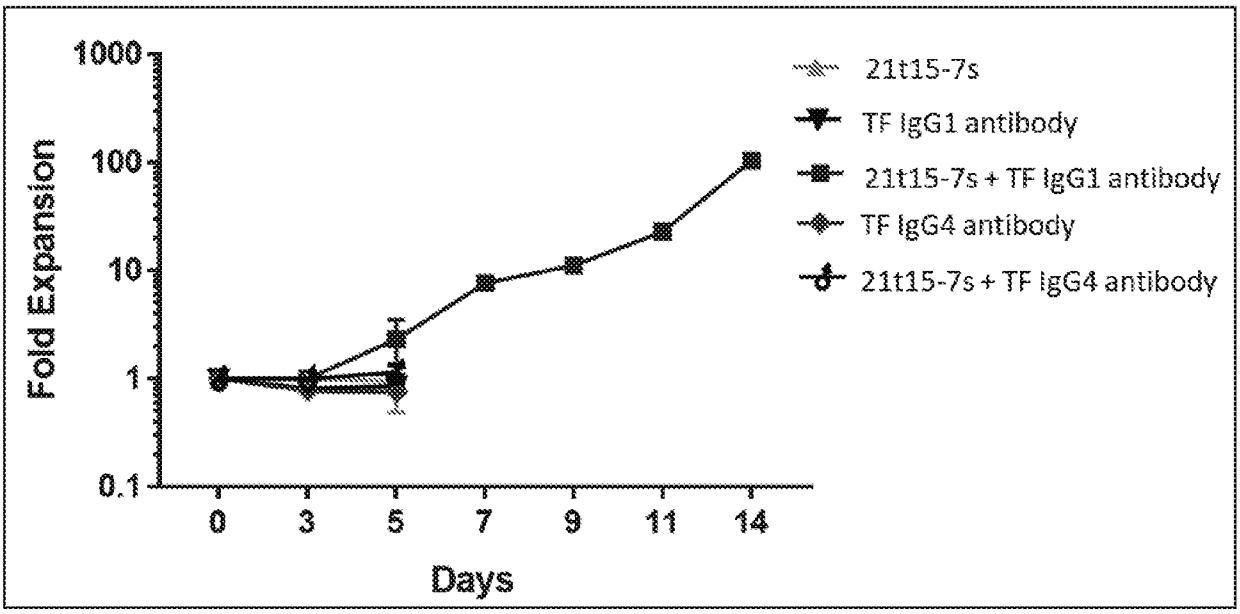


Figure 47

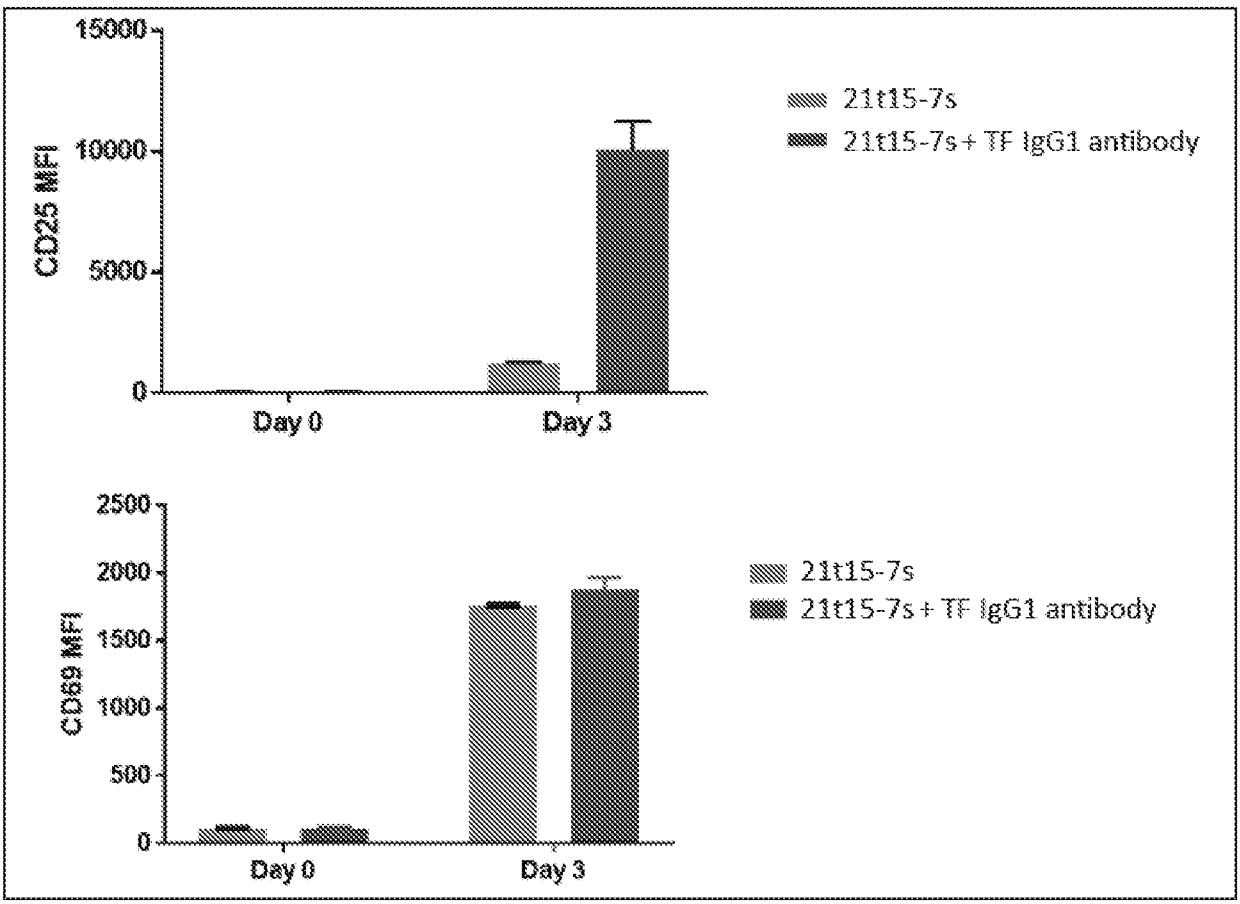


Figure 48

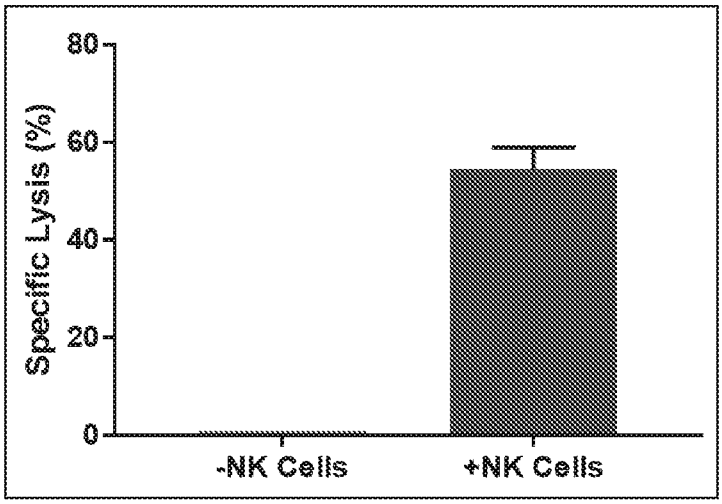


Figure 49

Figure 50

Figure 51

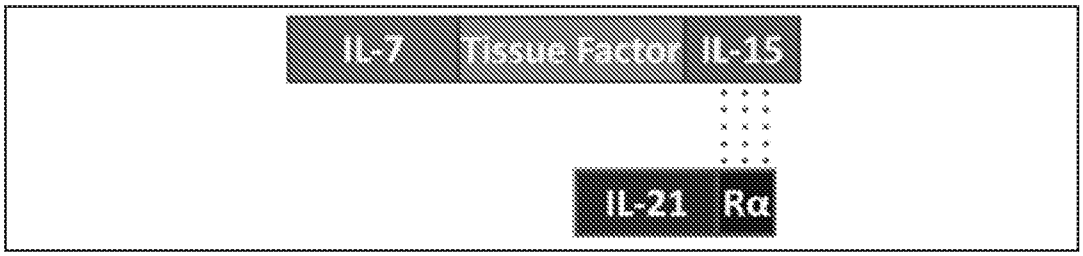


Figure 52

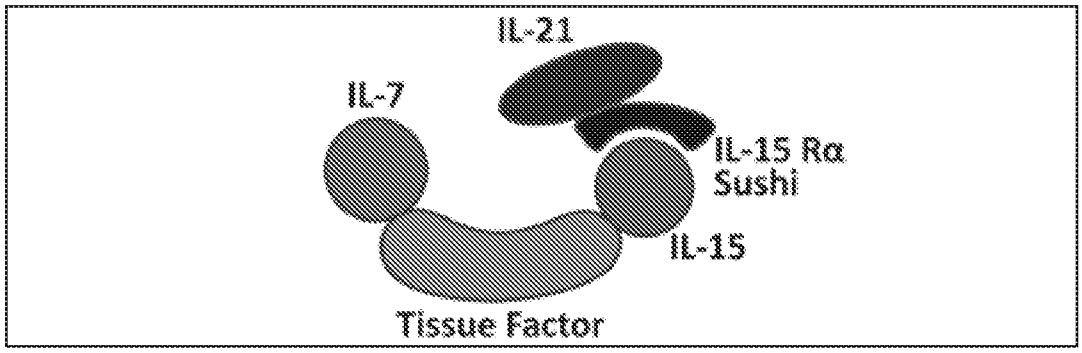


Figure 53

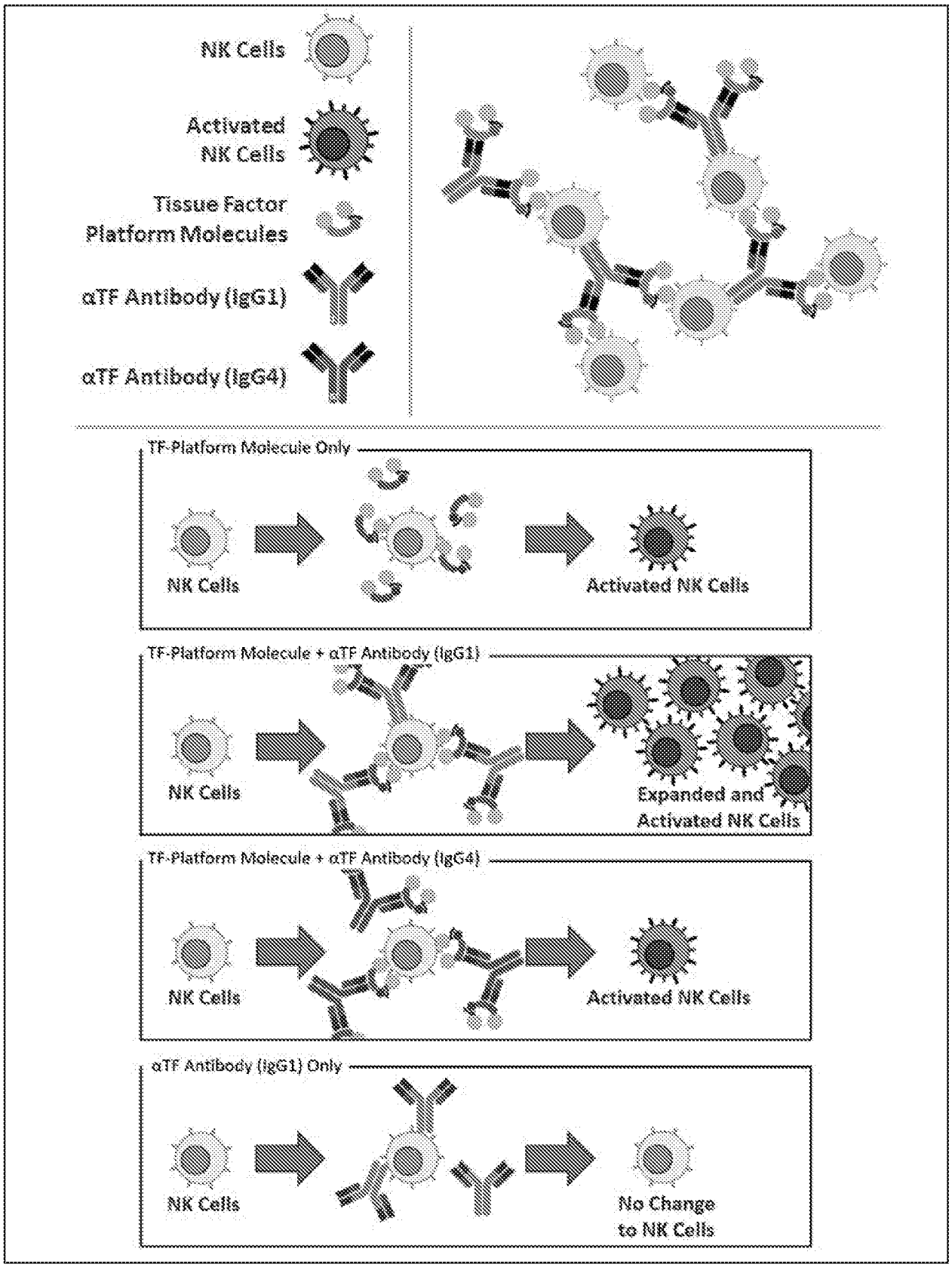

NK Cells
Activated NK Cells
Tissue Factor Platform Molecules
αTF Antibody (IgG1)
αTF Antibody (IgG4)
TF-Platform Molecule Only
NK Cells
Activated NK Cells
TF-Platform Molecule + αTF Antibody (IgG1)
NK Cells
Expanded and Activated NK Cells
TF-Platform Molecule + αTF Antibody (IgG4)
NK Cells
Activated NK Cells
αTF Antibody (IgG1) Only
NK Cells
No Change to NK Cells

Figure 54

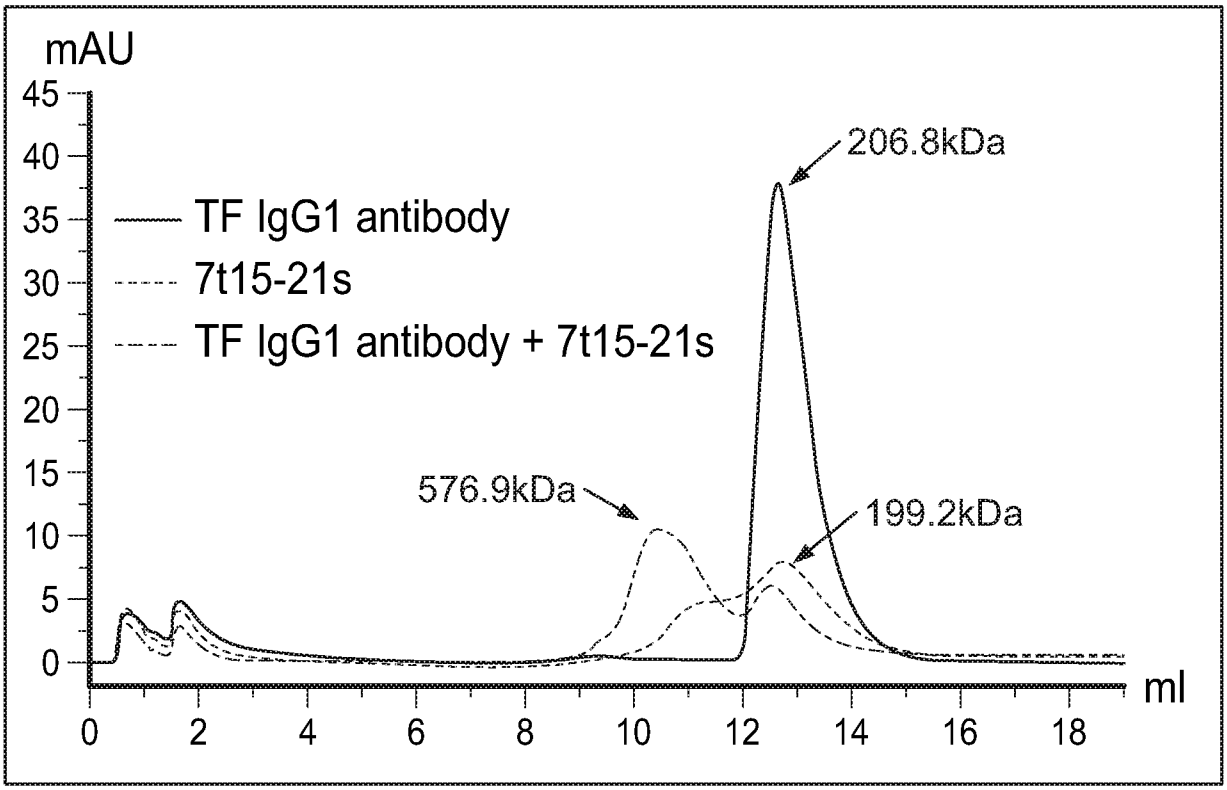

mAU
45
40
35
30
25
20
15
10
5
0
TF IgG1 antibody
7t15-21s
TF IgG1 antibody + 7t15-21s
206.8kDa
576.9kDa
199.2kDa
ml
0
2
4
6
8
10
12
14
16
18

Figure 55

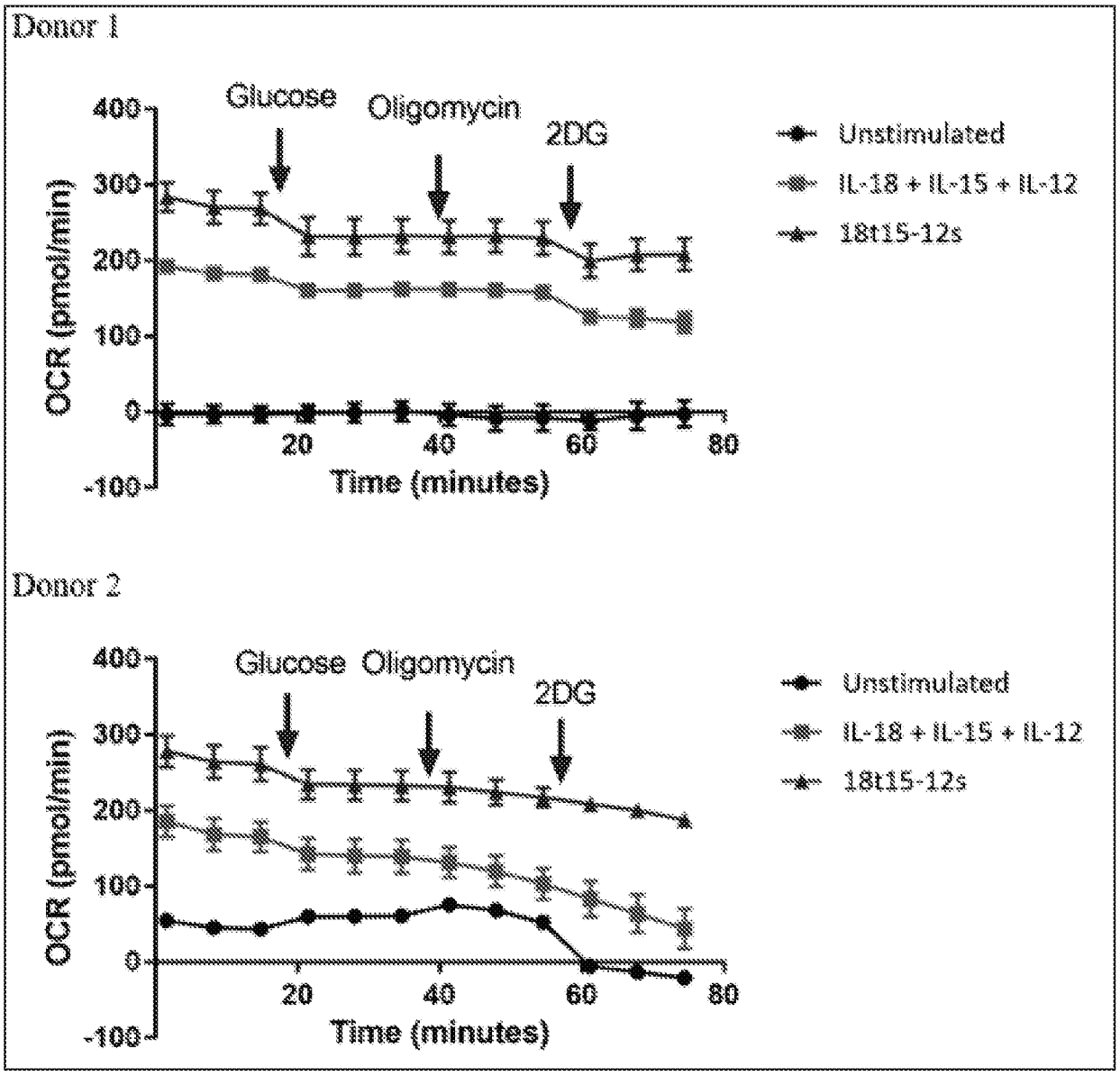

Donor 1
Glucose
Oligomycin
2DG
OCR (pmol/min)
400
300
200
100
0
-100
20
40
60
80
Time (minutes)
Unstimulated
IL-18 + IL-15 + IL-12
18t15-12s
Donor 2
Glucose
Oligomycin
2DG
OCR (pmol/min)
400
300
200
100
0
-100
20
40
60
80
Time (minutes)
Unstimulated
IL-18 + IL-15 + IL-12
18t15-12s

Figure 56

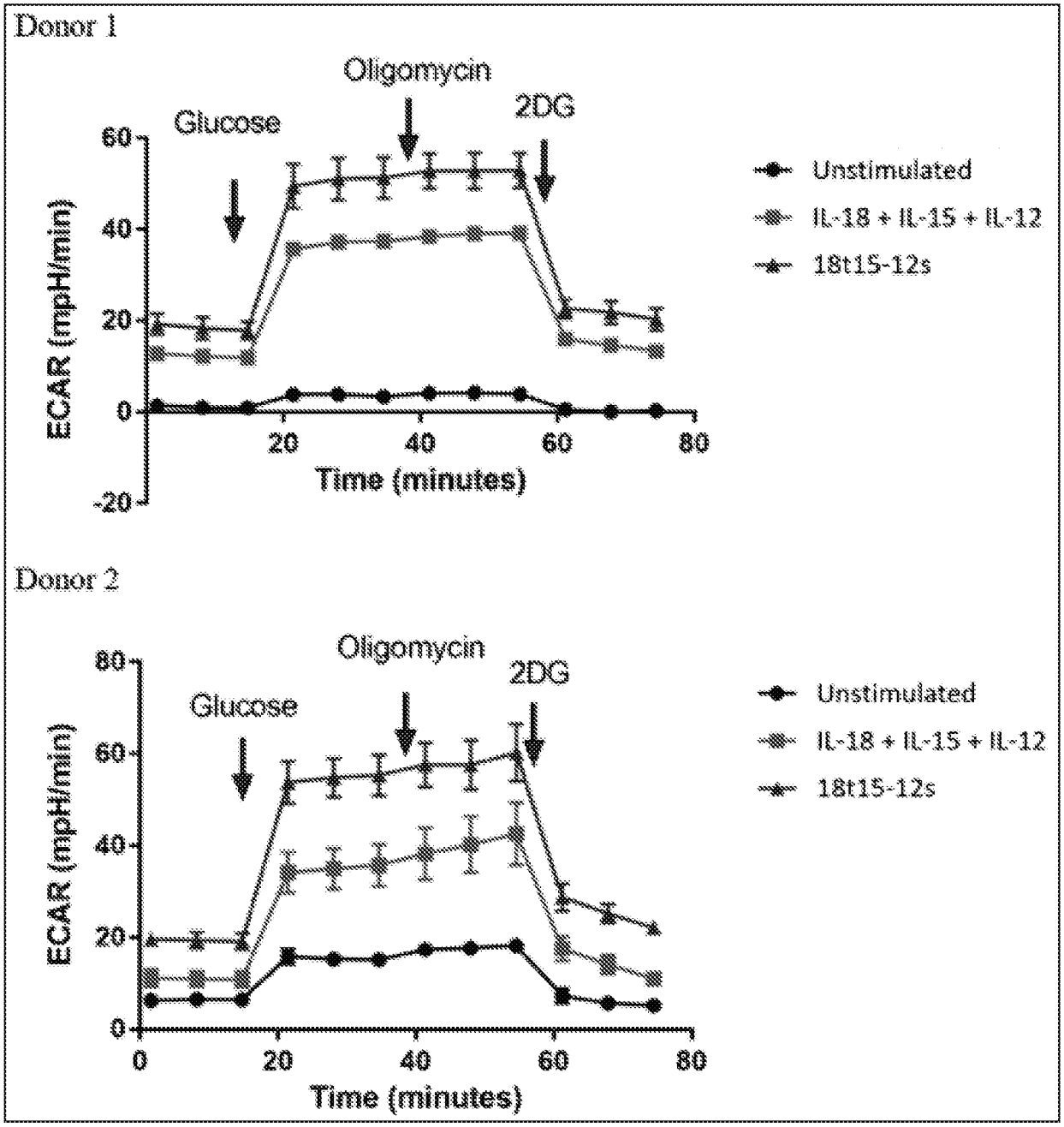

Donor 1
Oligomycin
2DG
Glucose
ECAR (mpH/min)
60
40
20
0
-20
20
40
60
80
Time (minutes)
Unstimulated
IL-18 + IL-15 + IL-12
18t15-12s
Donor 2
Oligomycin
2DG
Glucose
ECAR (mpH/min)
80
60
40
20
0
0
20
40
60
80
Time (minutes)
Unstimulated
IL-18 + IL-15 + IL-12
18t15-12s

Figure 57

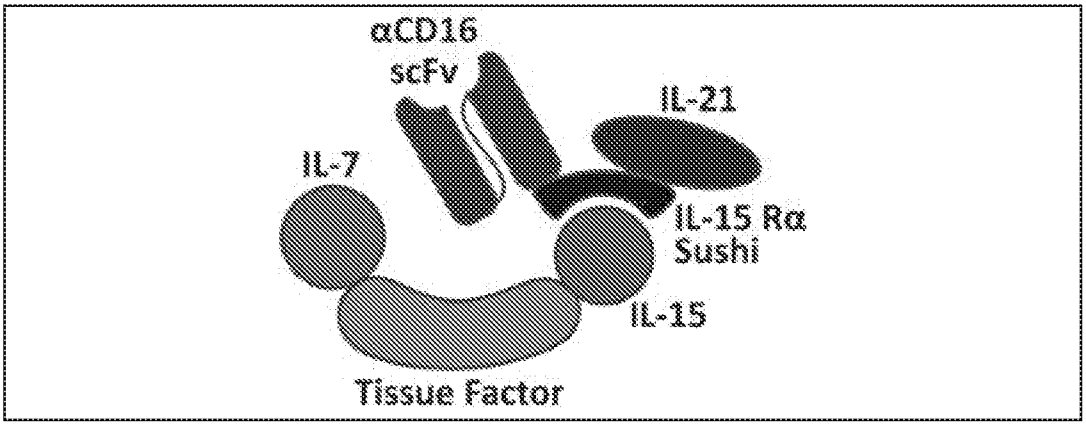


Figure 58

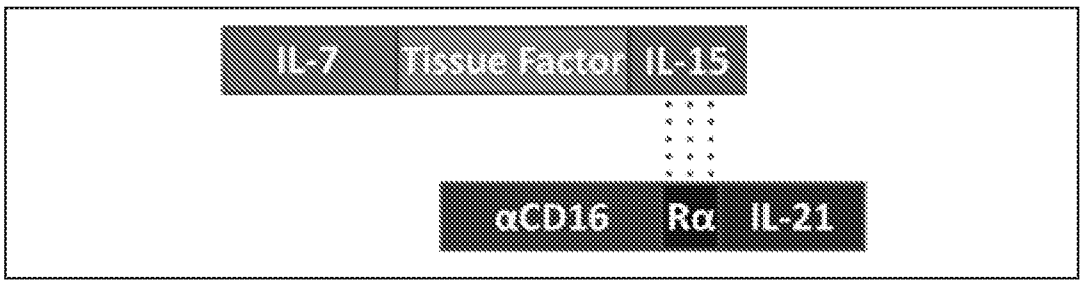


Figure 59

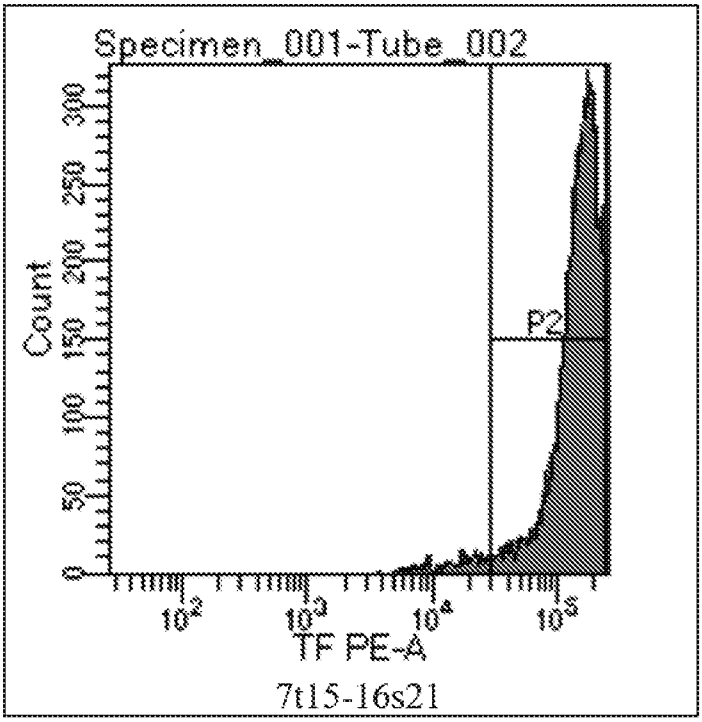


Figure 60A

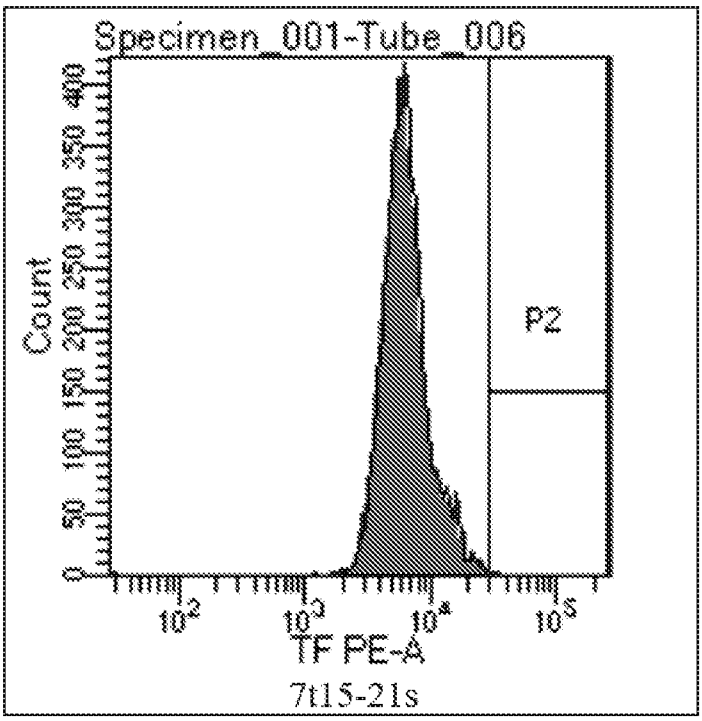


Figure 60B

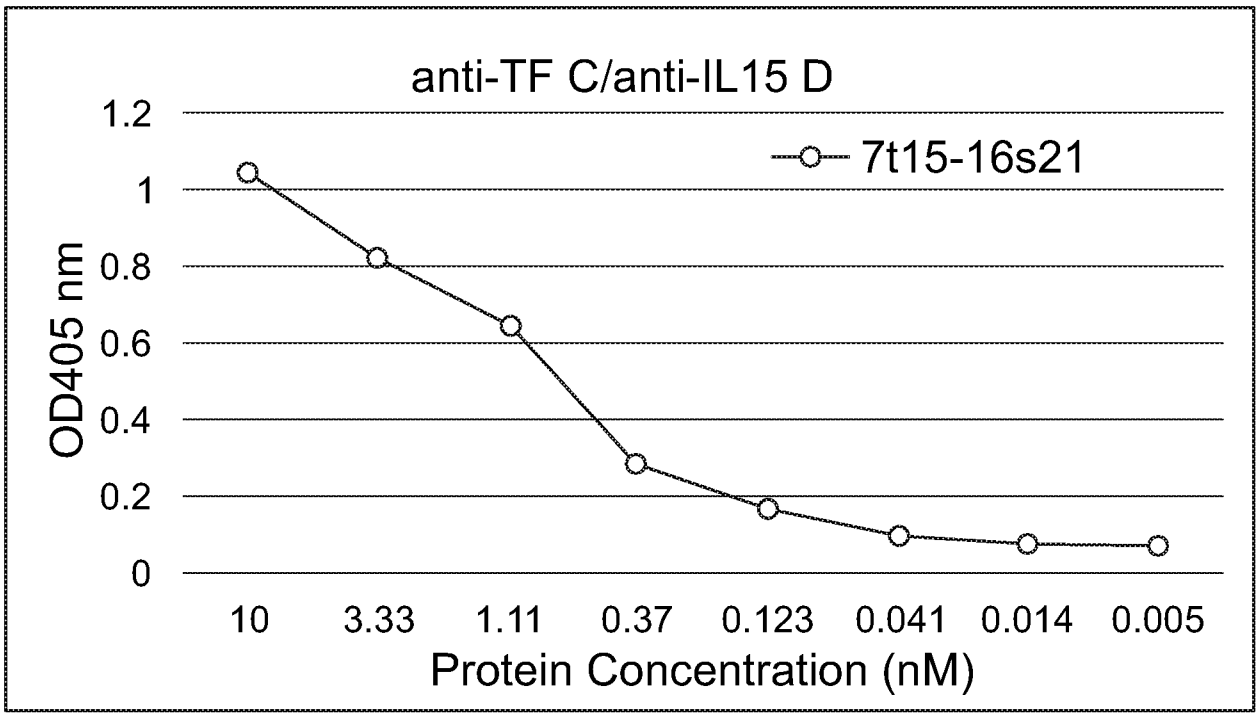


Figure 61A

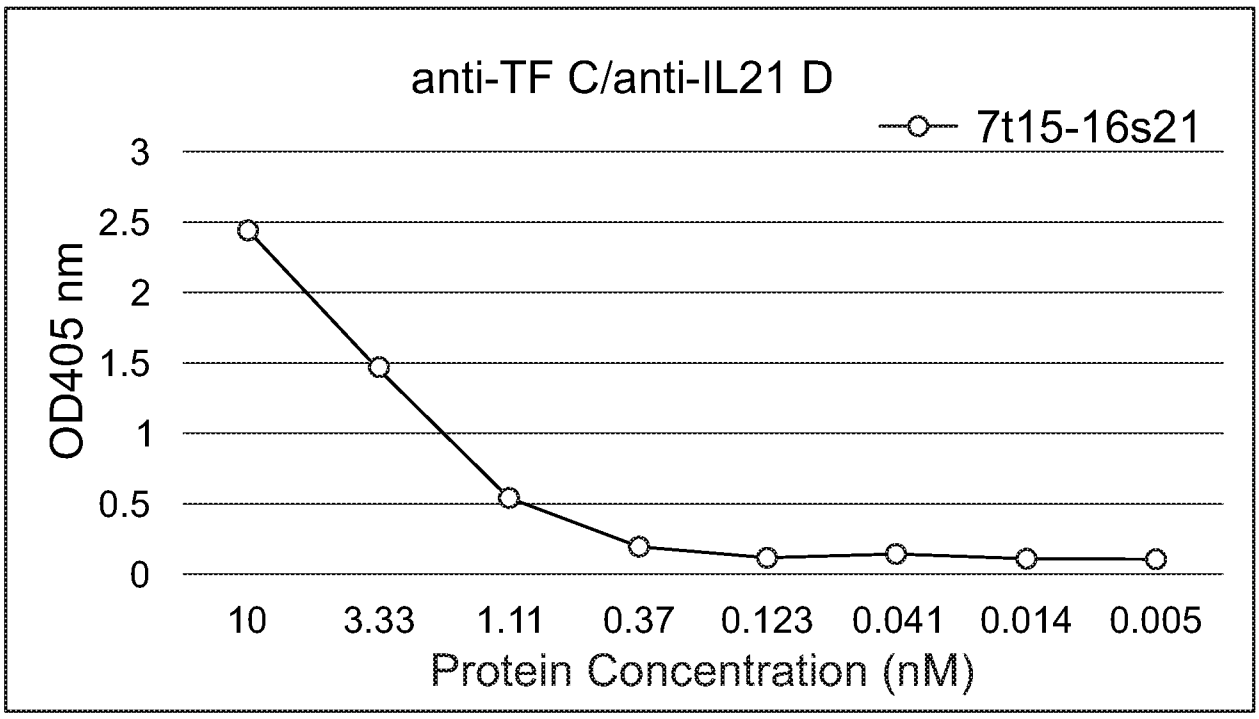


Figure 61B

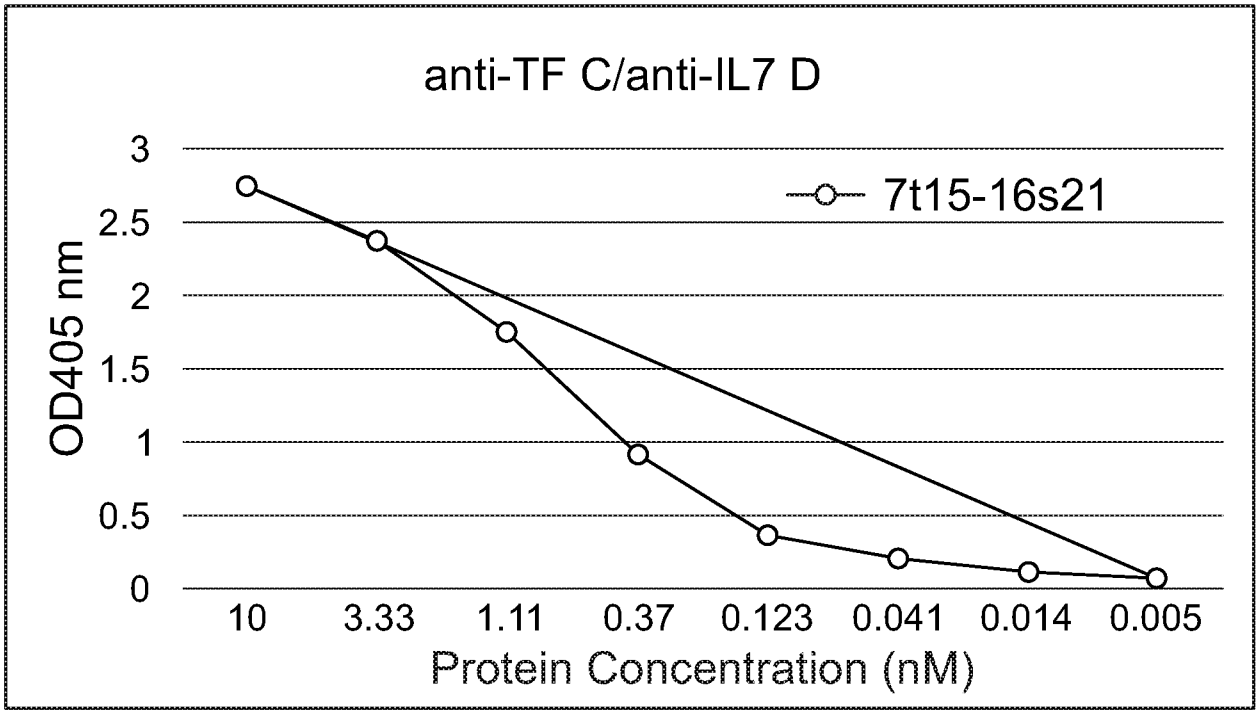


Figure 61C

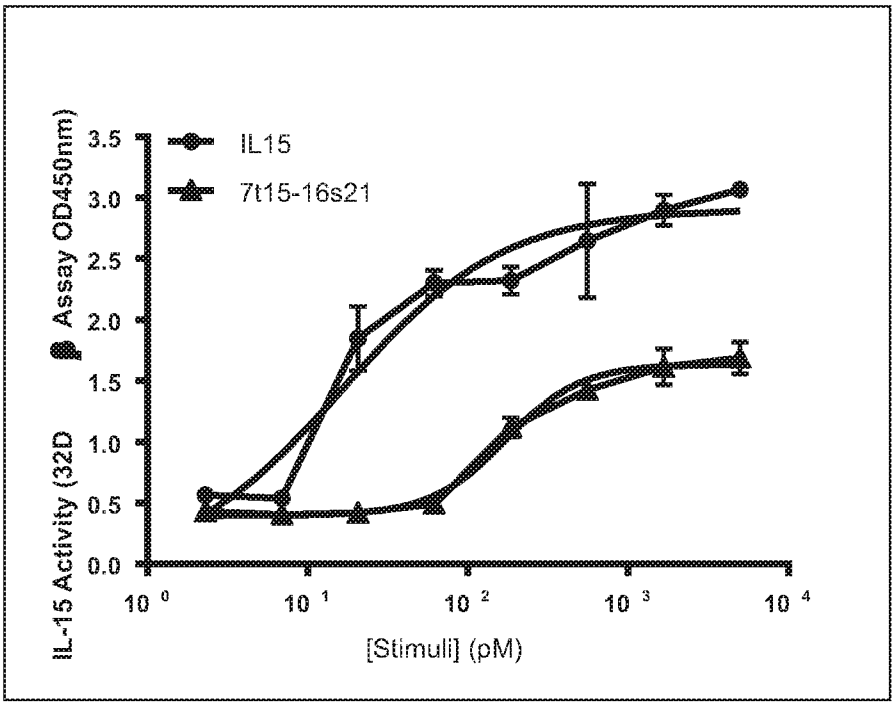


Figure 62

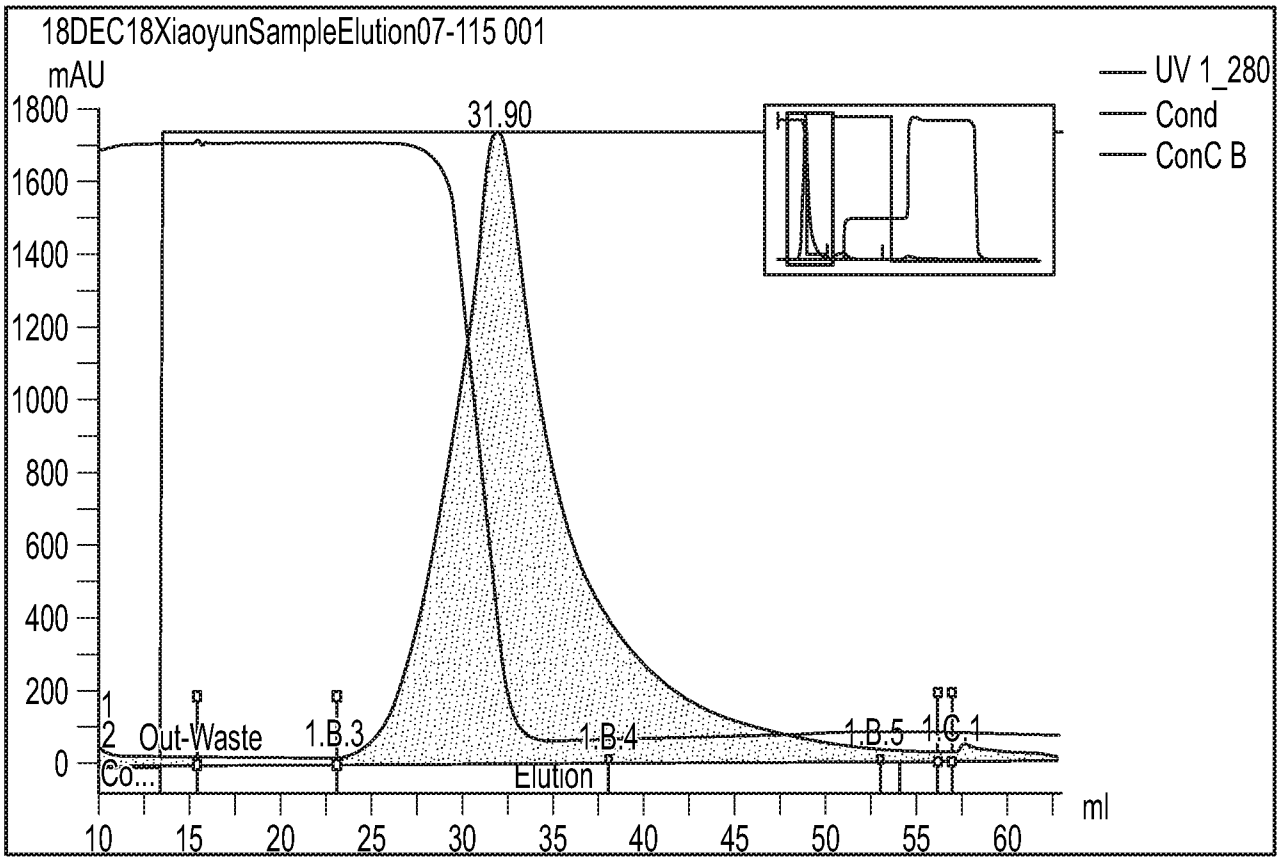

18DEC18XiaoyunSampleElution07-115 001
mAU
1800
1600
1400
1200
1000
800
600
400
200
0
31.90
UV 1_280
Cond
ConC B
1
2 Out-Waste
1.B.3
1.B.4
1.B.5
1.C.1
Co...
Elution
ml
10
15
20
25
30
35
40
45
50
55
60

Figure 63

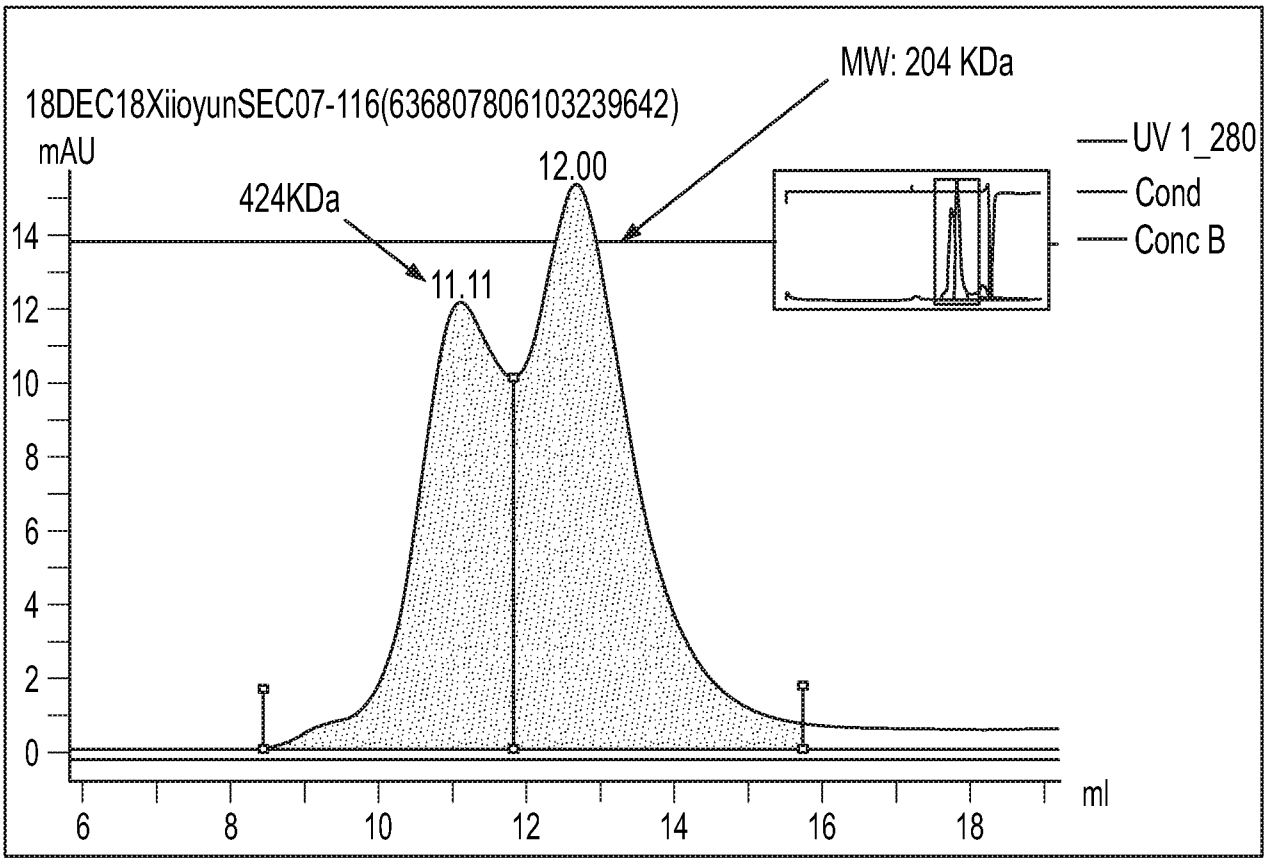

18DEC18XiioyunSEC07-116(636807806103239642)
MW: 204 KDa
mAU
12.00
424KDa
11.11
UV 1_280
Cond
Conc B
14
12
10
8
6
4
2
0
6
8
10
12
14
16
18
ml

Figure 64

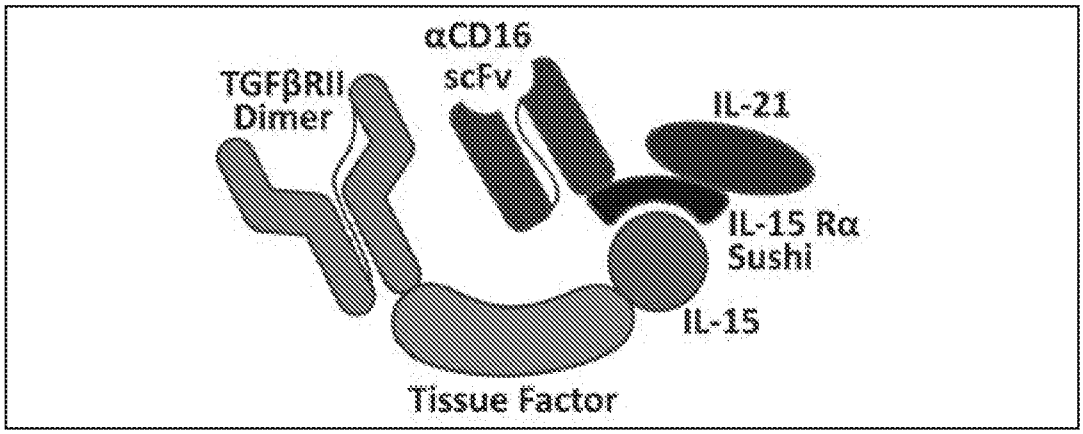


Figure 65

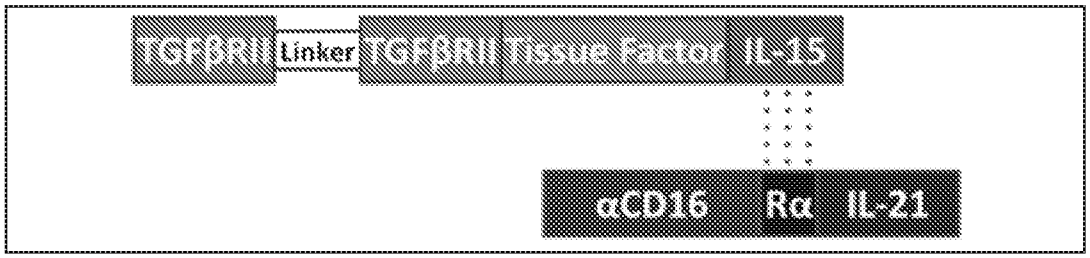


Figure 66

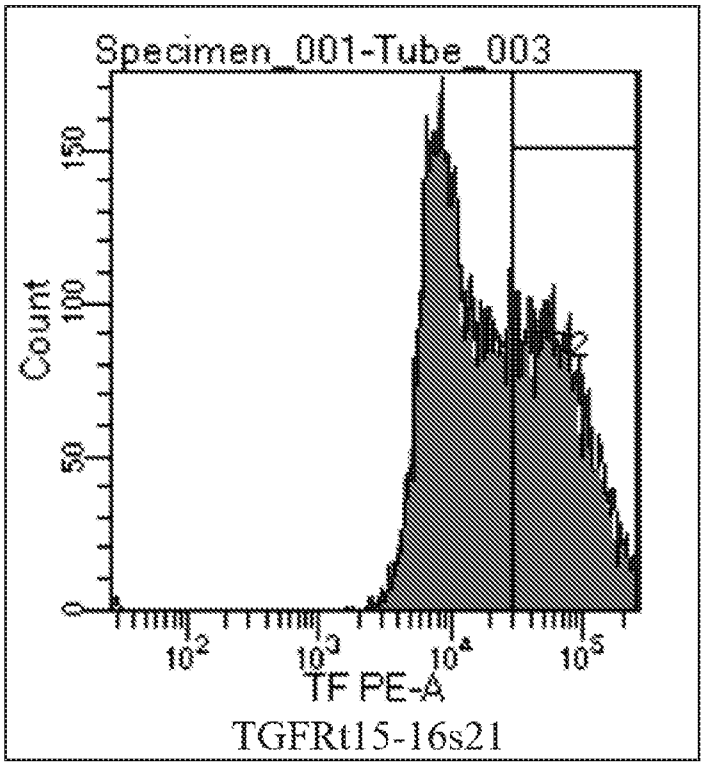


Figure 67A

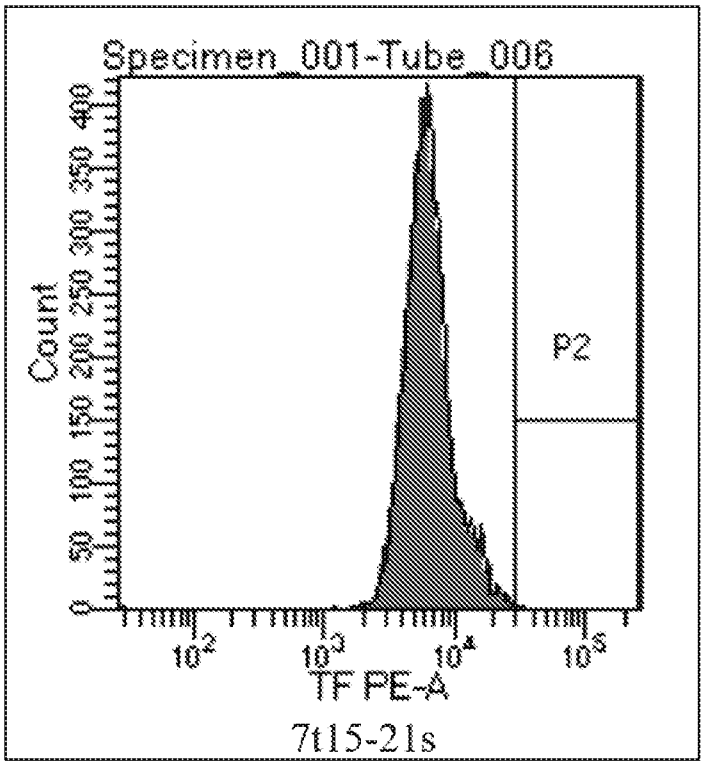


Figure 67B

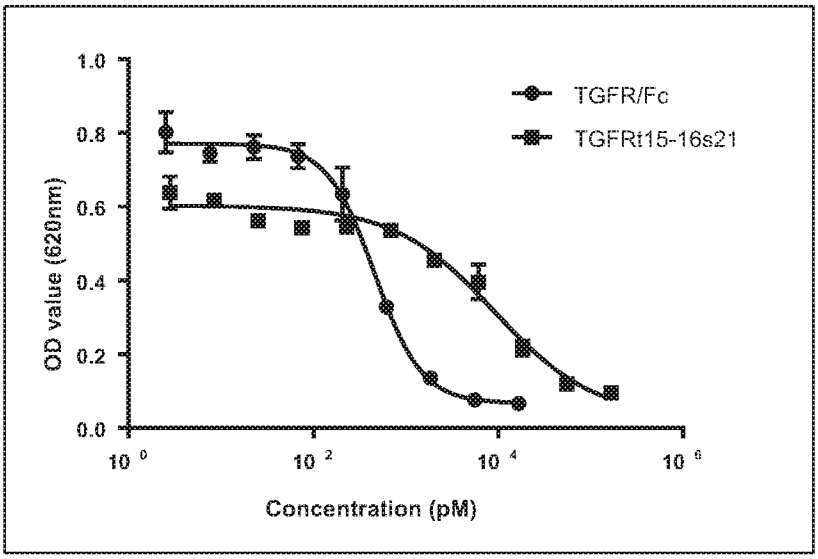


Figure 68

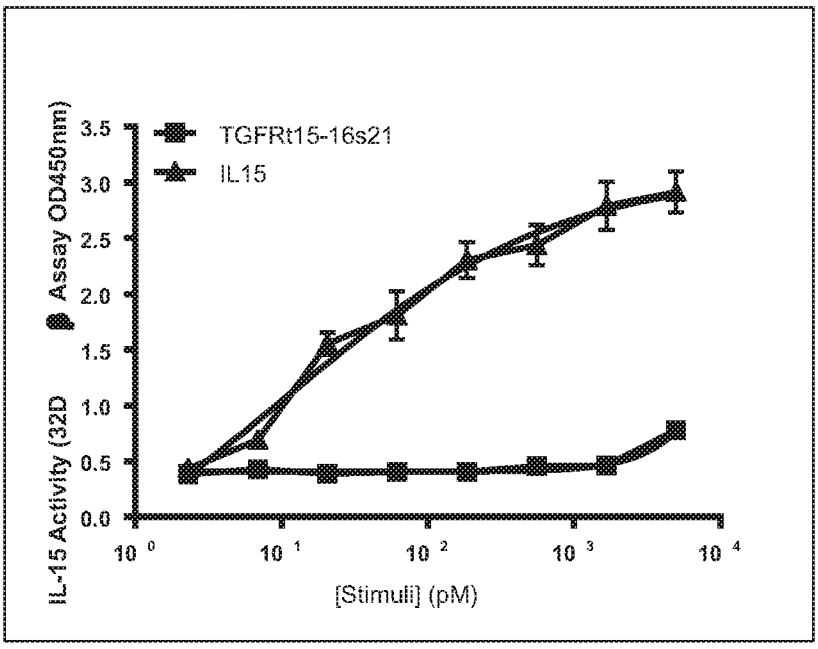


Figure 69

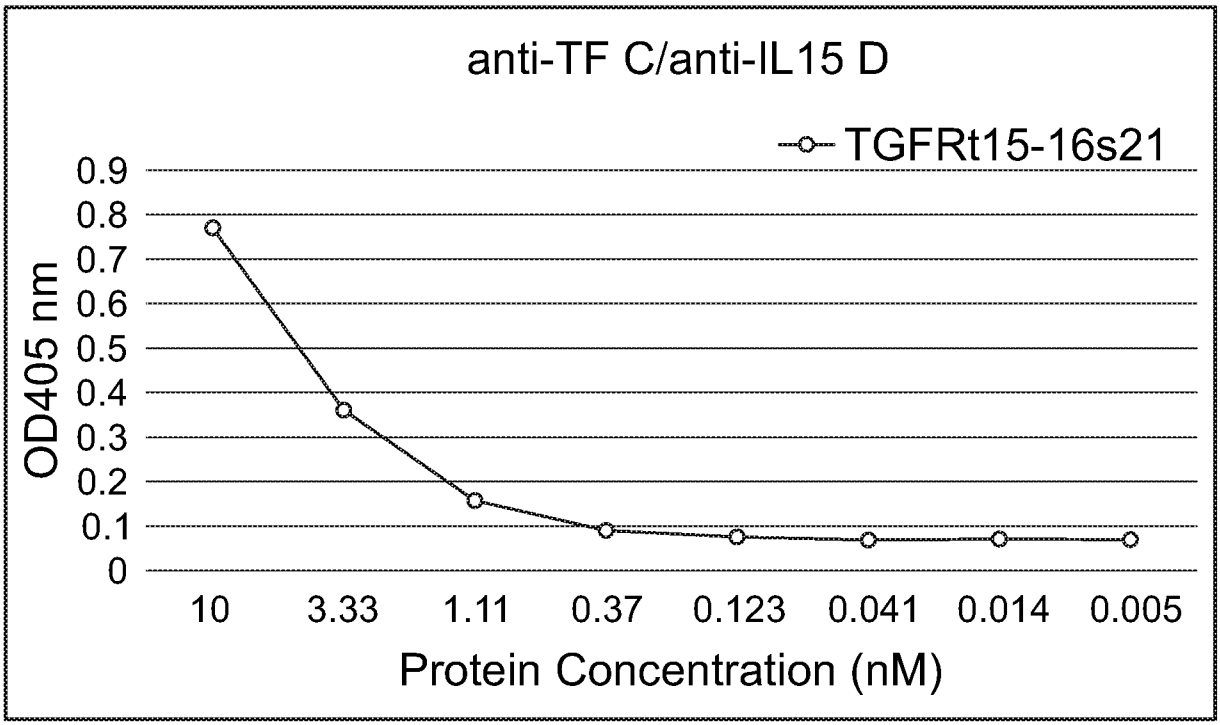


Figure 70A

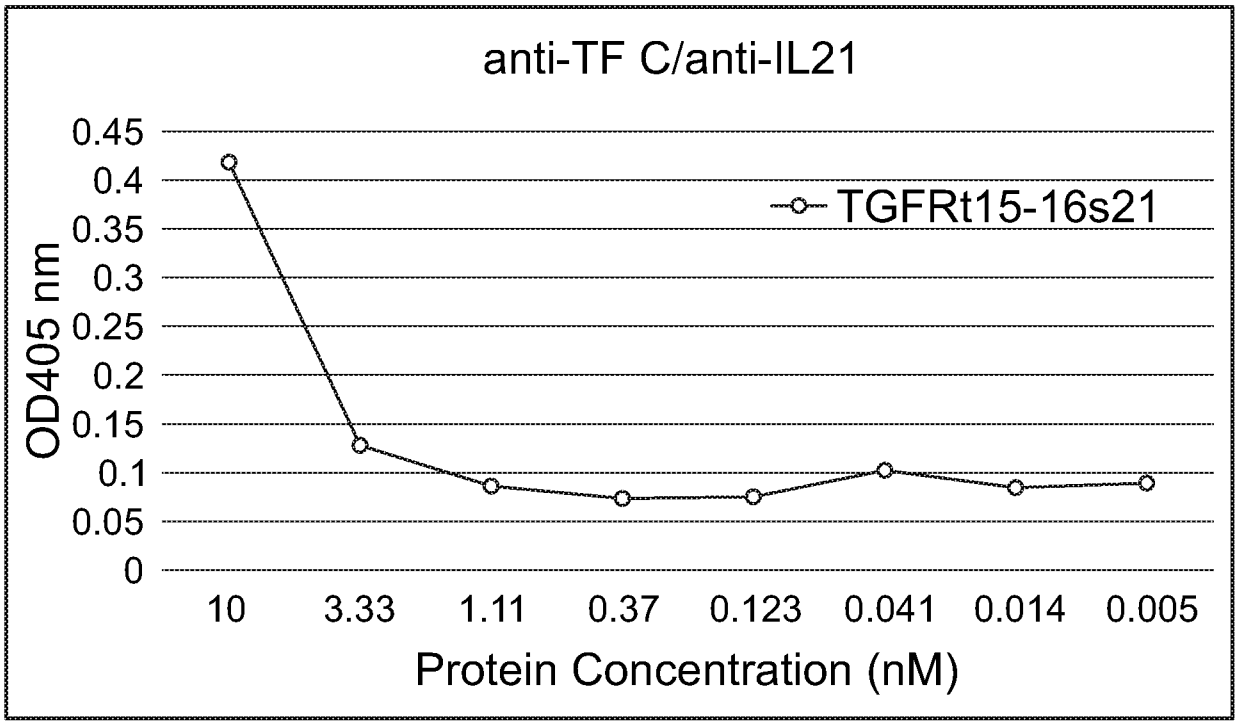


Figure 70B

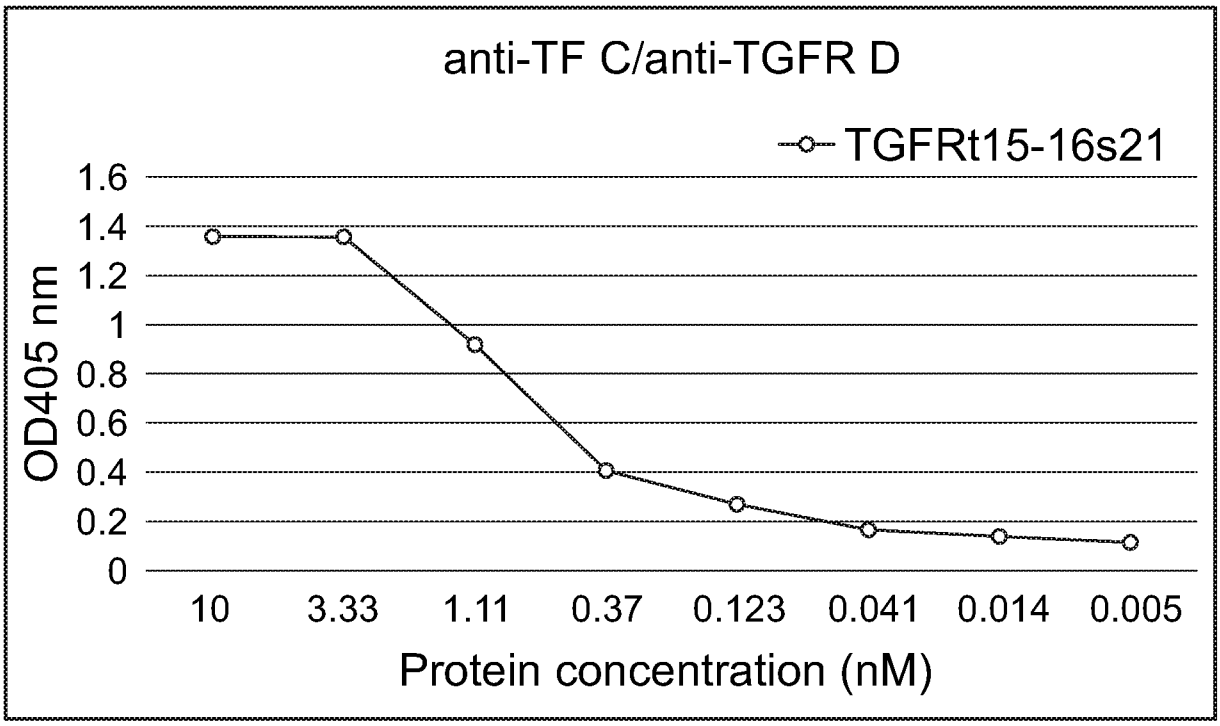

anti-TF C/anti-TGFR D
TGFRt15-16s21
OD405 nm
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
10
3.33
1.11
0.37
0.123
0.041
0.014
0.005
Protein concentration (nM)

Figure 70C

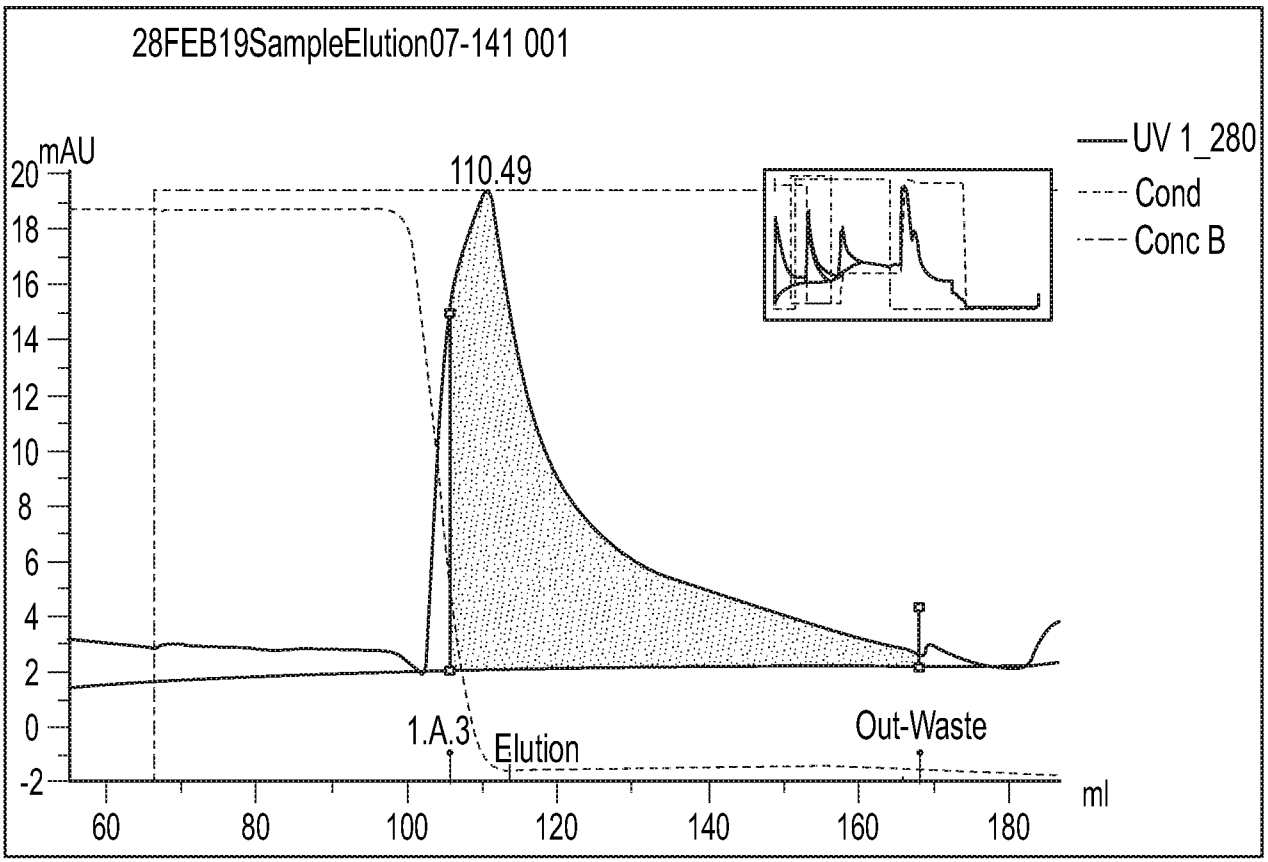


Figure 71

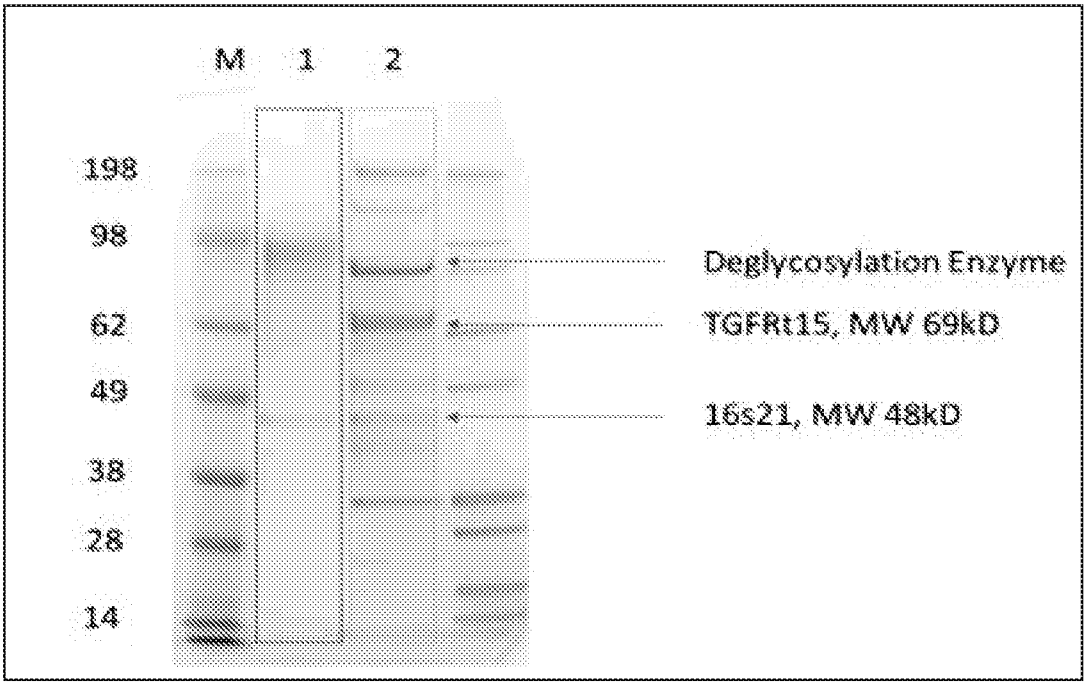


Figure 72

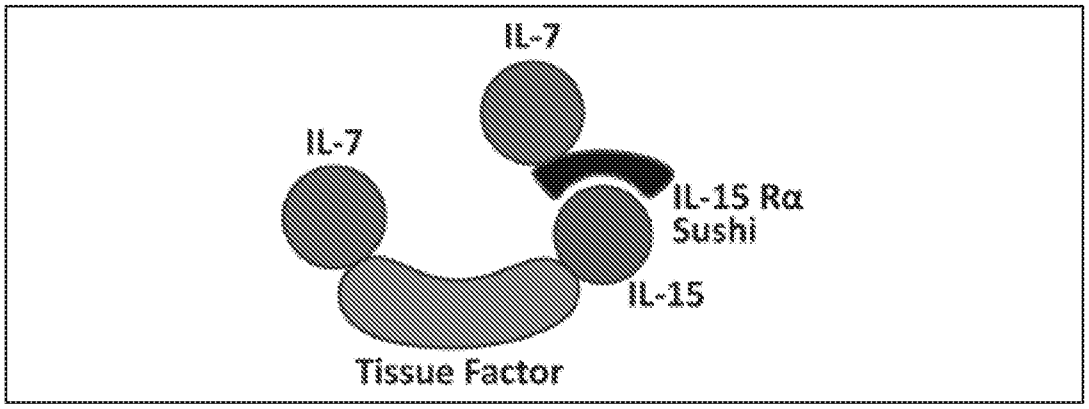


Figure 73

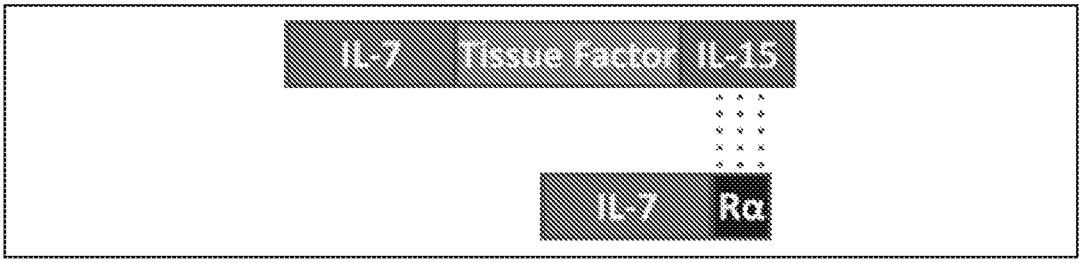


Figure 74

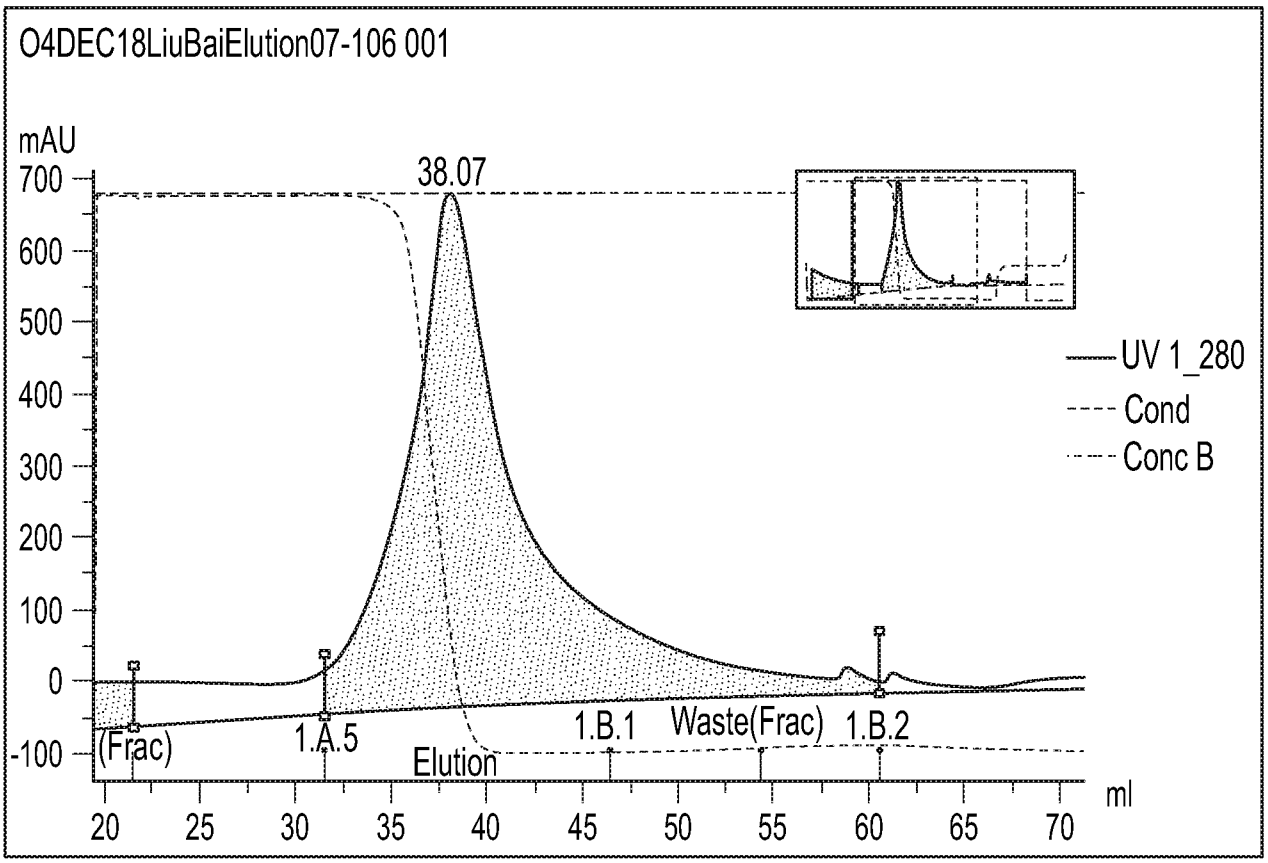


Figure 75

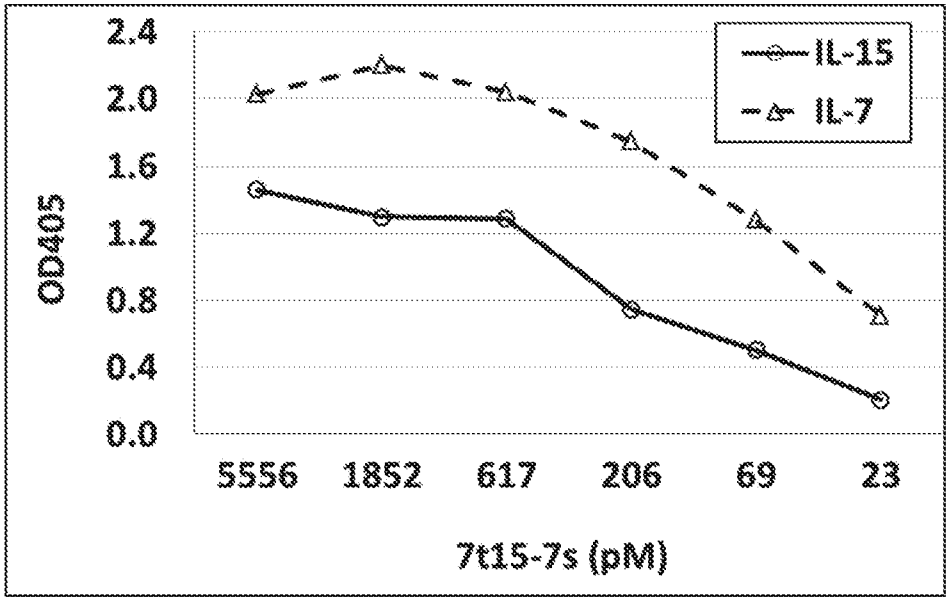


Figure 76

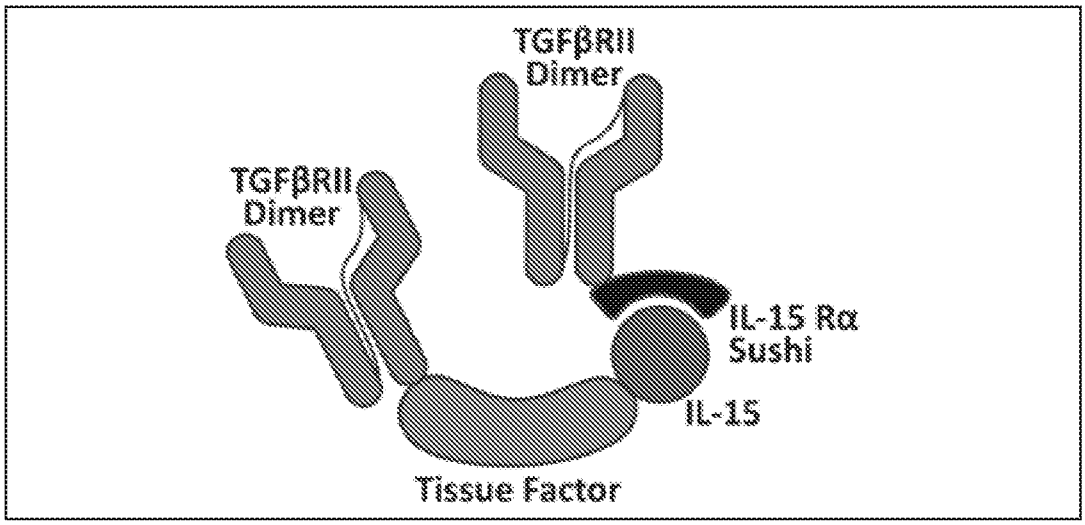


Figure 77

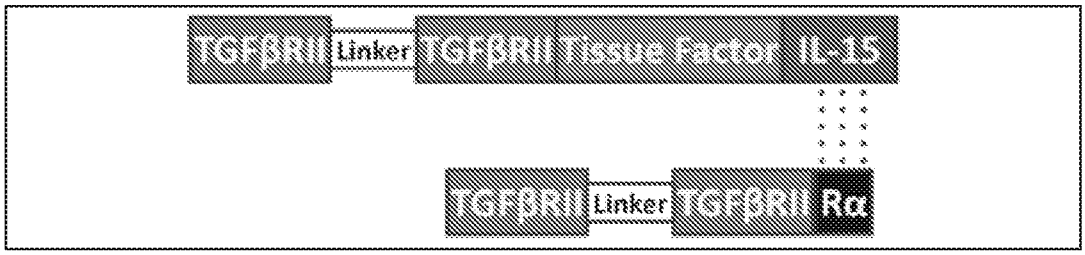


Figure 78

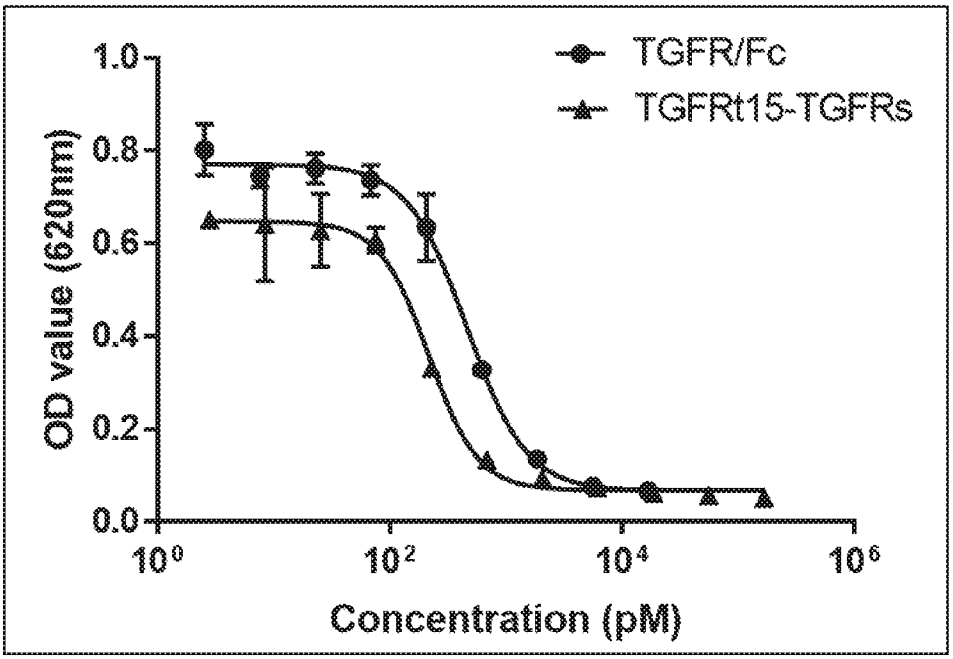


Figure 79

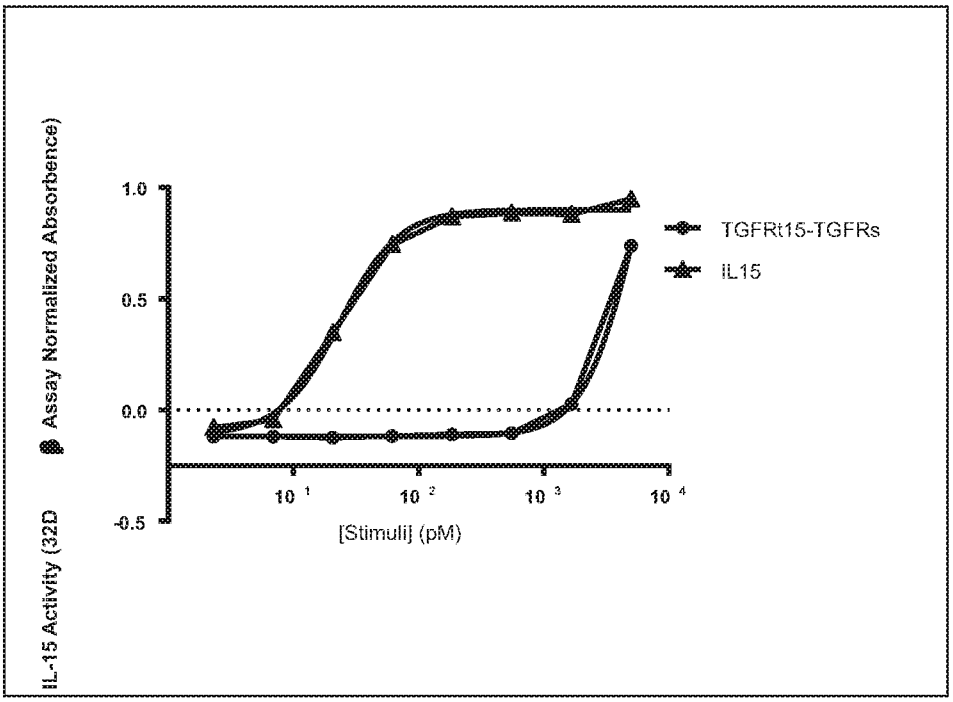


Figure 80

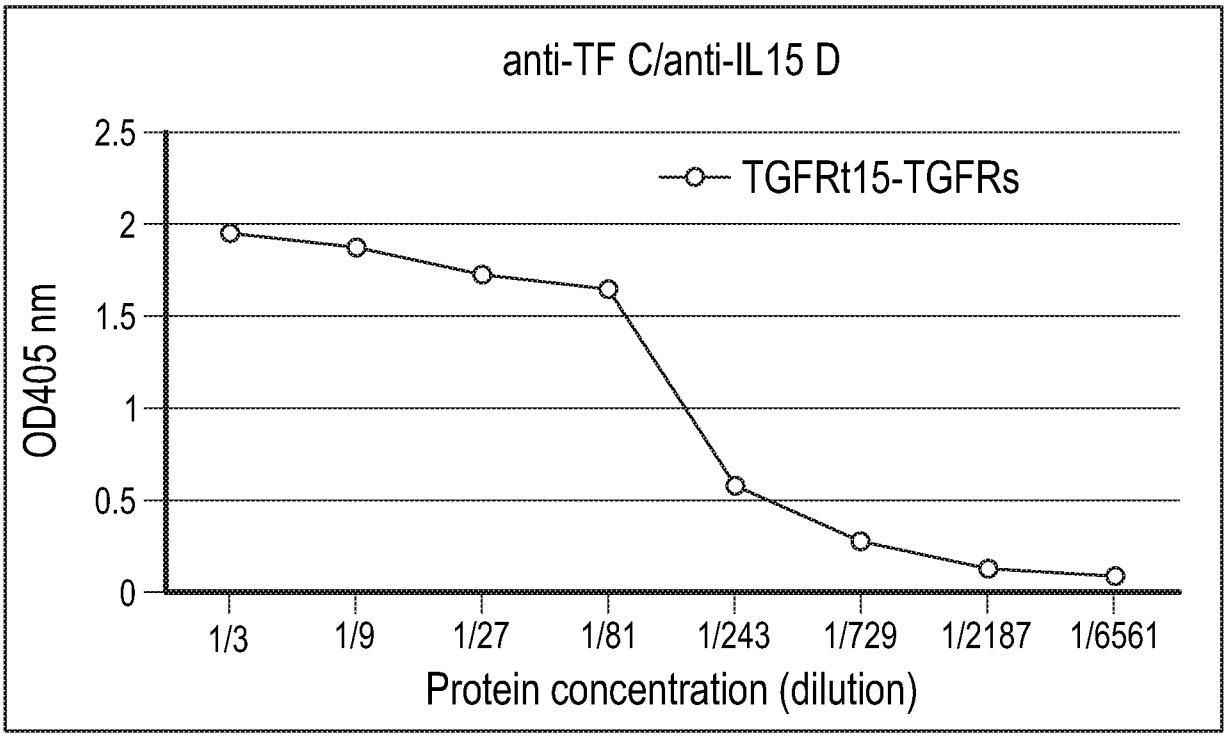


Figure 81A

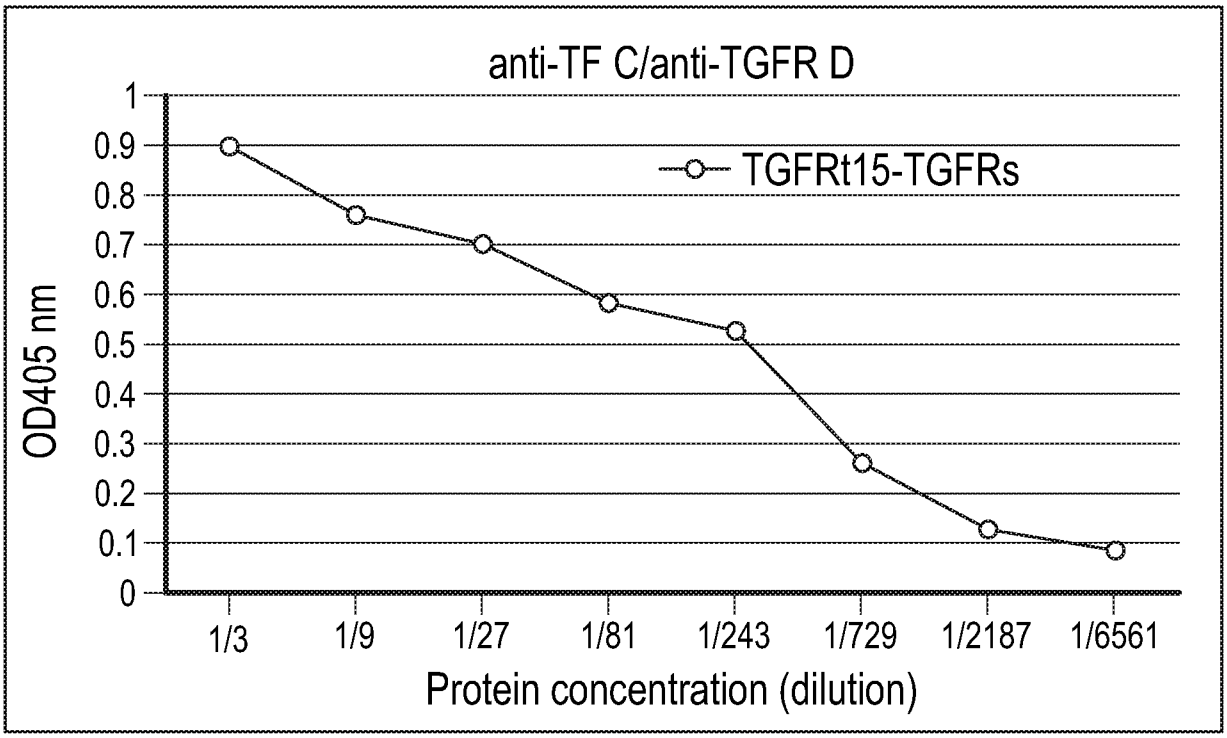


Figure 81B

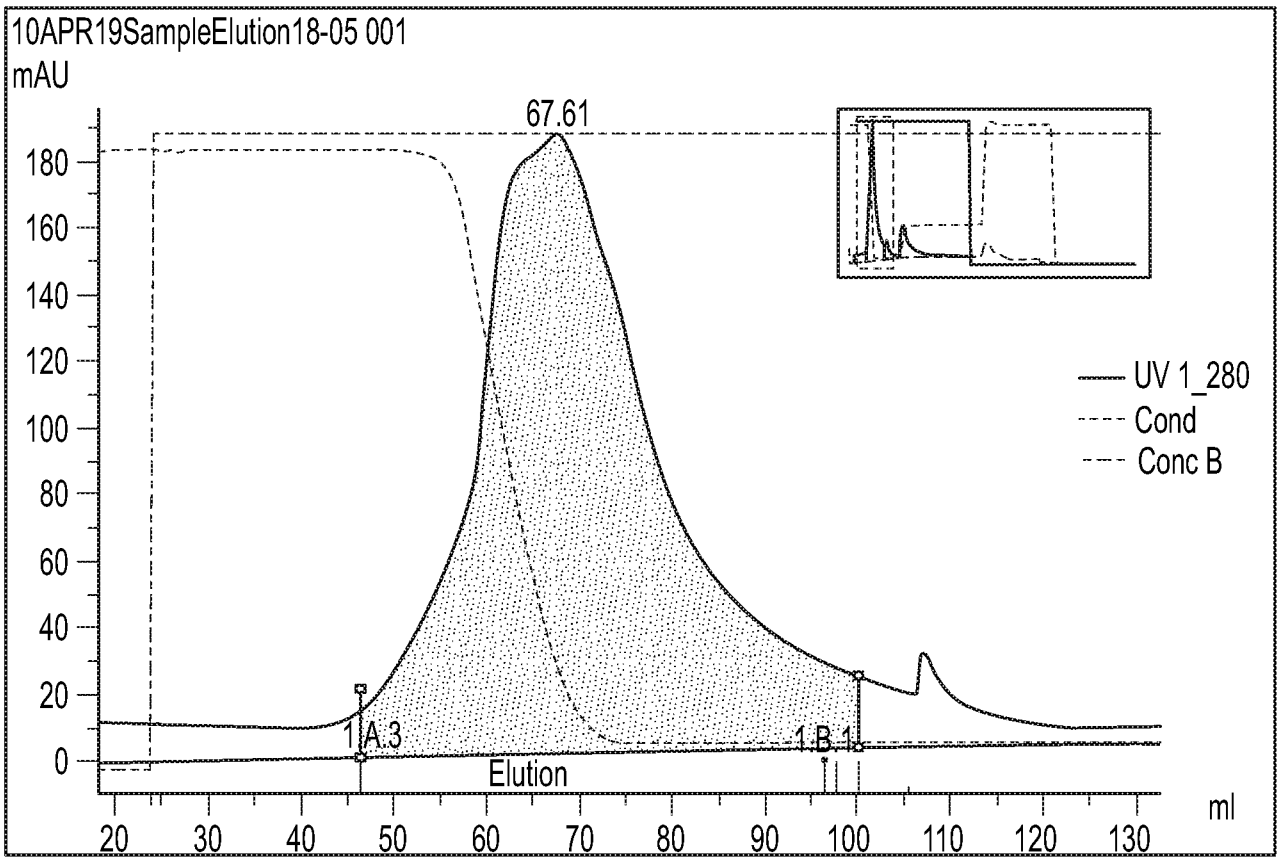


Figure 82

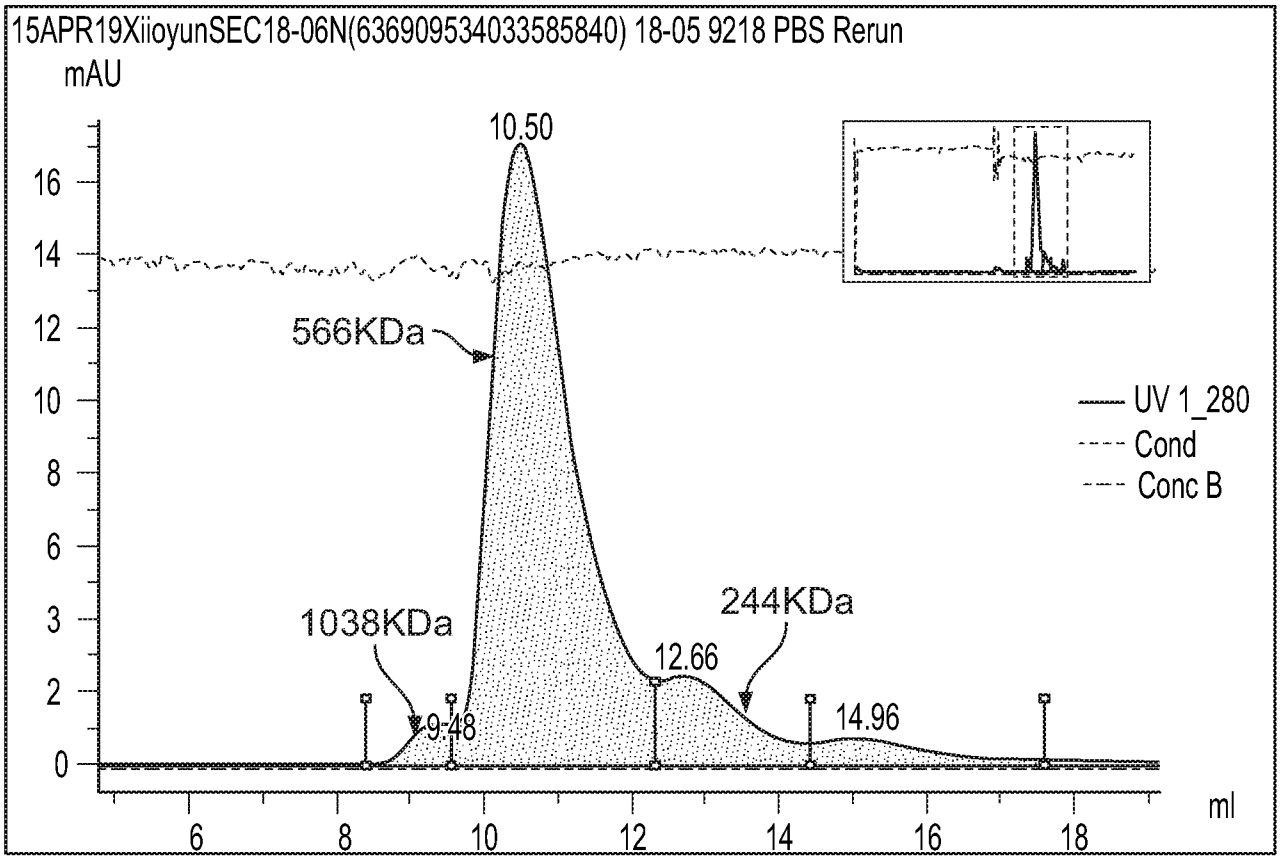


Figure 83

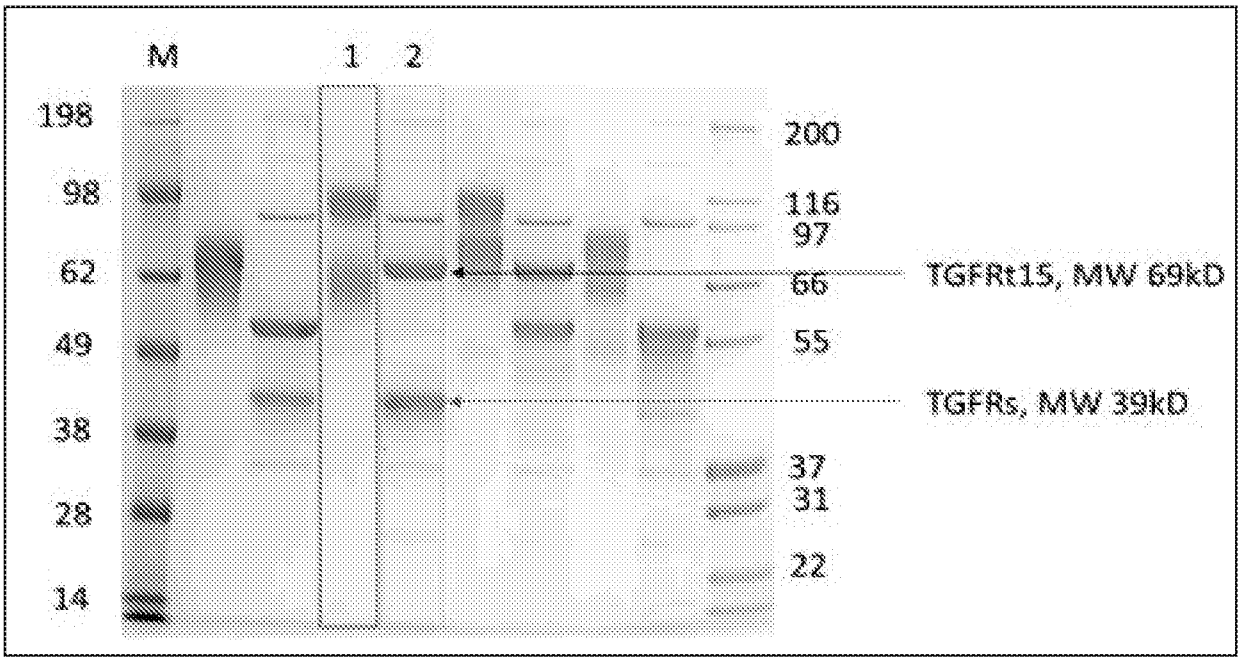


Figure 84

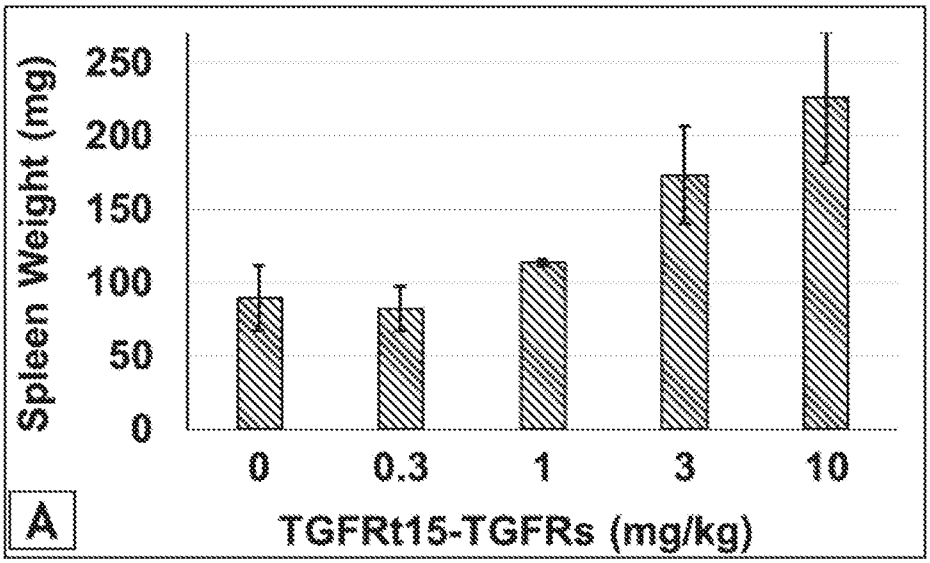


Figure 85A

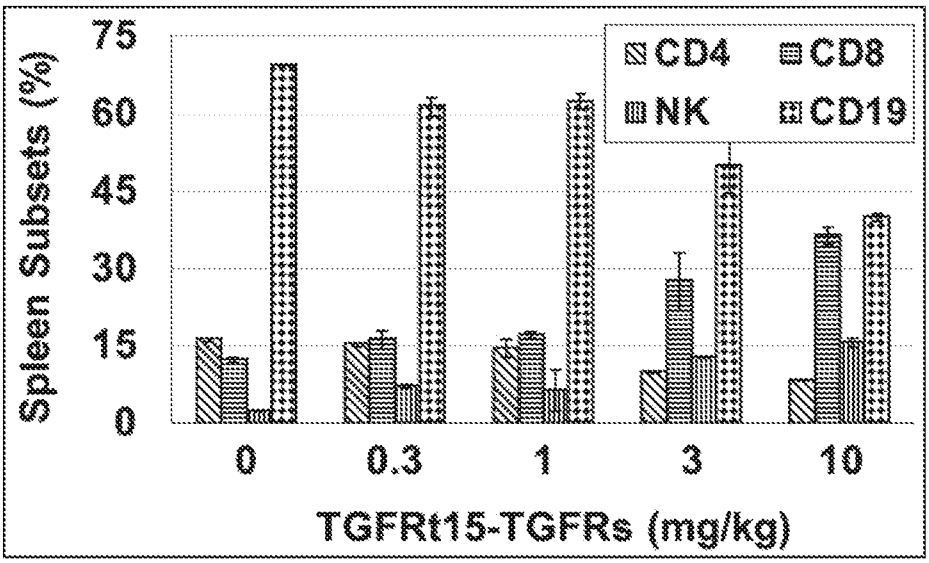


Figure 85B

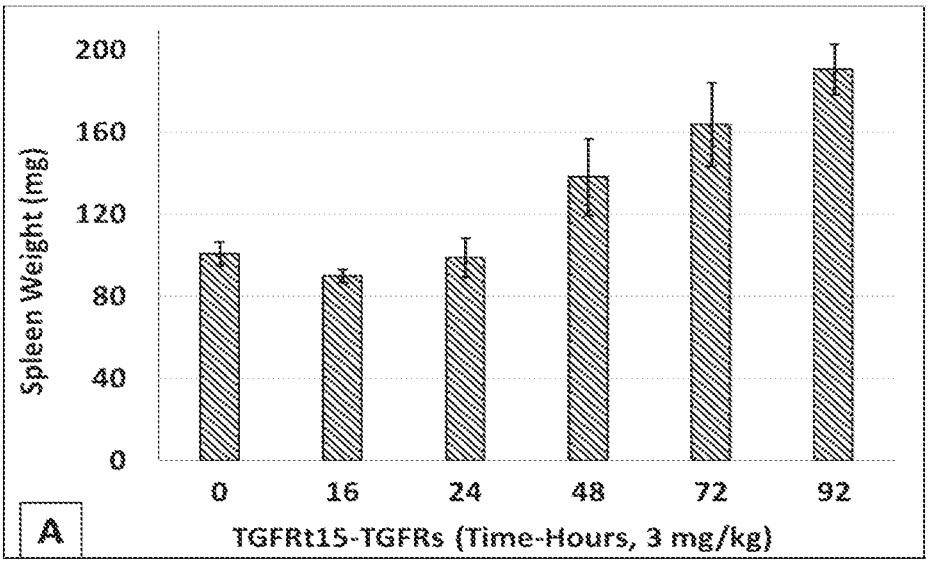


Figure 86A

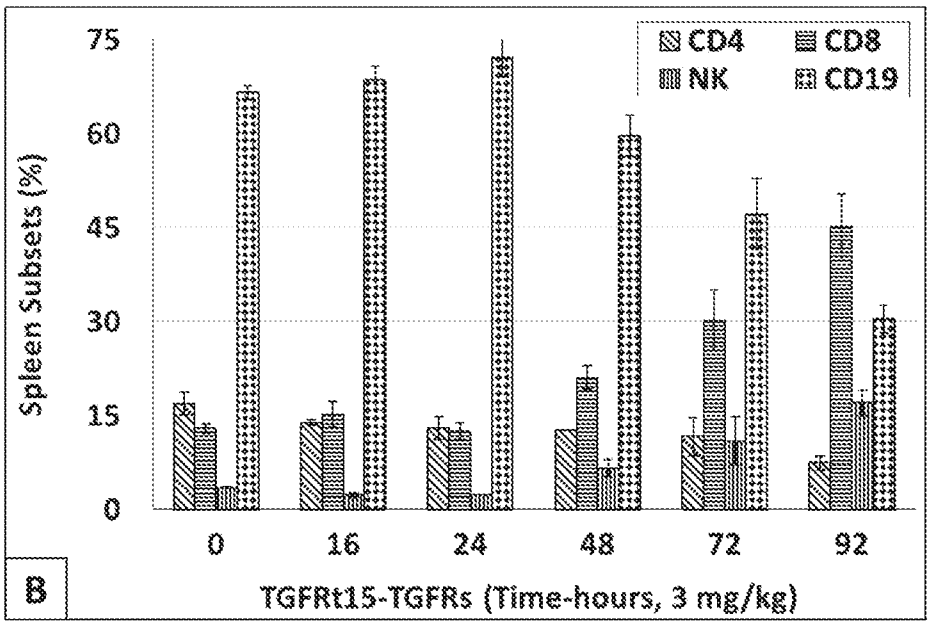


Figure 86B

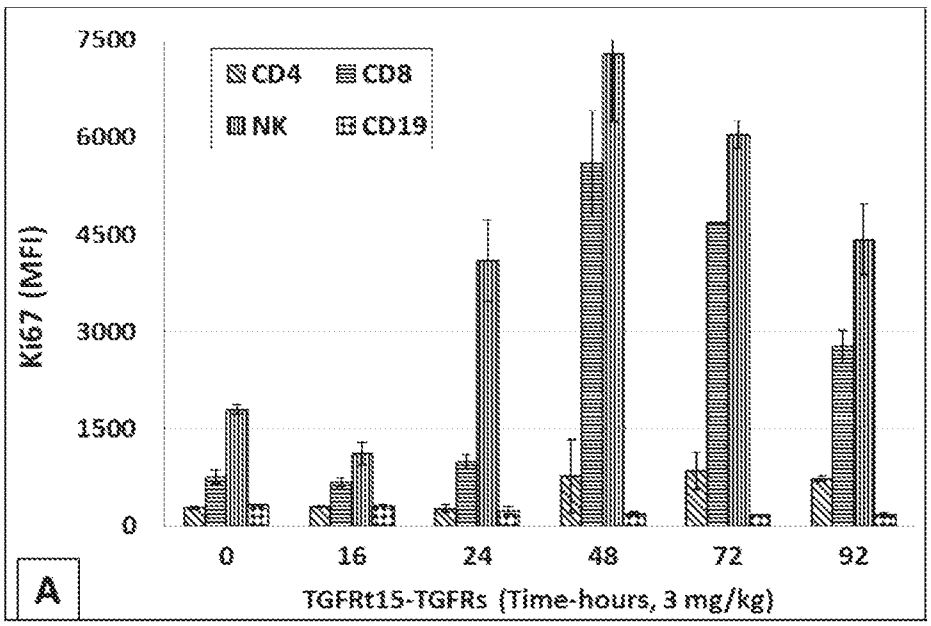


Figure 87A

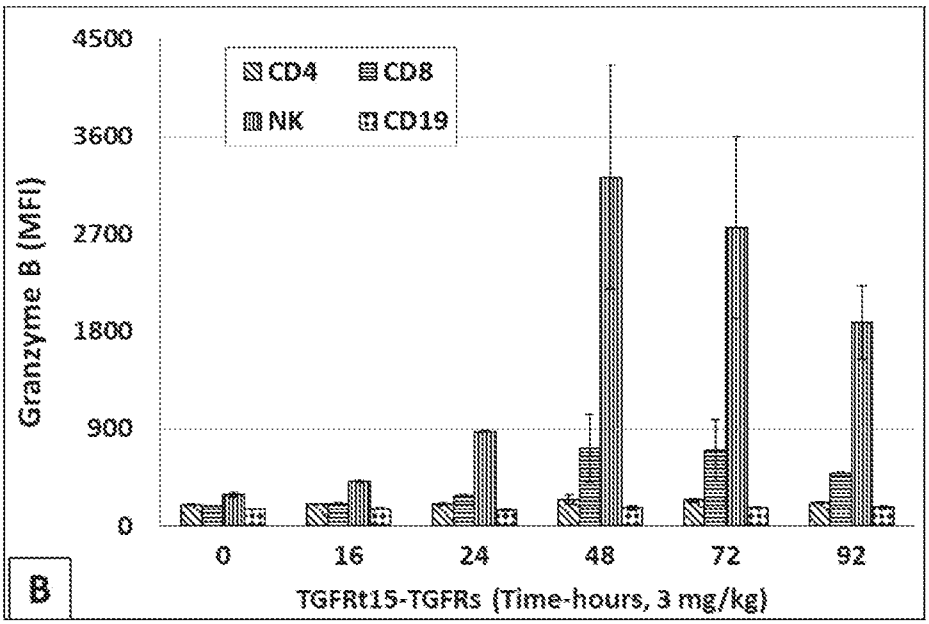


Figure 87B

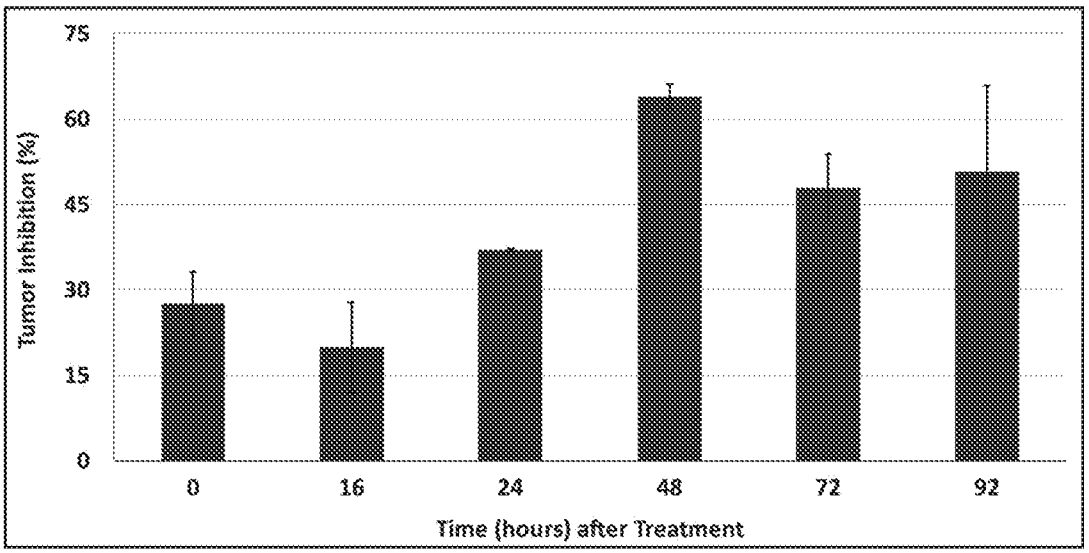


Figure 88

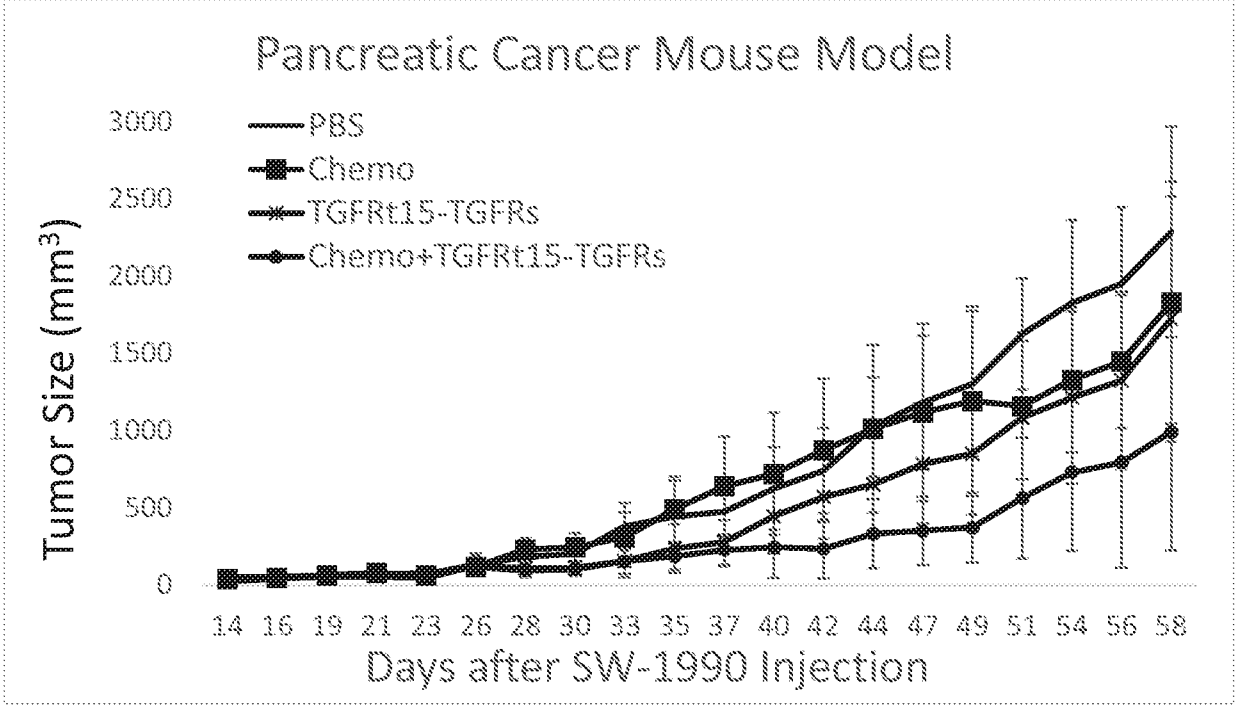


Figure 89

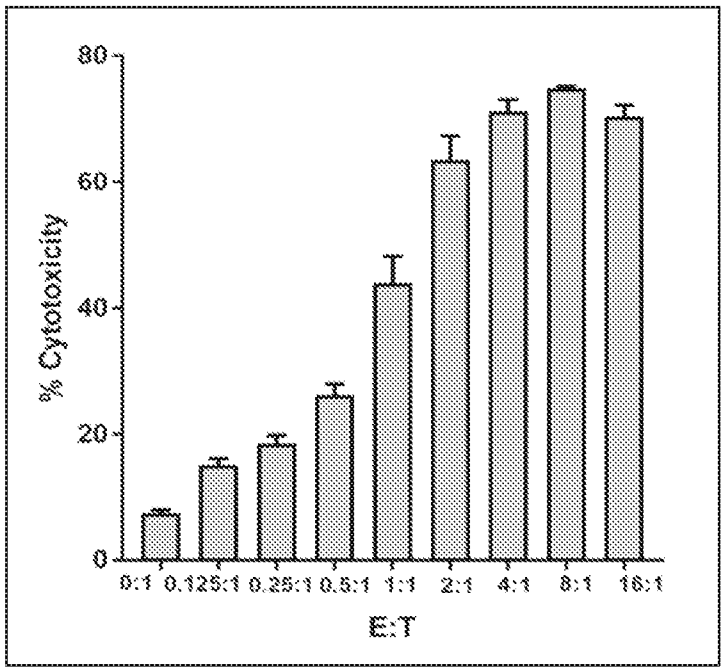


Figure 90

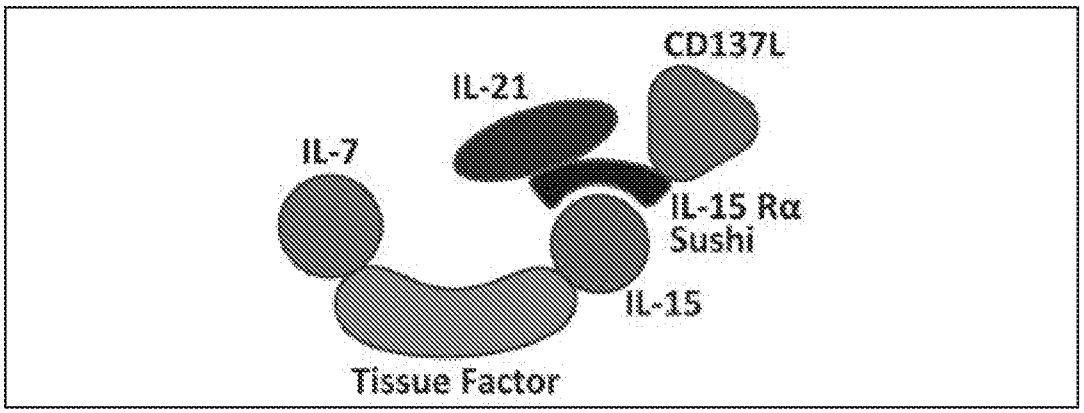


Figure 91

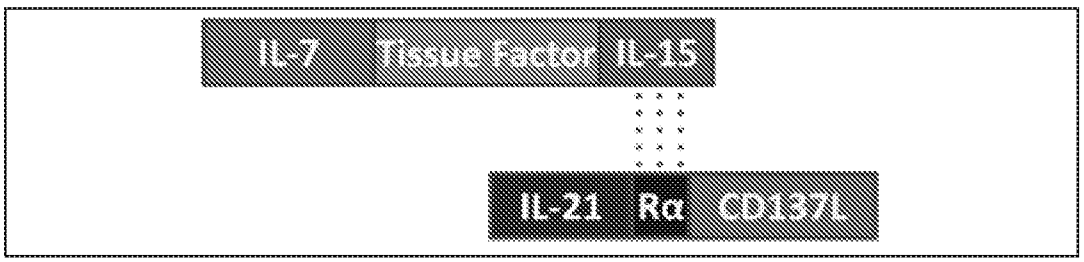


Figure 92

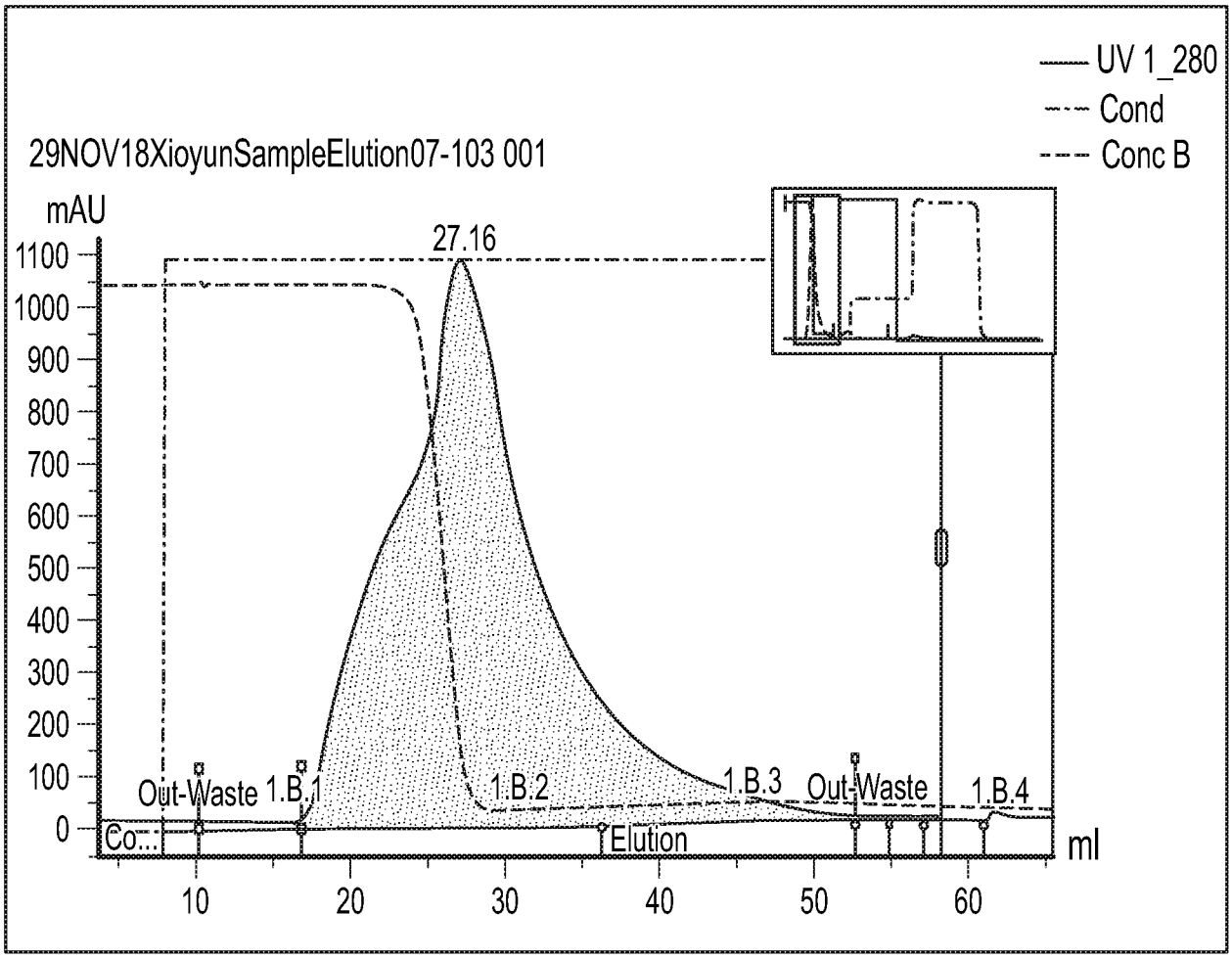

UV 1_280
Cond
Conc B
29NOV18XioyunSampleElution07-103 001
mAU
1100
1000
900
800
700
600
500
400
300
200
100
0
27.16
Out-Waste
1.B.1
1.B.2
1.B.3
Out-Waste
1.B.4
Co...
Elution
ml
10
20
30
40
50
60

Figure 93

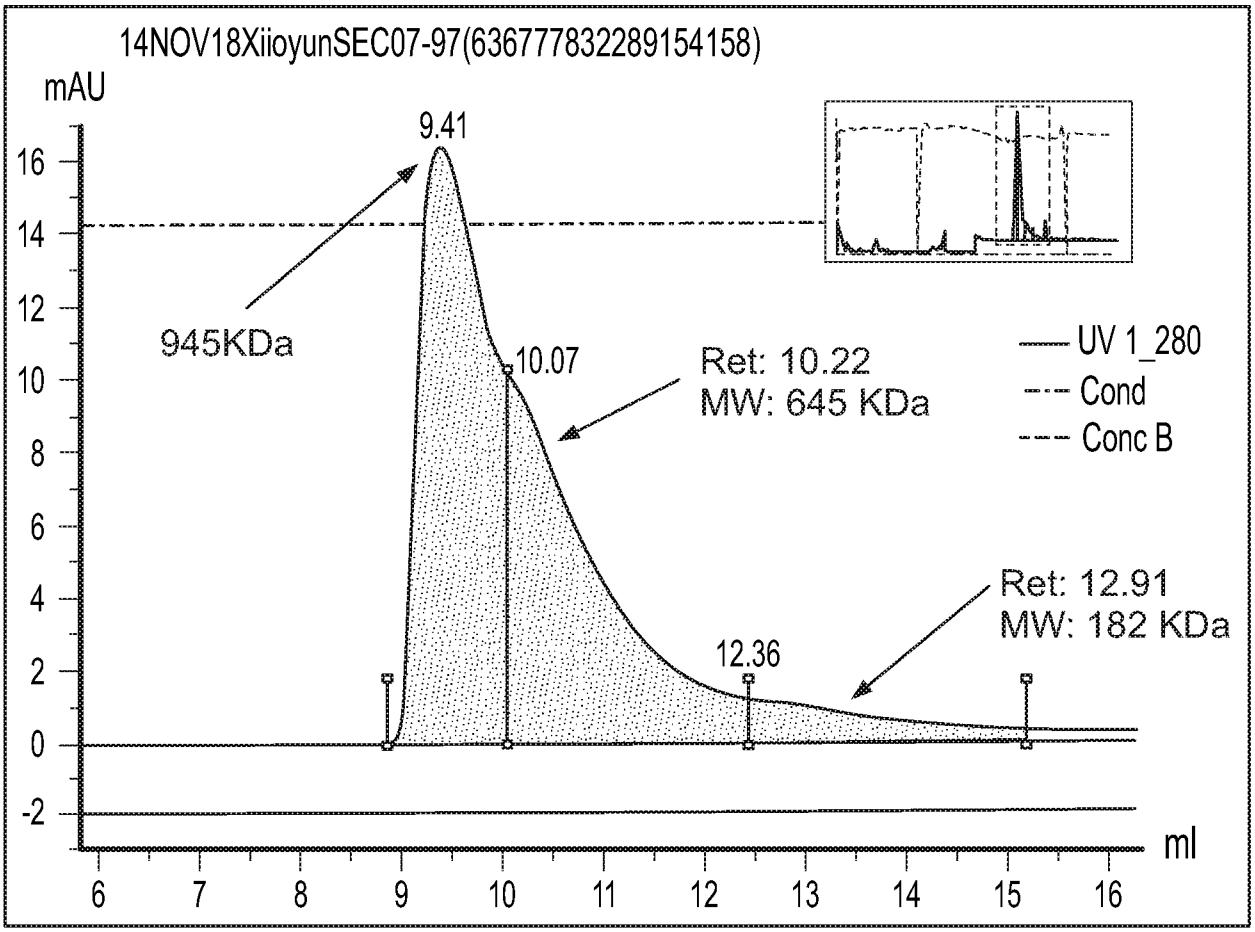

14NOV18XiioyunSEC07-97(636777832289154158)
mAU
9.41
945KDa
10.07
Ret: 10.22
MW: 645 KDa
UV 1_280
Cond
Conc B
Ret: 12.91
MW: 182 KDa
12.36
ml
16
14
12
10
8
6
4
2
0
-2
6
7
8
9
10
11
12
13
14
15
16

Figure 94

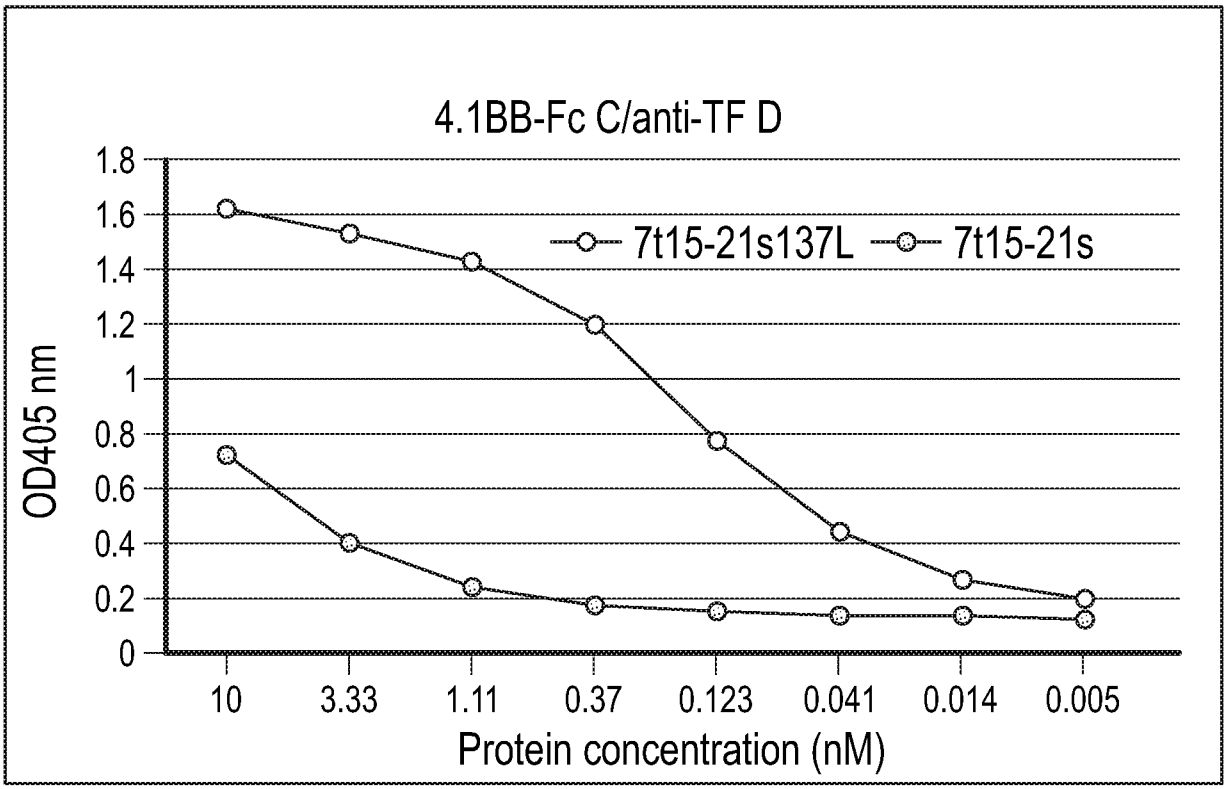

4.1BB-Fc C/anti-TF D
OD405 nm
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
7t15-21s137L
7t15-21s
10
3.33
1.11
0.37
0.123
0.041
0.014
0.005
Protein concentration (nM)

Figure 95

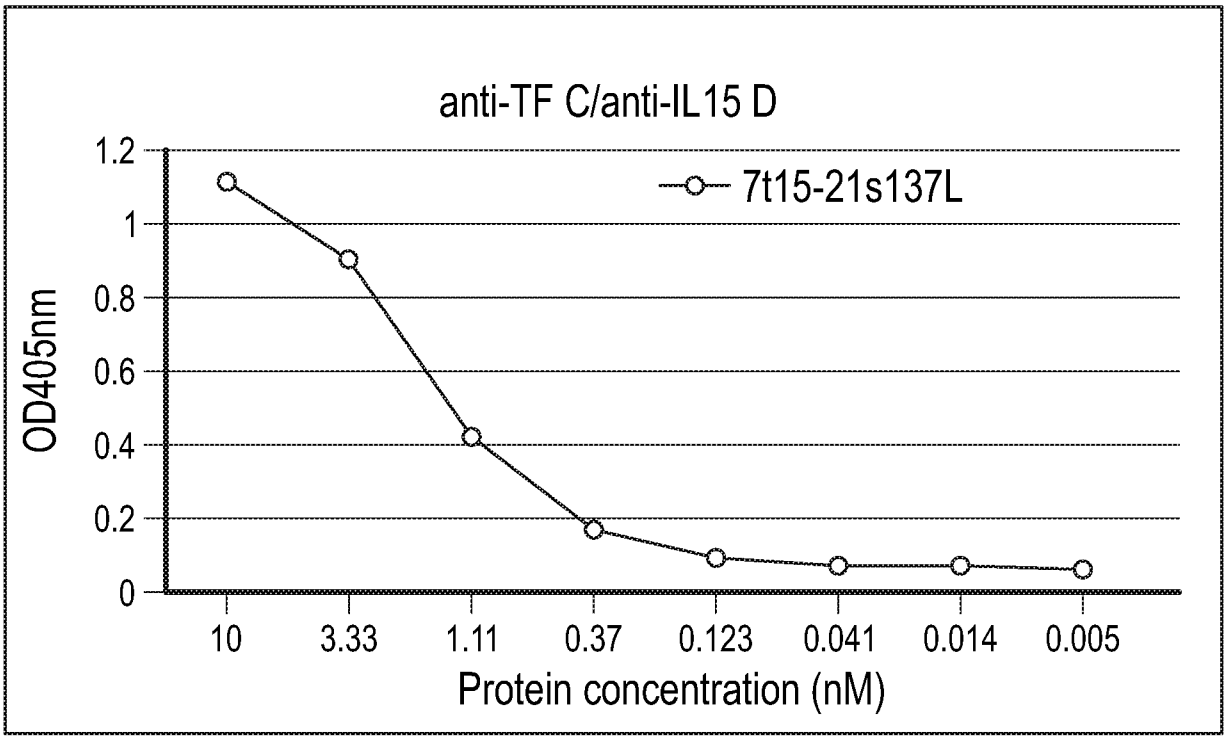


Figure 96A

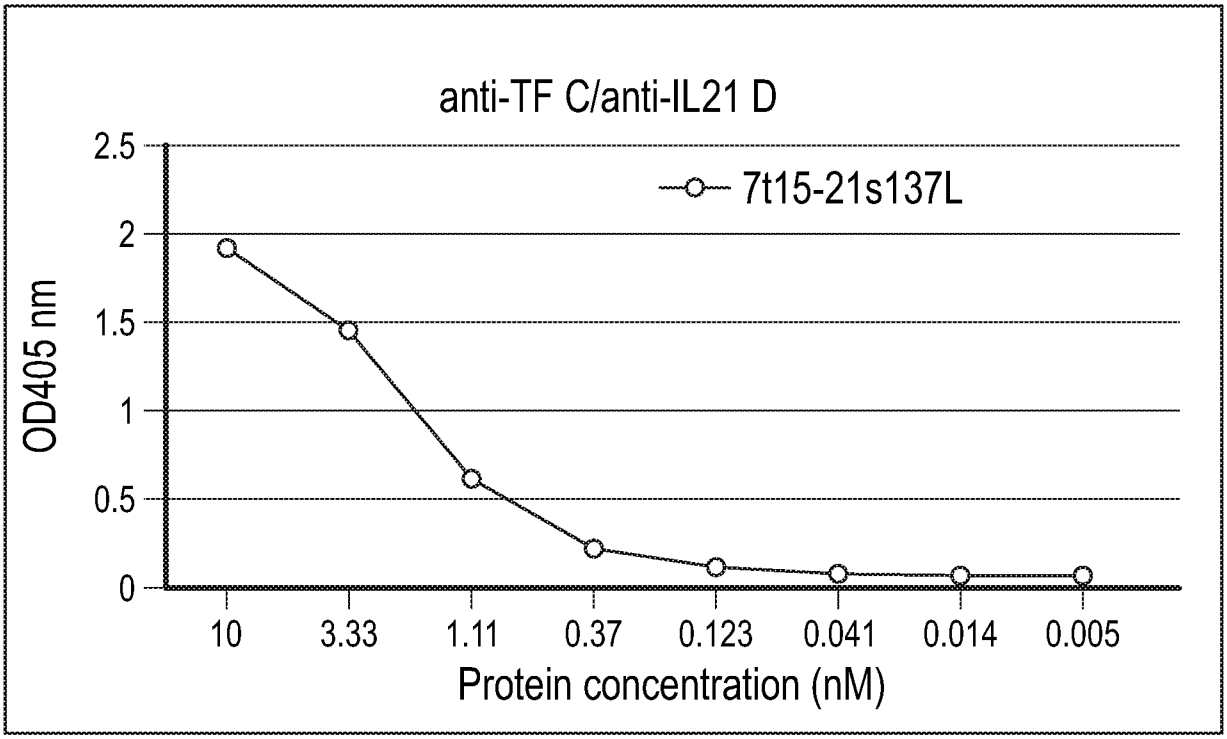


Figure 96B

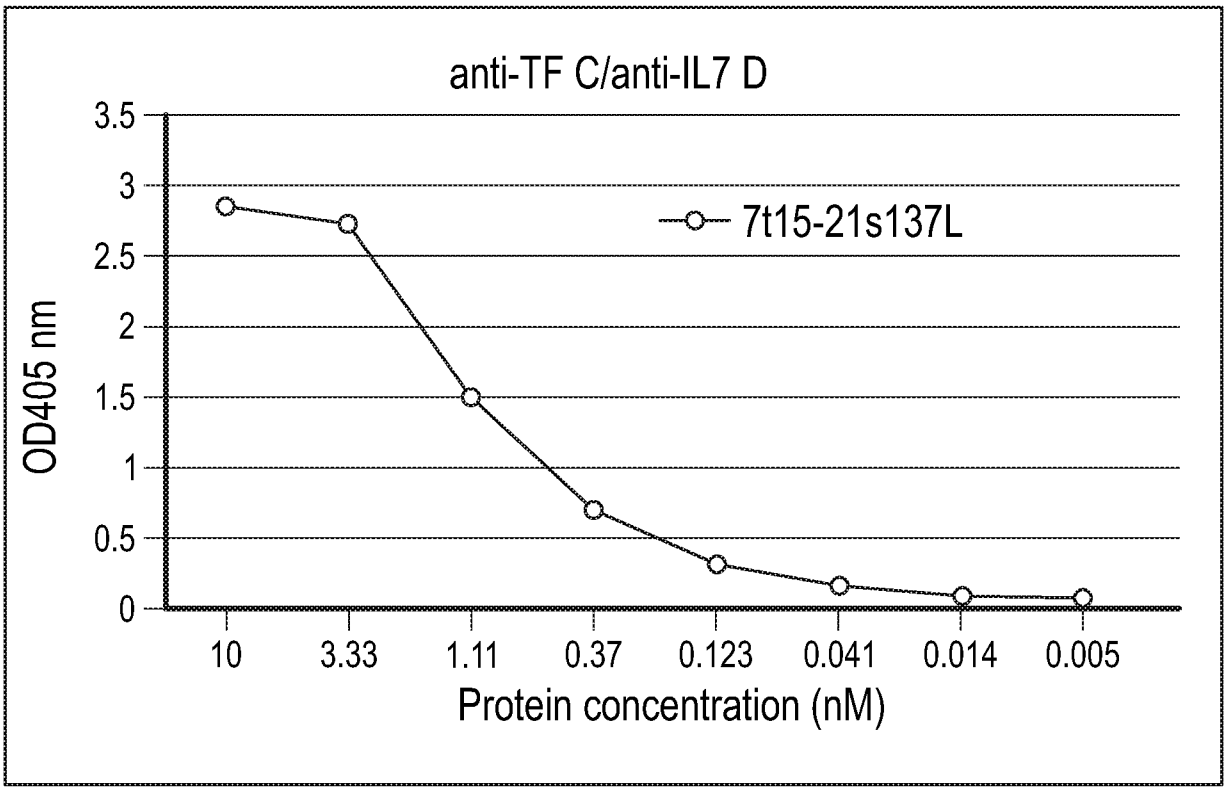

anti-TF C/anti-IL7 D
OD405 nm
3.5
3
2.5
2
1.5
1
0.5
0
7t15-21s137L
10
3.33
1.11
0.37
0.123
0.041
0.014
0.005
Protein concentration (nM)

Figure 96C

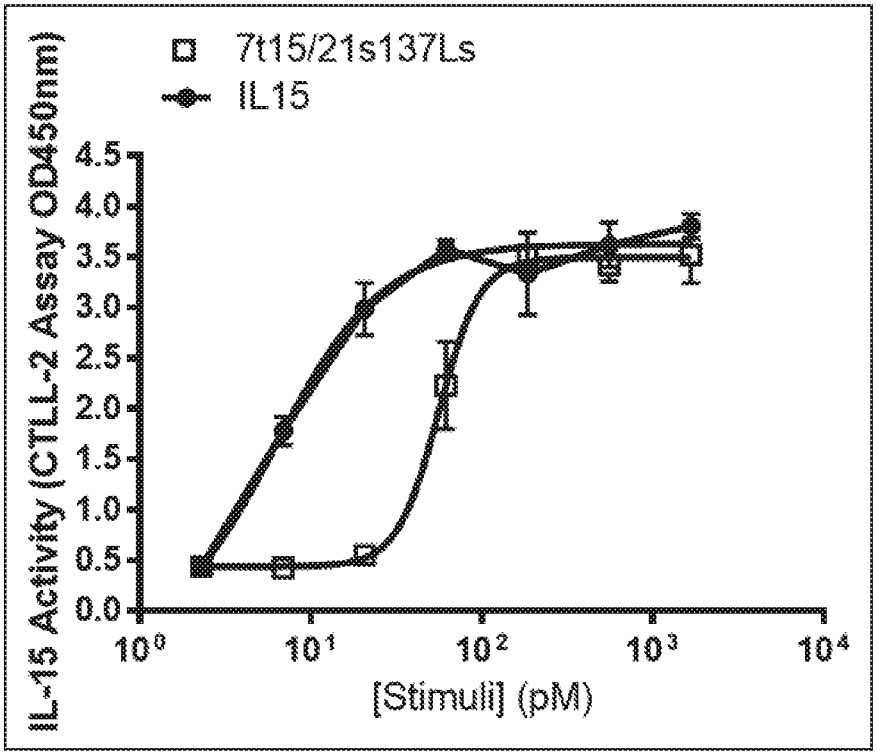


Figure 97

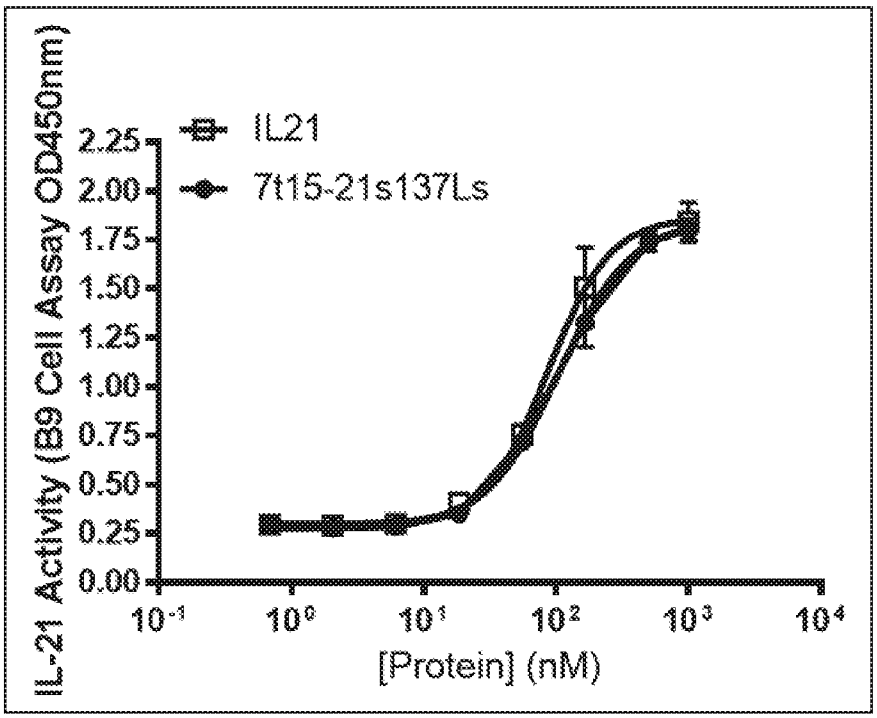


Figure 98

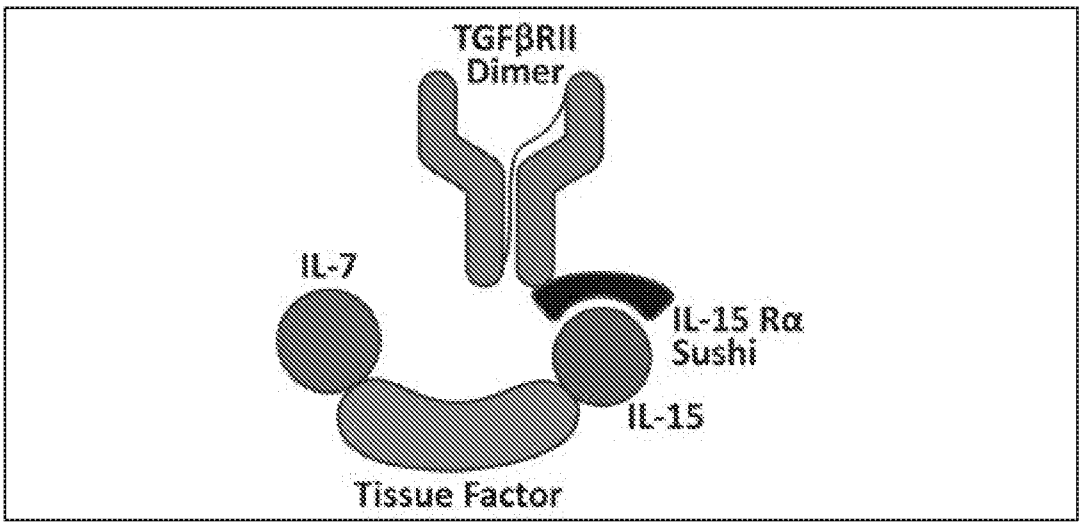


Figure 99

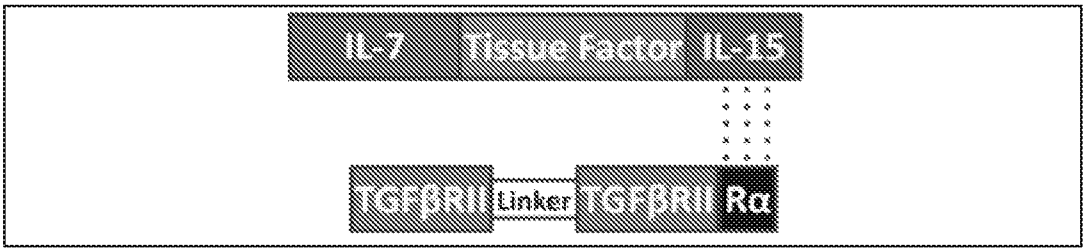


Figure 100

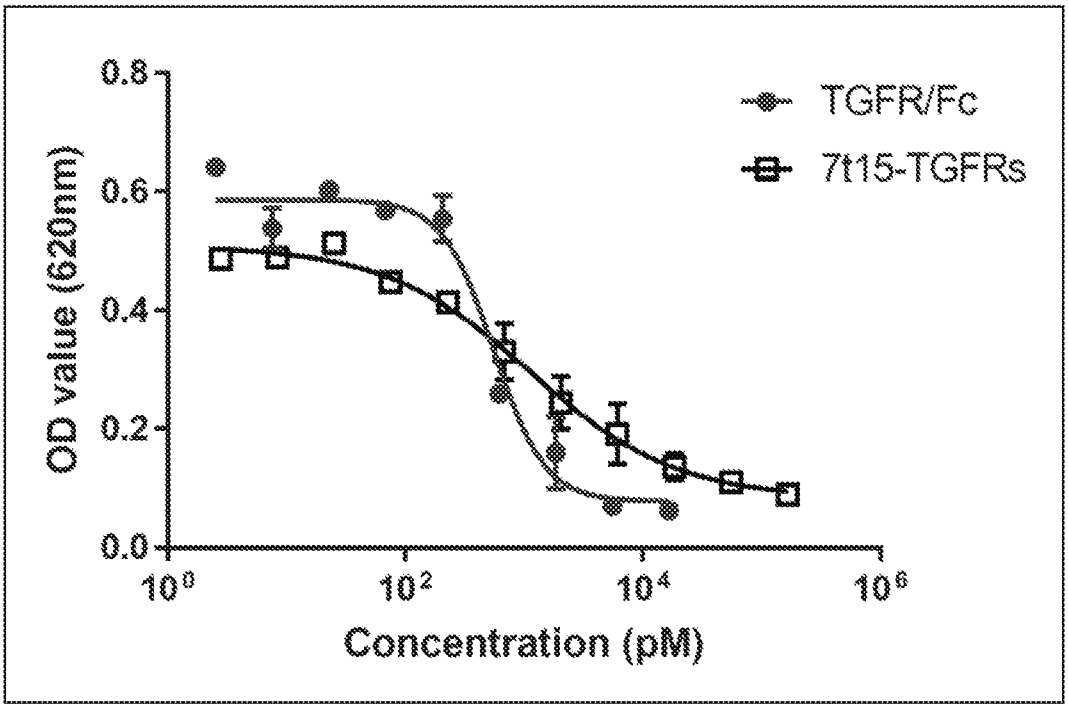

0.8
0.6
0.4
0.2
0.0
OD value (620nm)
10^0
10^2
10^4
10^6
Concentration (pM)
TGFR/Fc
7t15-TGFRs

Figure 101

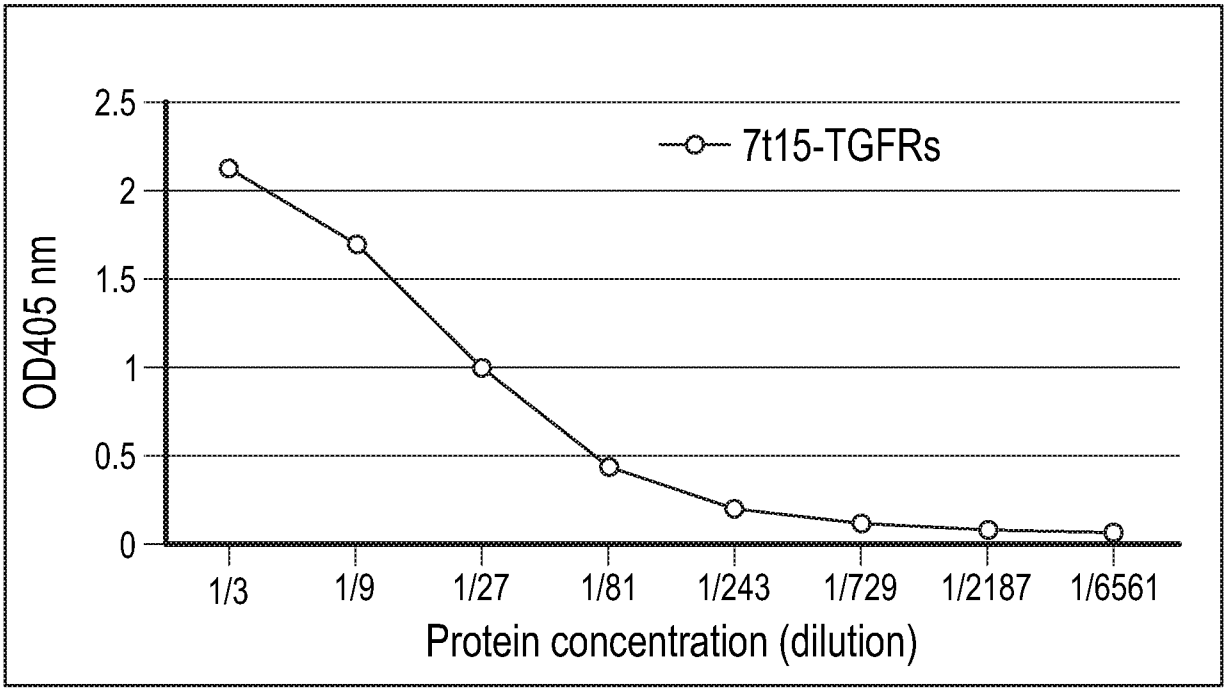


Figure 102A

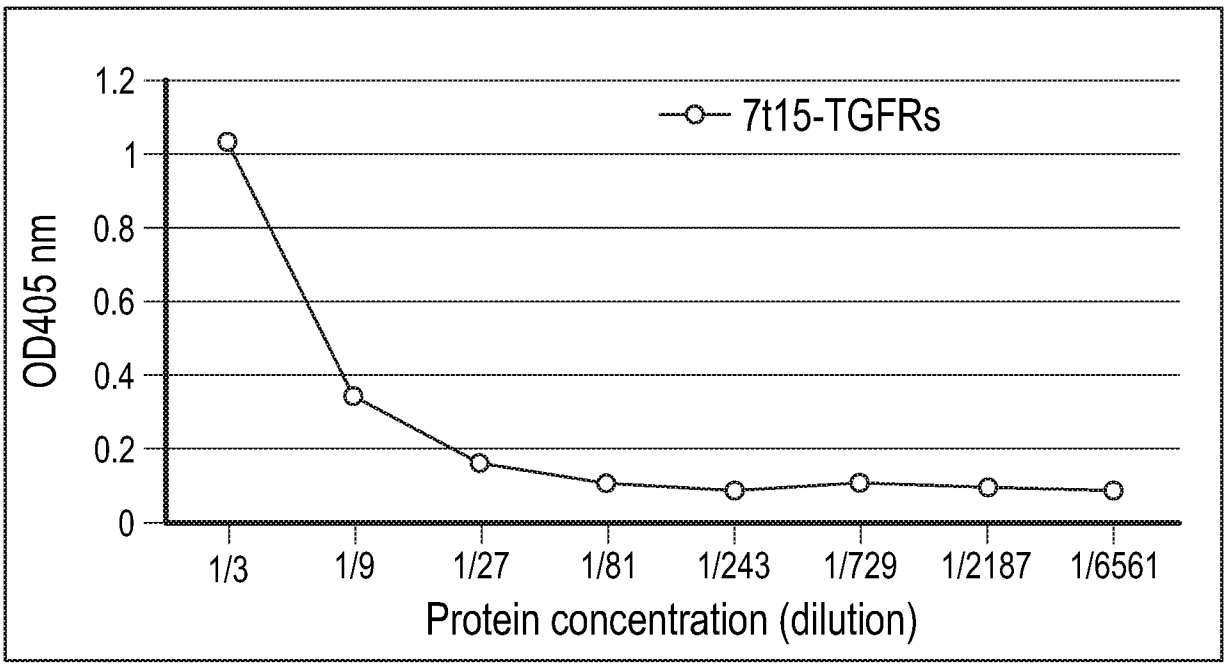


Figure 102B

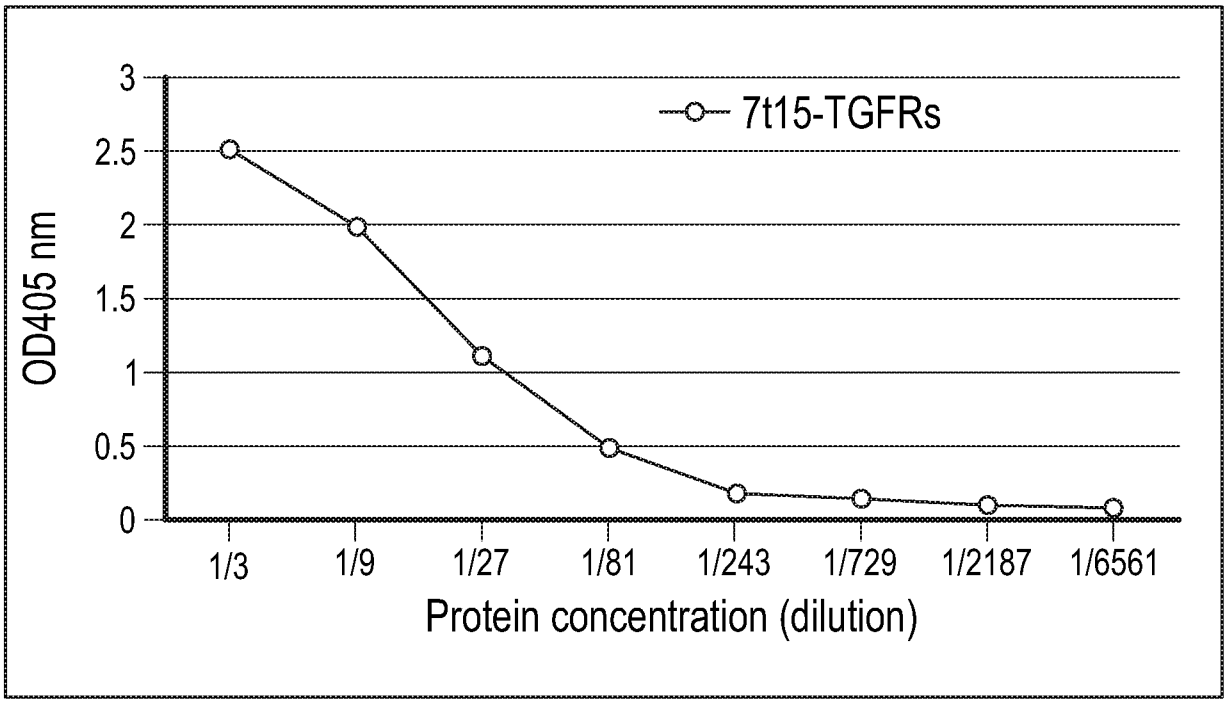

3
2.5
2
1.5
1
0.5
0
OD405 nm
7t15-TGFRs
1/3
1/9
1/27
1/81
1/243
1/729
1/2187
1/6561
Protein concentration (dilution)

Figure 102C

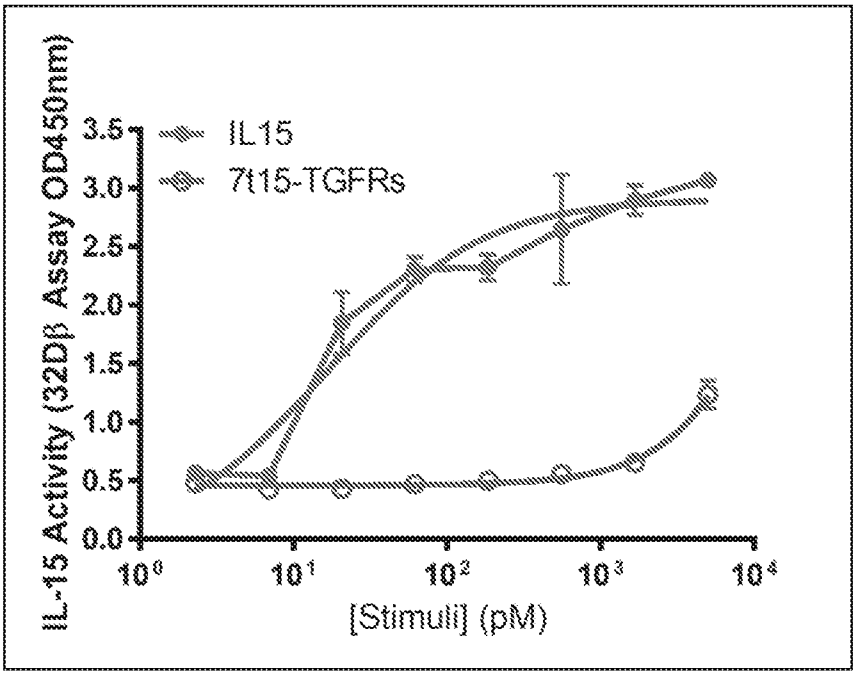


Figure 103

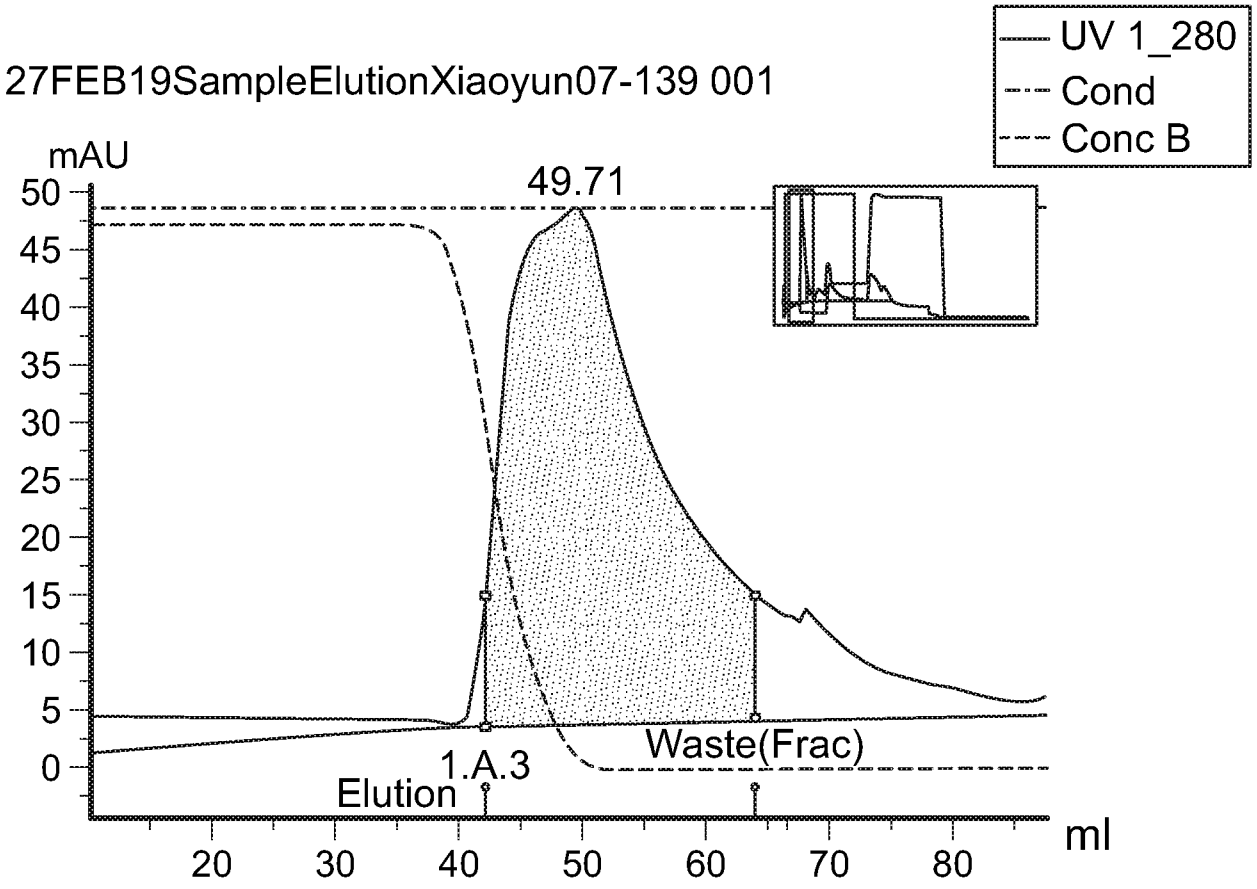


Figure 104

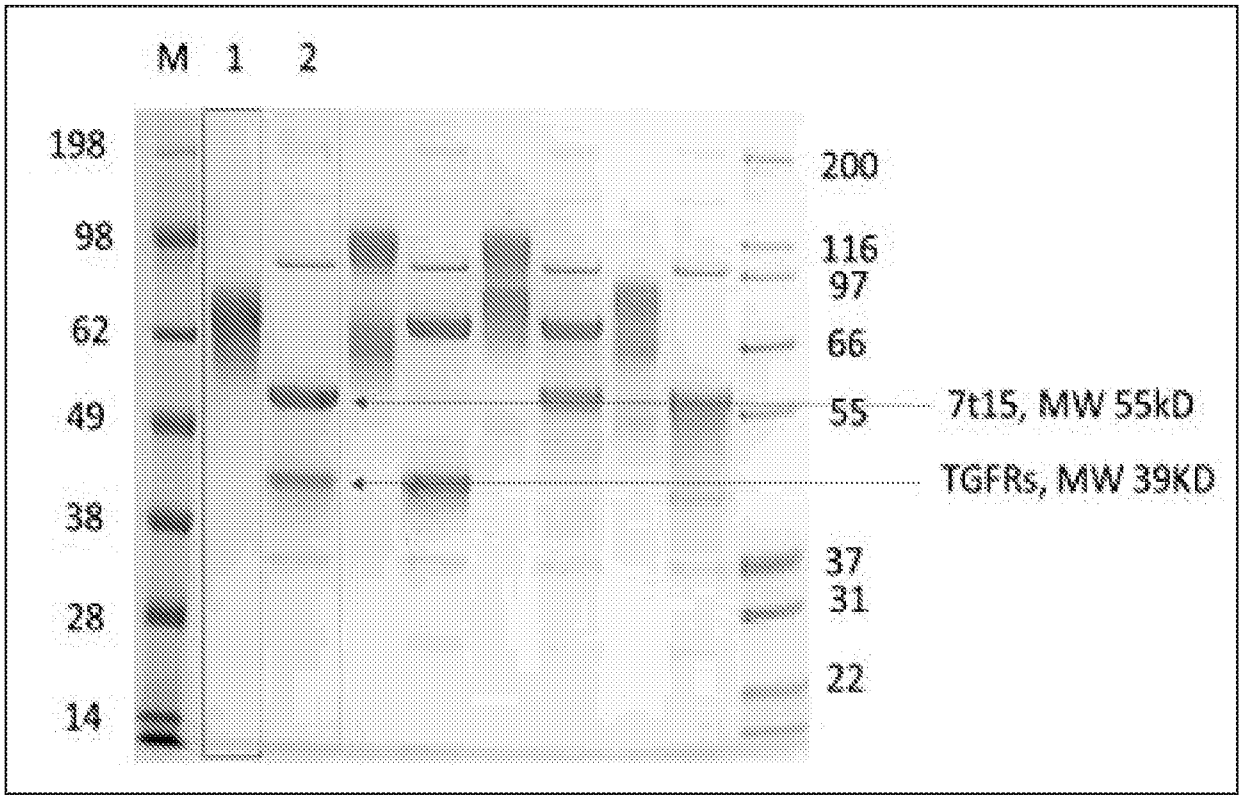


Figure 105

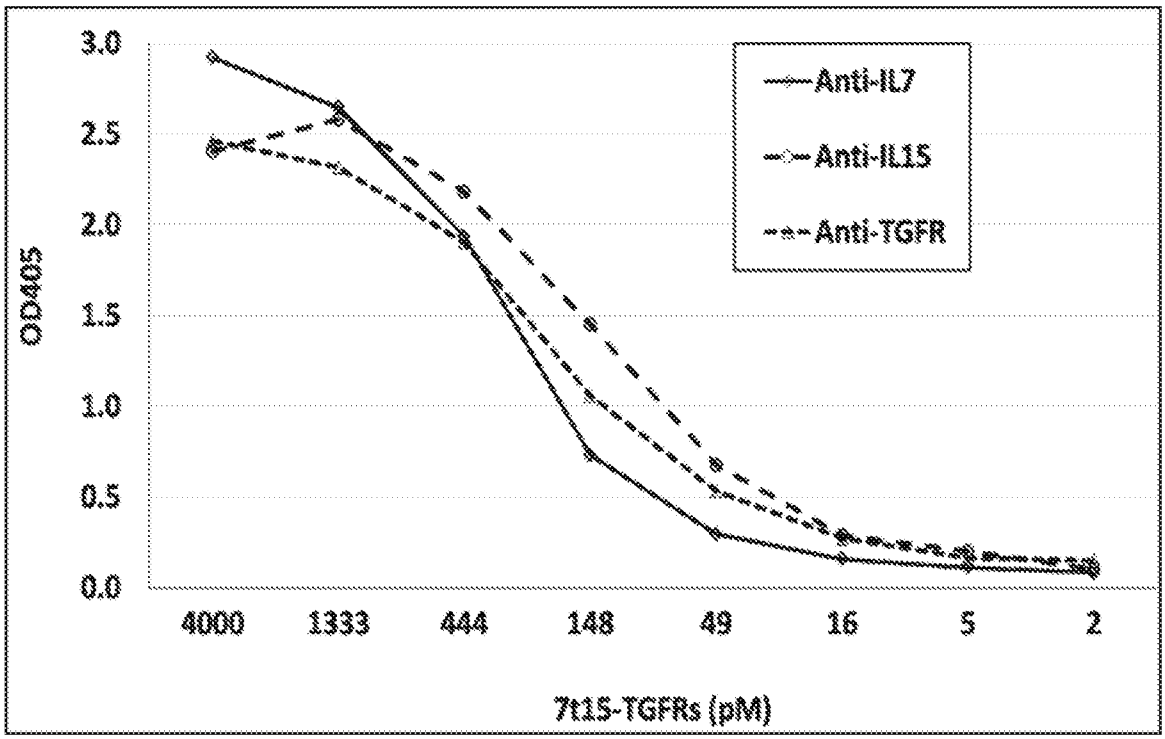


Figure 106

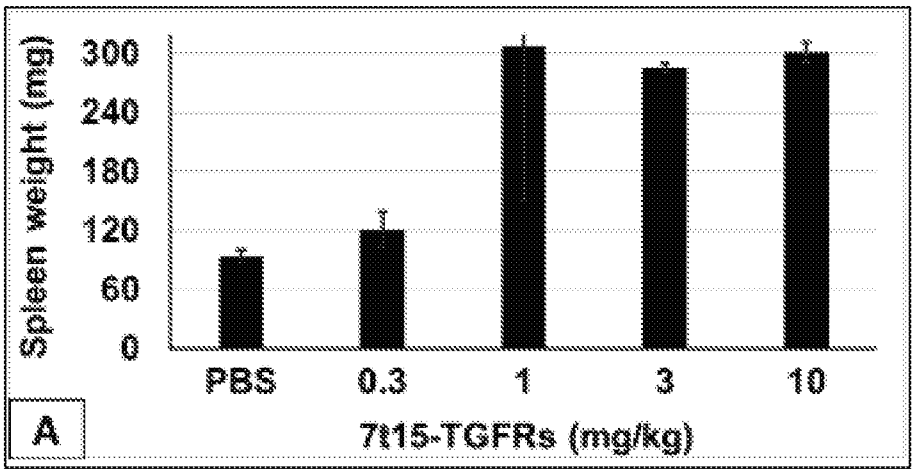


Figure 107A

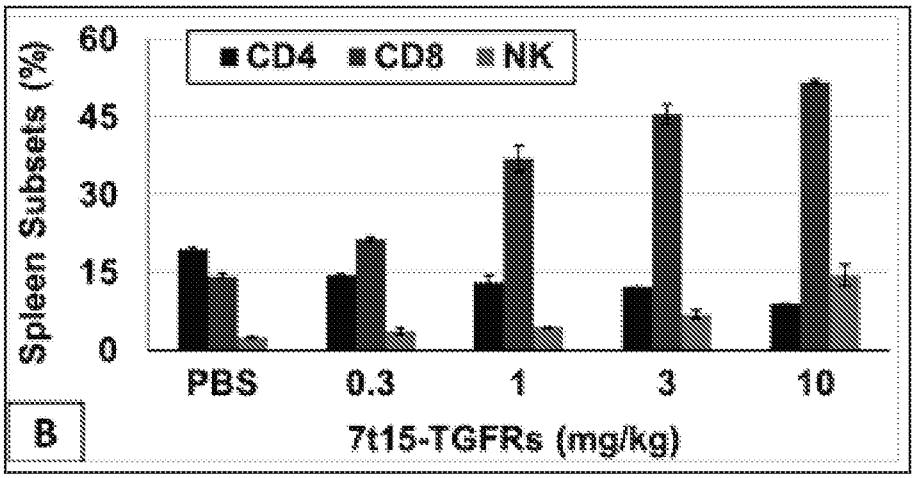


Figure 107B

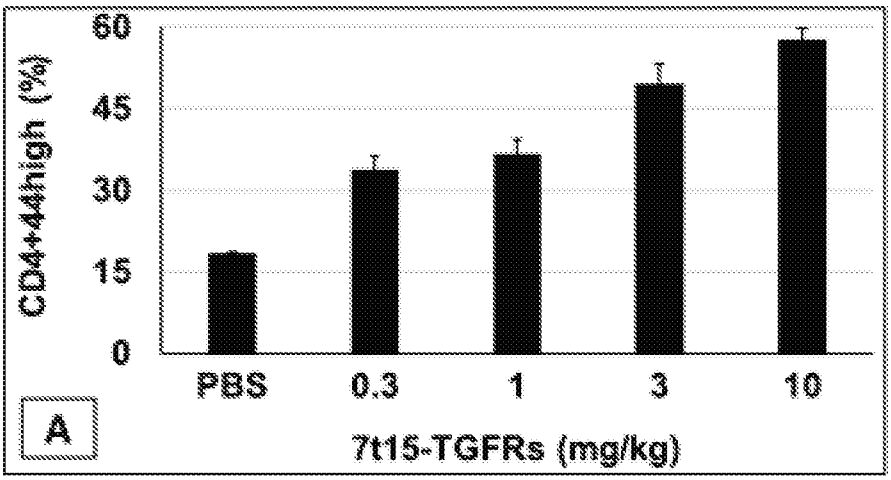


Figure 108A

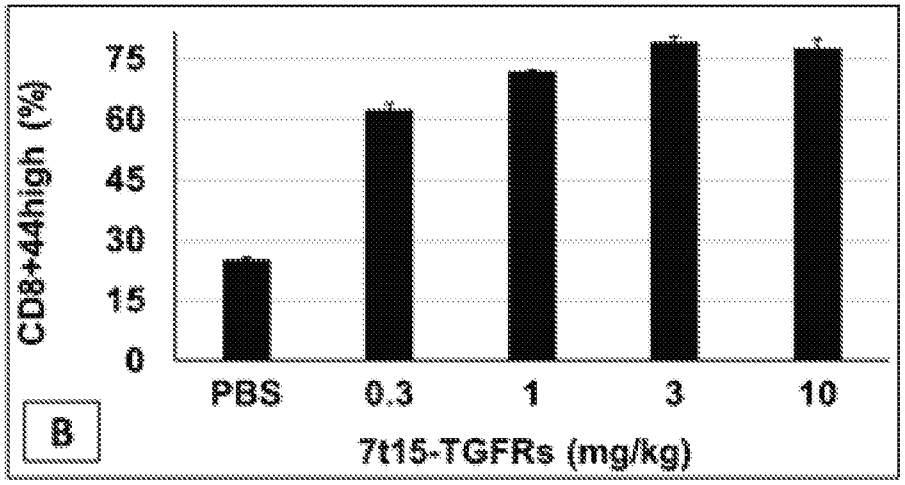


Figure 108B

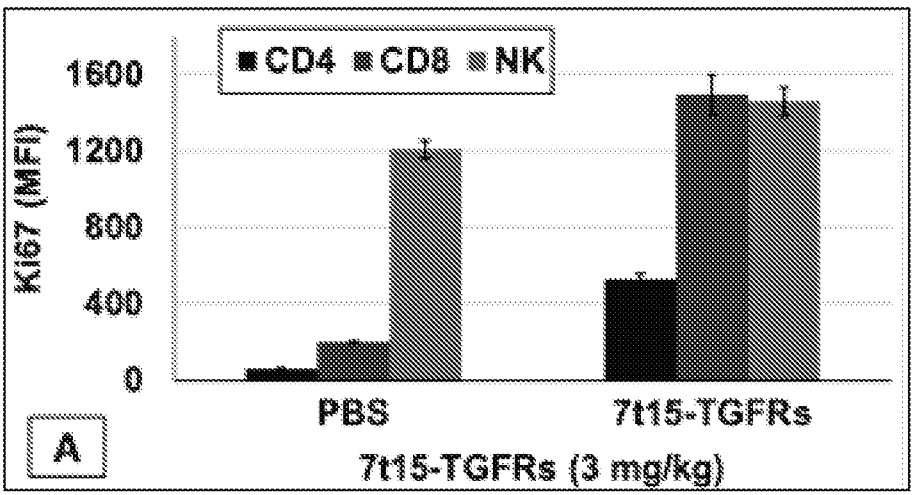


Figure 109A

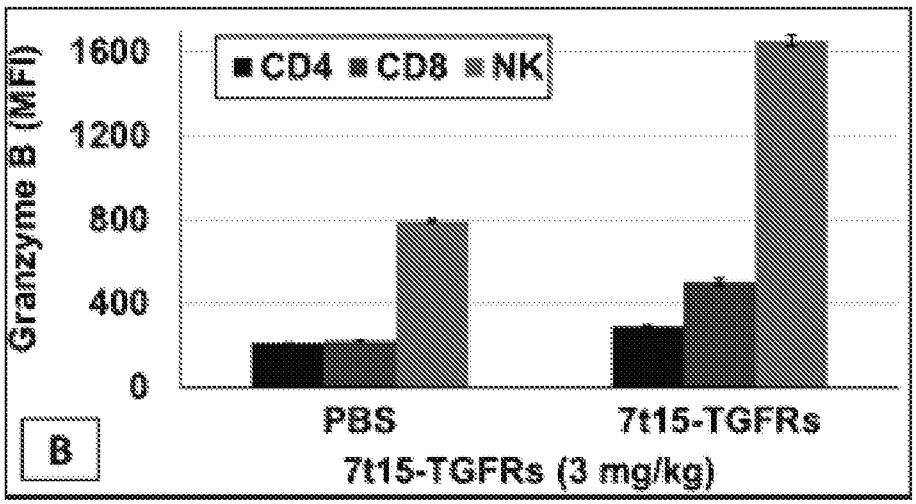


Figure 109B

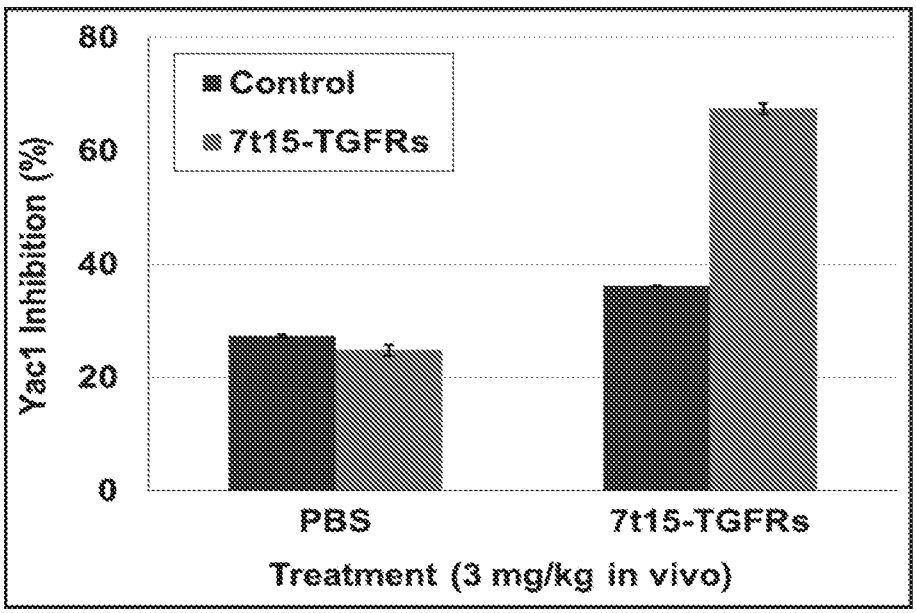


Figure 110

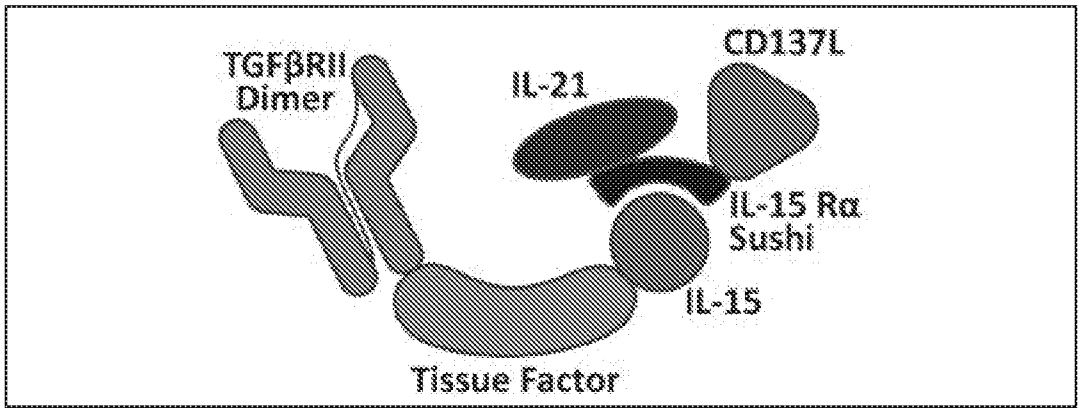


Figure 111

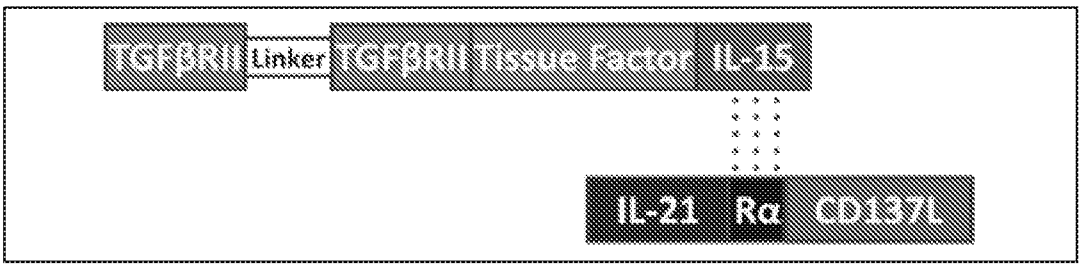


Figure 112

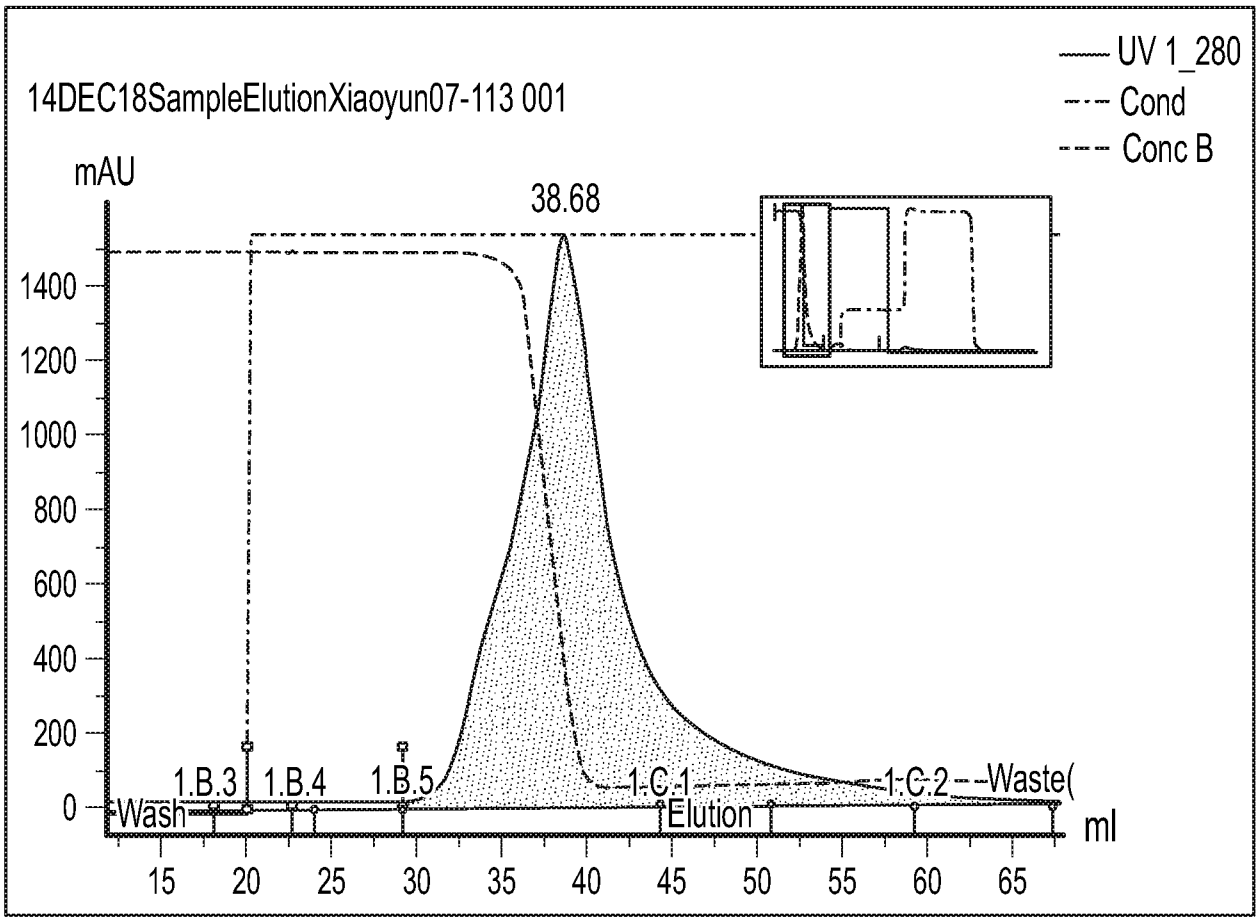

14DEC18SampleElutionXiaoyun07-113 001
UV 1_280
Cond
Conc B
mAU
38.68
1400
1200
1000
800
600
400
200
0
1.B.3
1.B.4
1.B.5
1.C.1
1.C.2
Waste(
Wash
Elution
ml
15
20
25
30
35
40
45
50
55
60
65

Figure 113

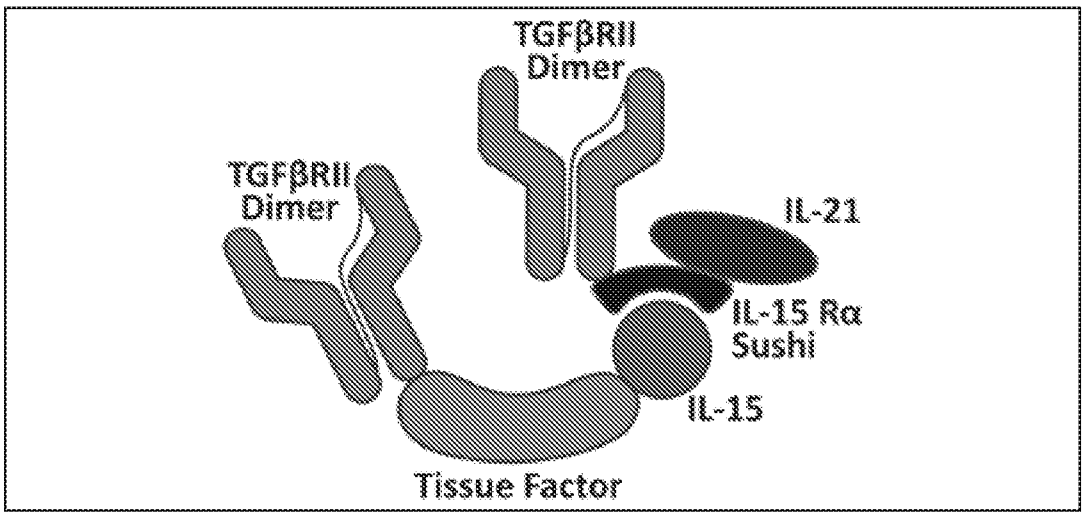


Figure 114

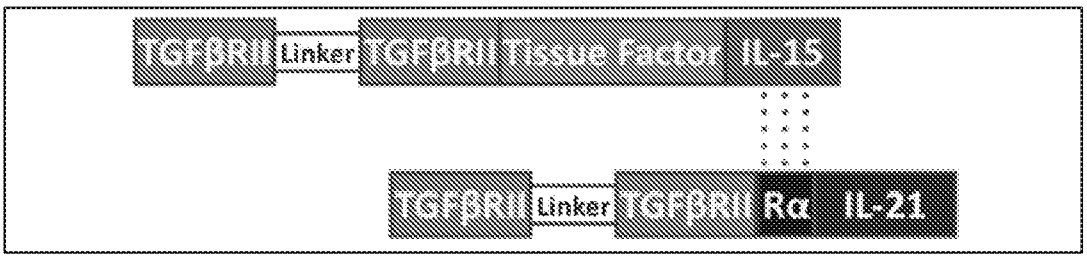


Figure 115

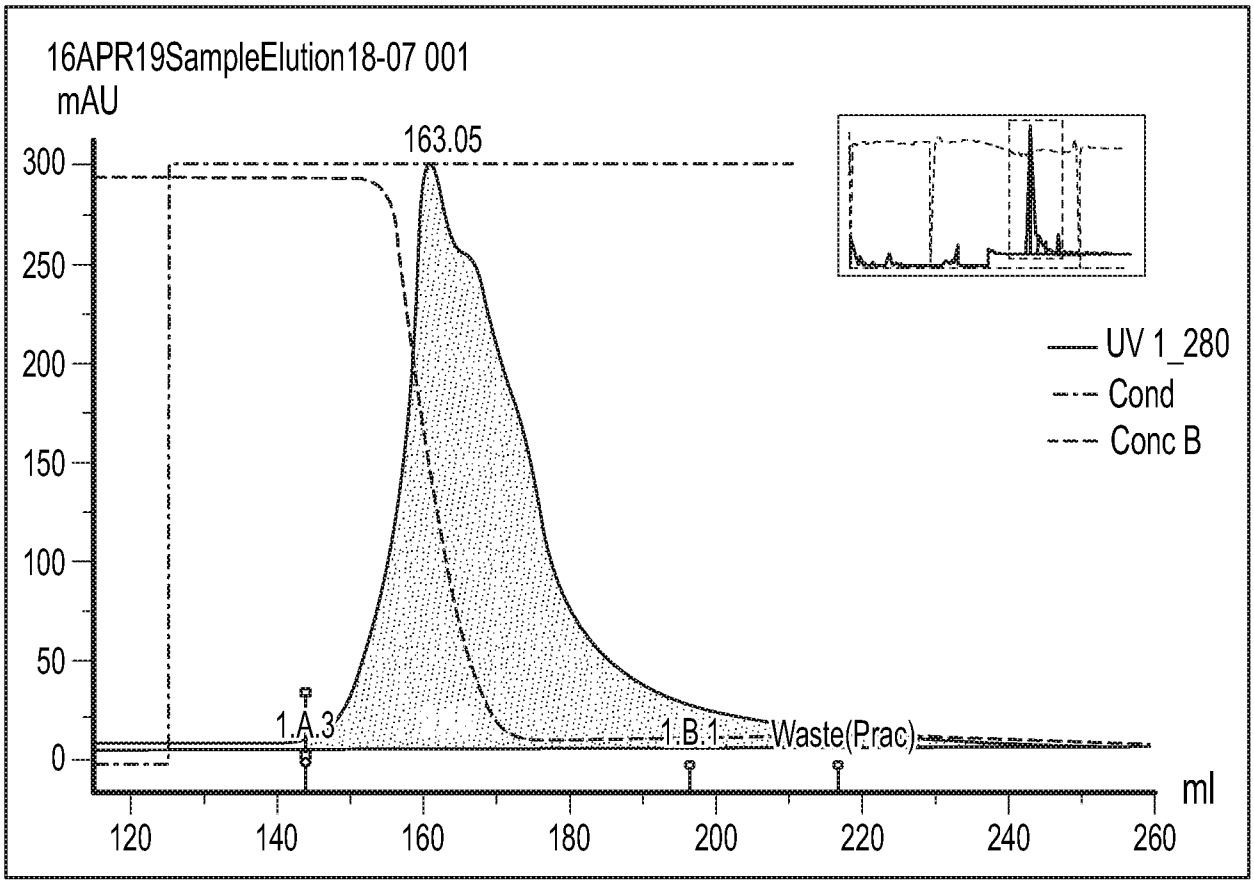


Figure 116

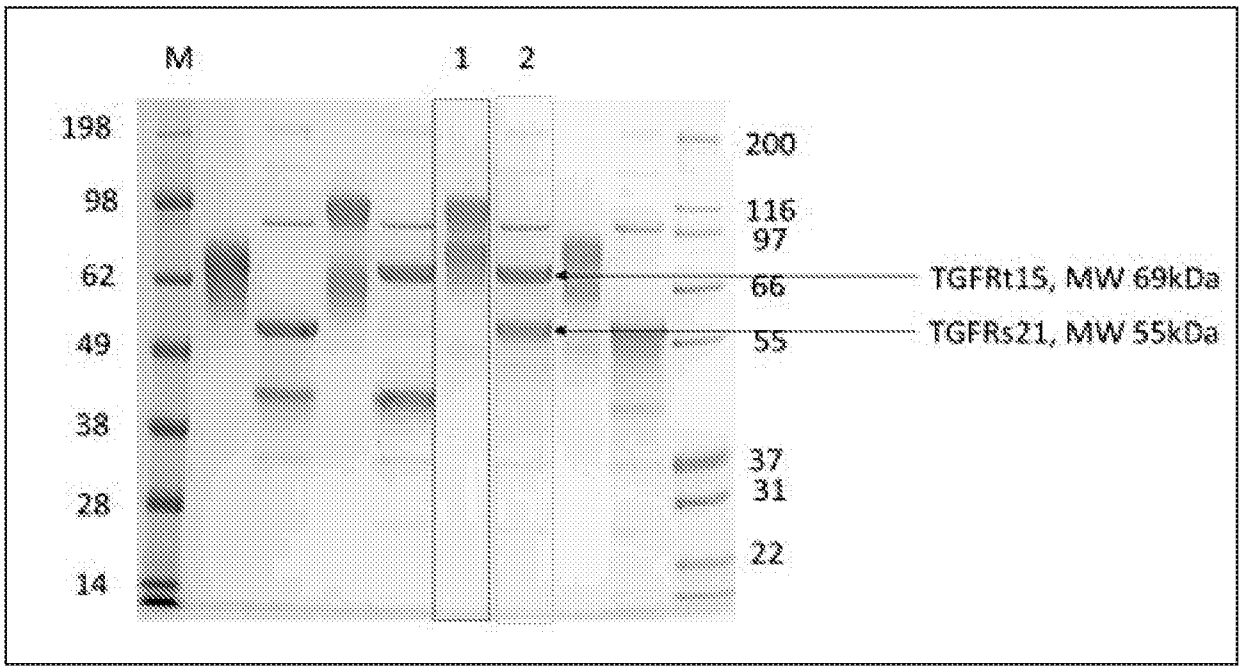


Figure 117

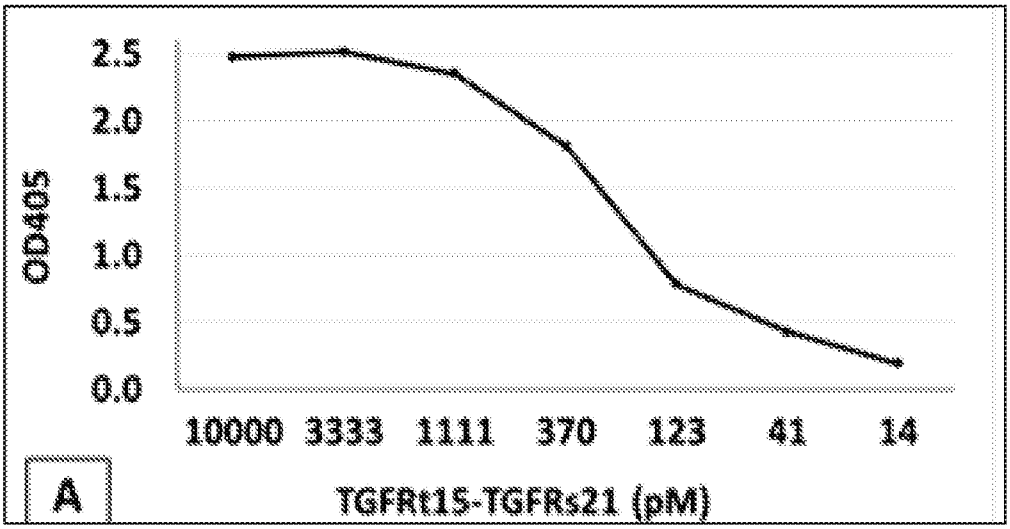


Figure 118A

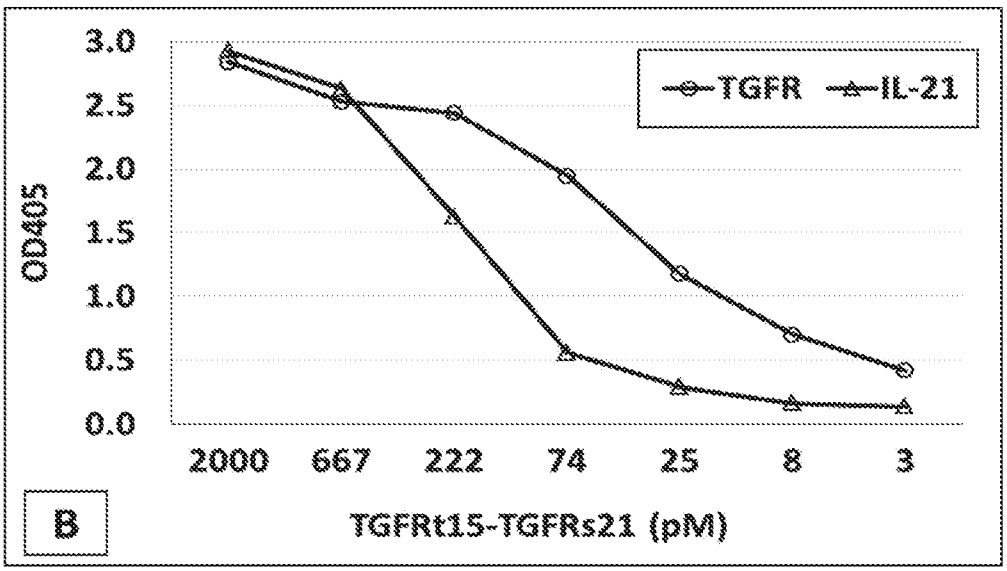


Figure 118B

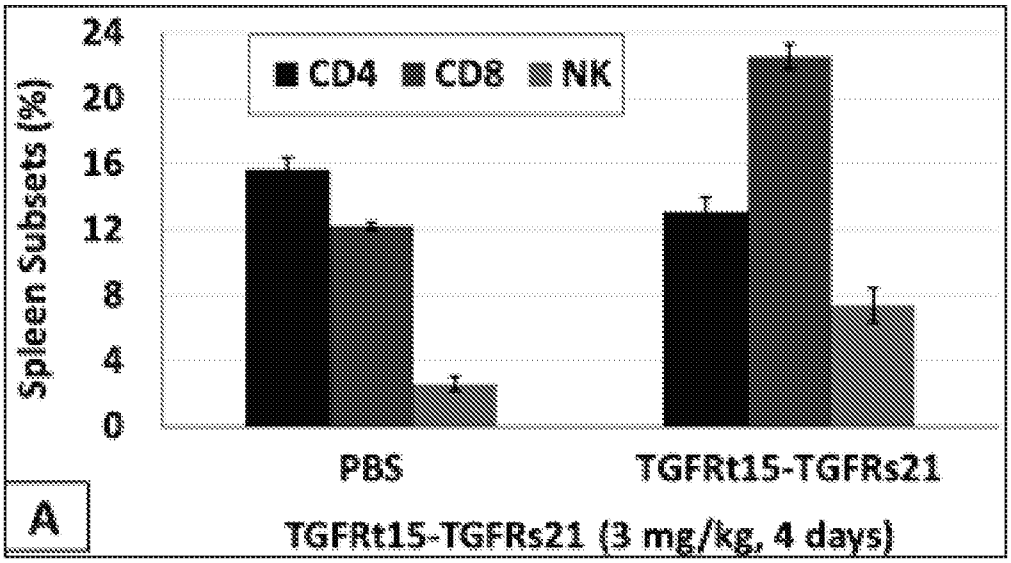


Figure 119A

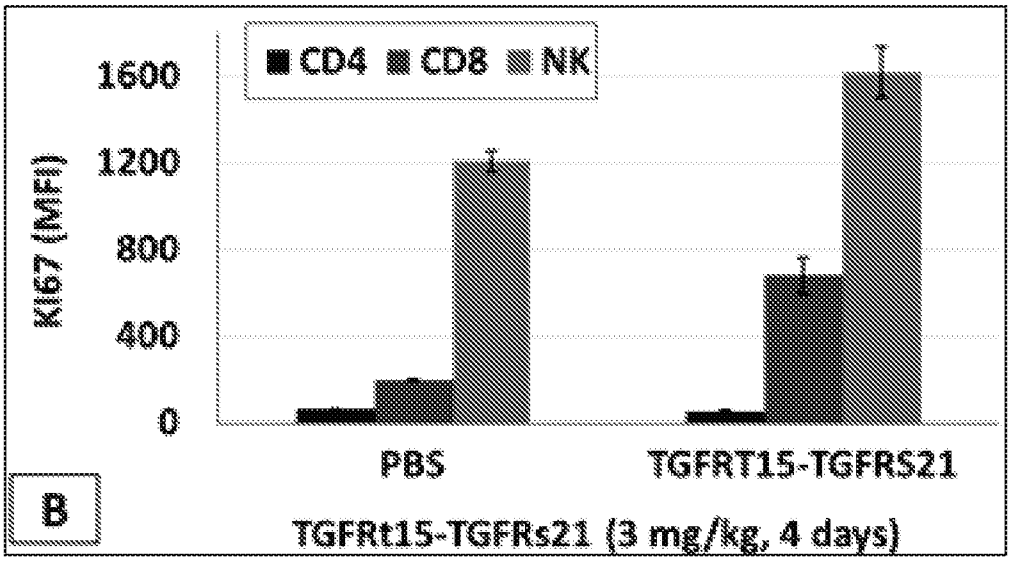


Figure 119B

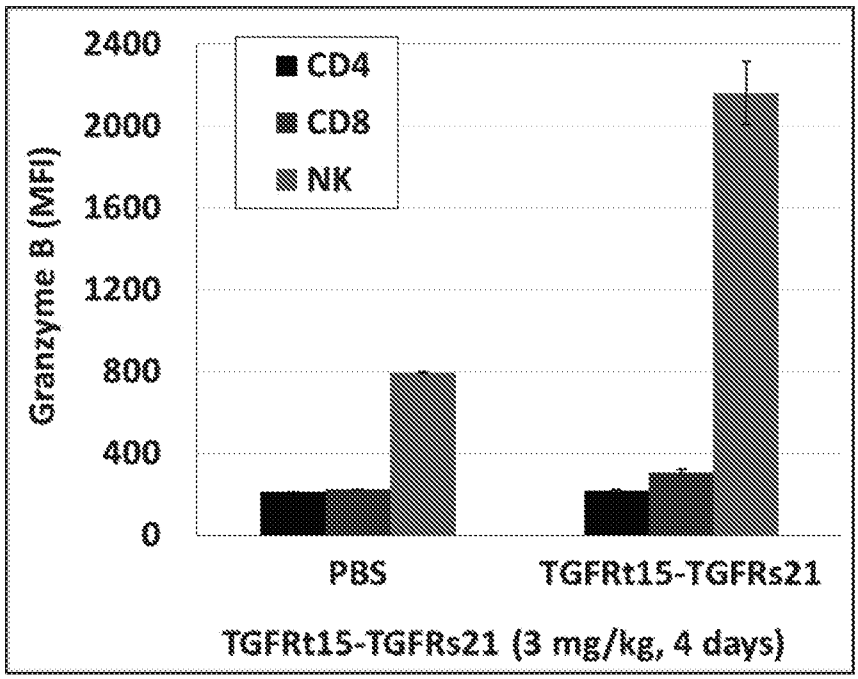


Figure 120

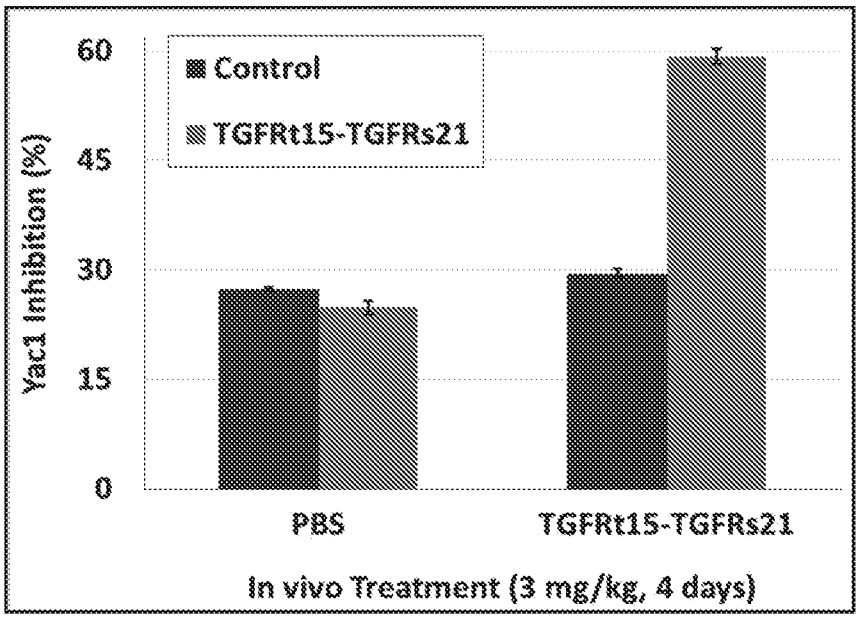


Figure 121

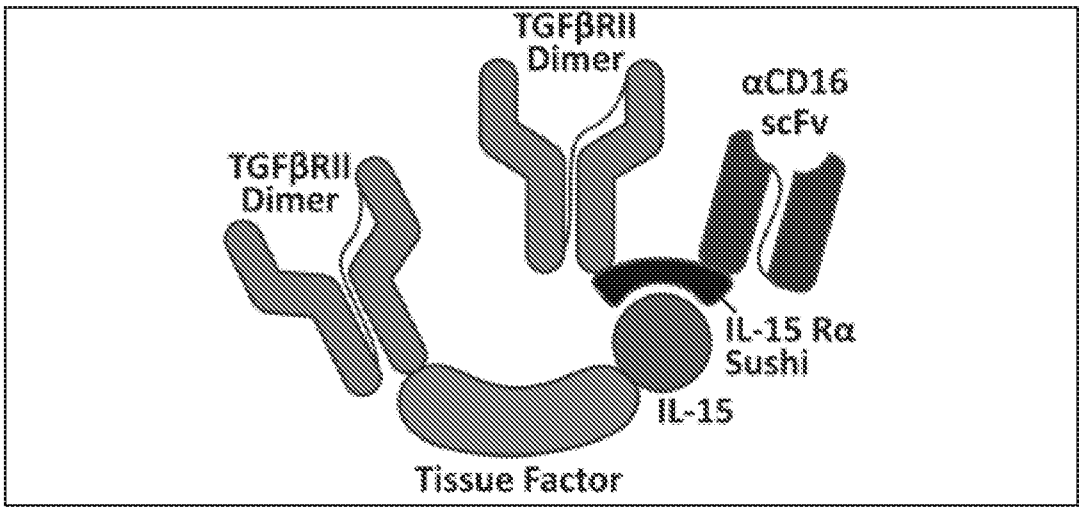


Figure 122

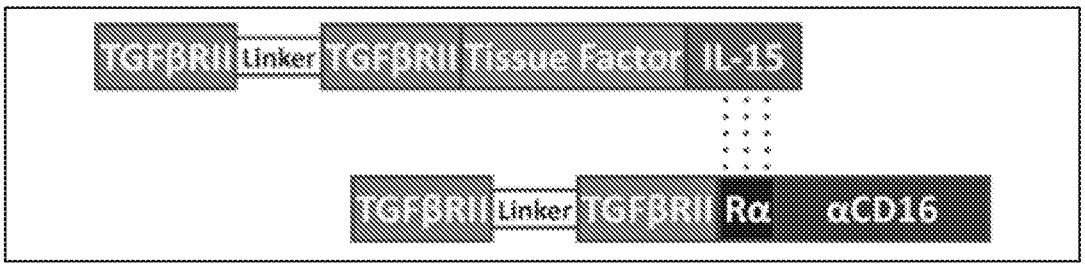


Figure 123

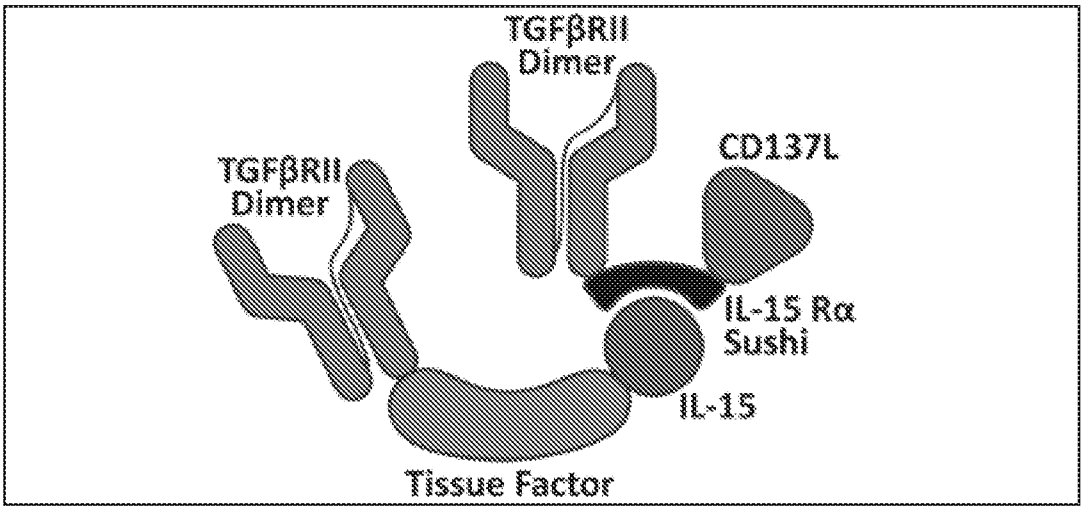


Figure 124

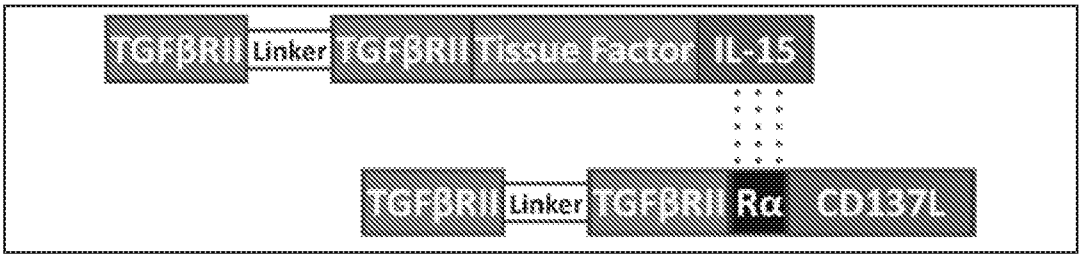


Figure 125

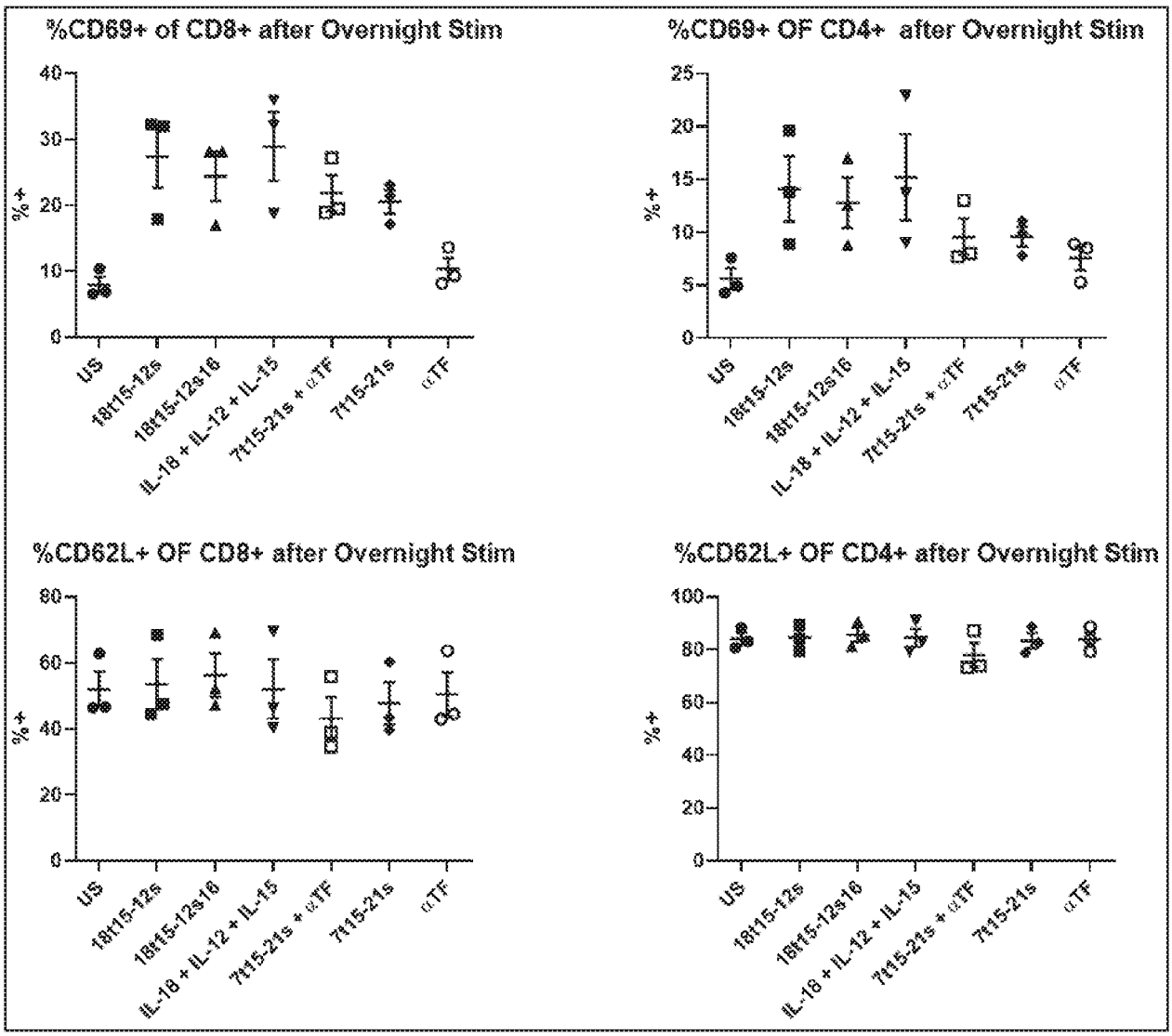

%CD69+ of CD8+ after Overnight Stim
%CD69+ OF CD4+ after Overnight Stim
%CD62L+ OF CD8+ after Overnight Stim
%CD62L+ OF CD4+ after Overnight Stim
%+
US
18t15-12s
18t15-12s16
IL-18 + IL-12 + IL-15
7t15-21s + αTF
7t15-21s
αTF

Figure 126

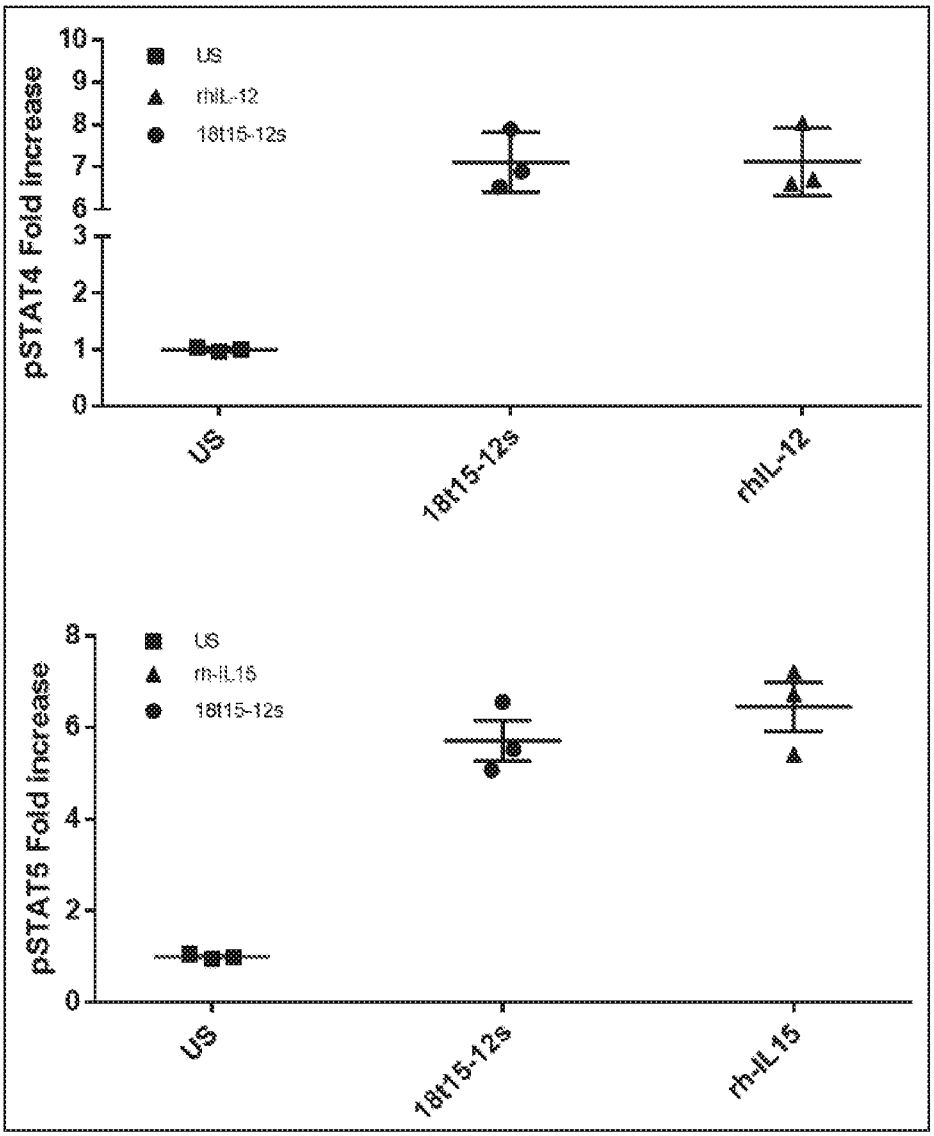

pSTAT4 Fold increase
US
rhIL-12
18t15-12s
US
18t15-12s
rhIL-12
pSTAT5 Fold increase
US
rh-IL15
18t15-12s
US
18t15-12s
rh-IL15

Figure 127

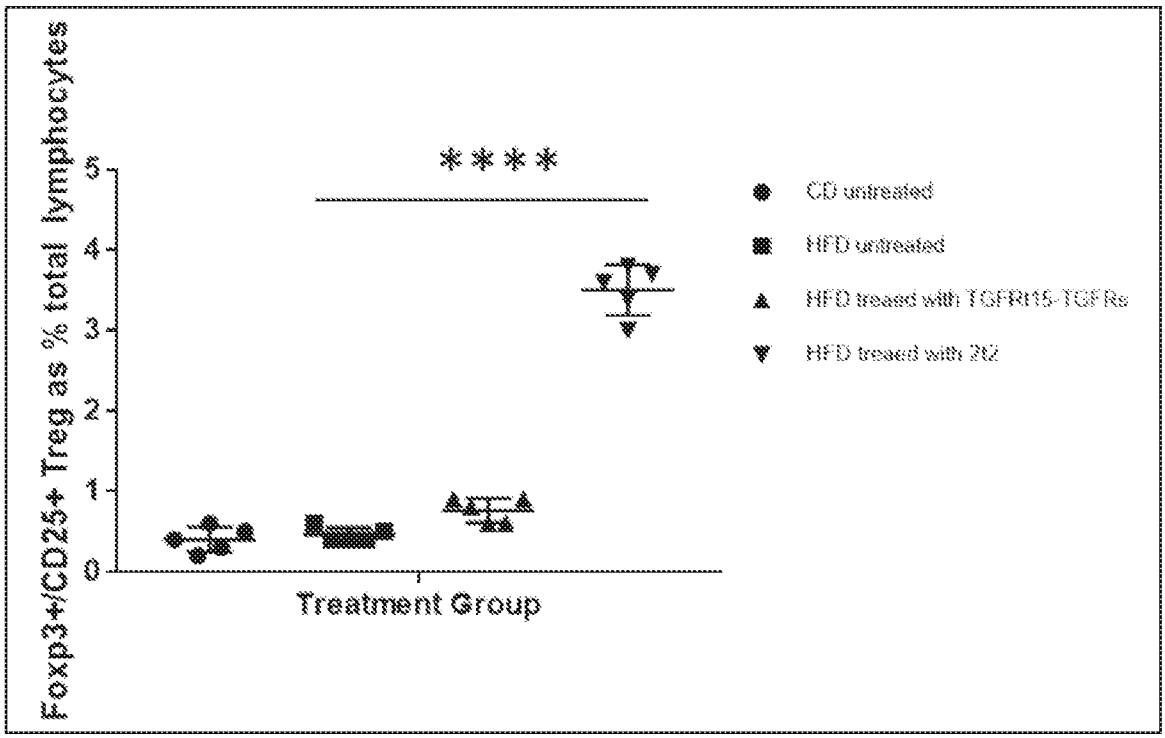


Figure 128A

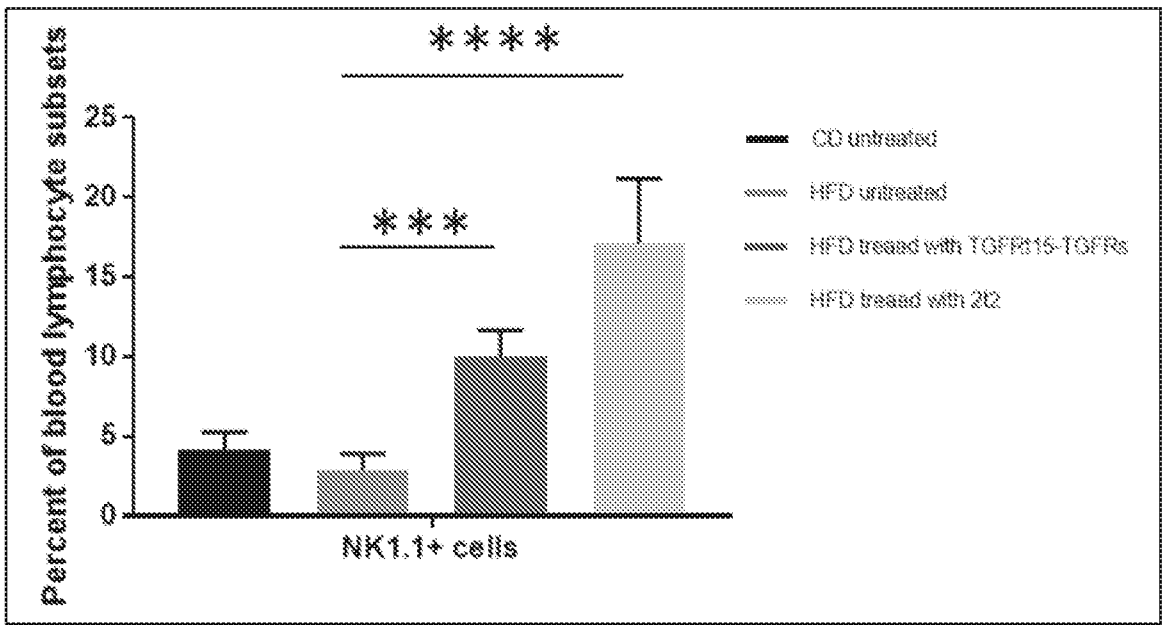


Figure 128B

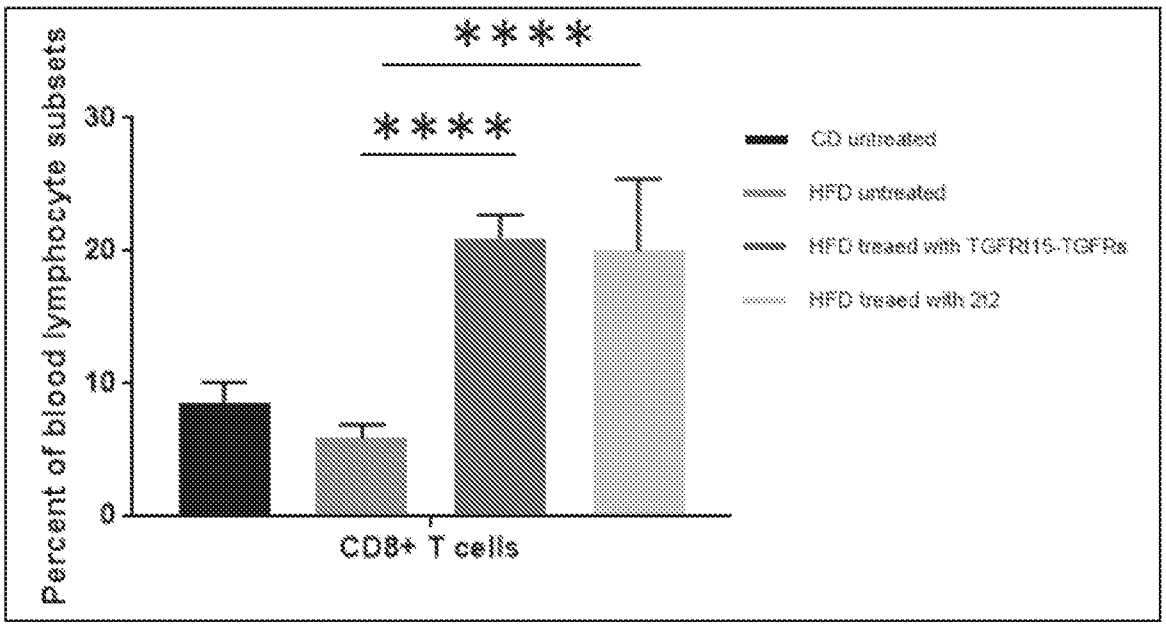

Percent of blood lymphocyte subsets
30
20
10
0
****
****
CD8+ T cells
CD untreated
HFD untreated
HFD treaed with TGFR1S-TGFRa
HFD treaed with 212

Figure 128C

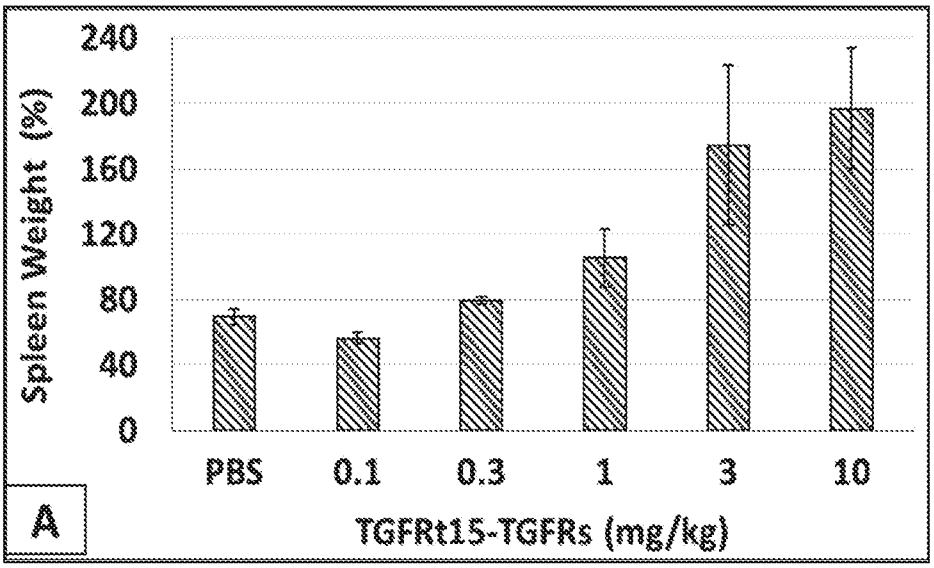


Figure 129A

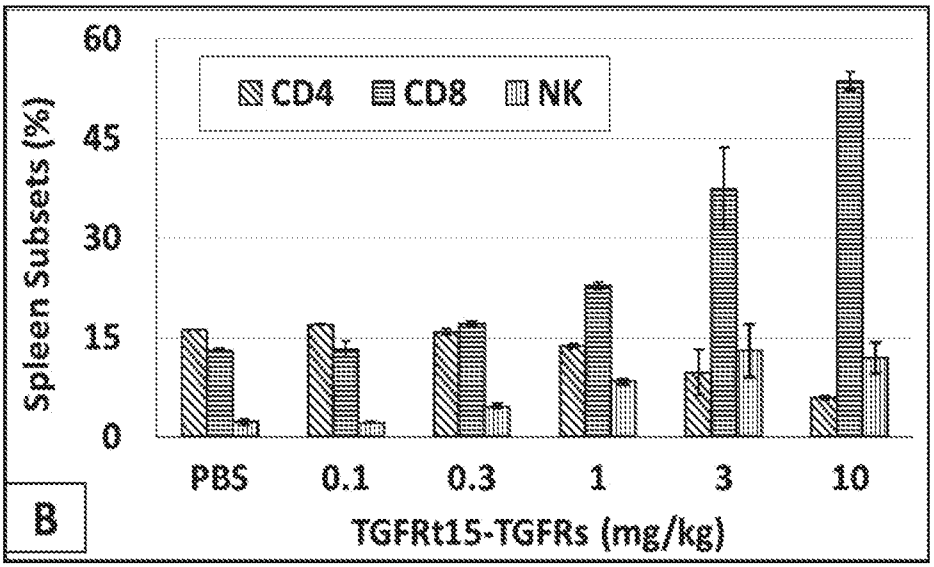


Figure 129B

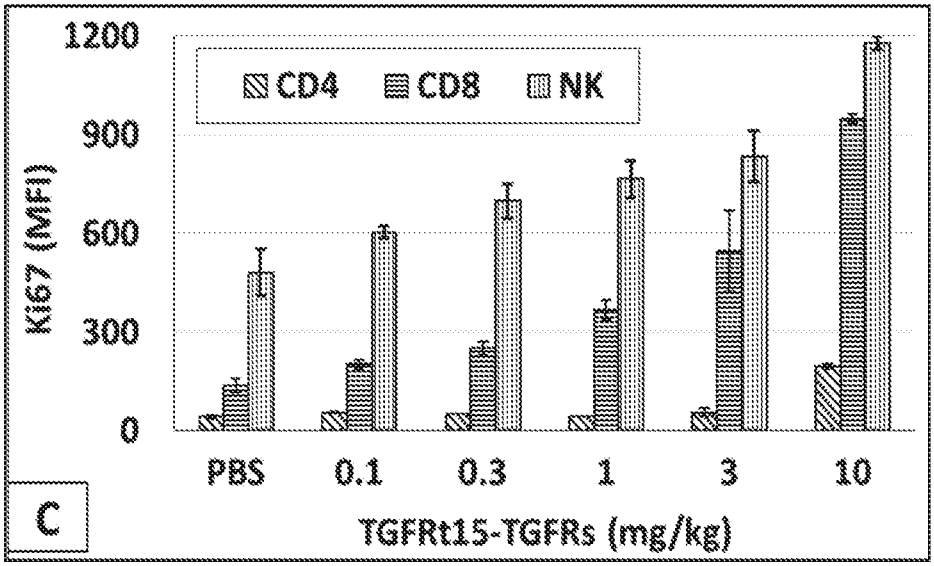

1200
900
600
300
0
Ki67 (MFI)
CD4
CD8
NK
PBS
0.1
0.3
1
3
10
TGFRt15-TGFRs (mg/kg)
C

Figure 129C

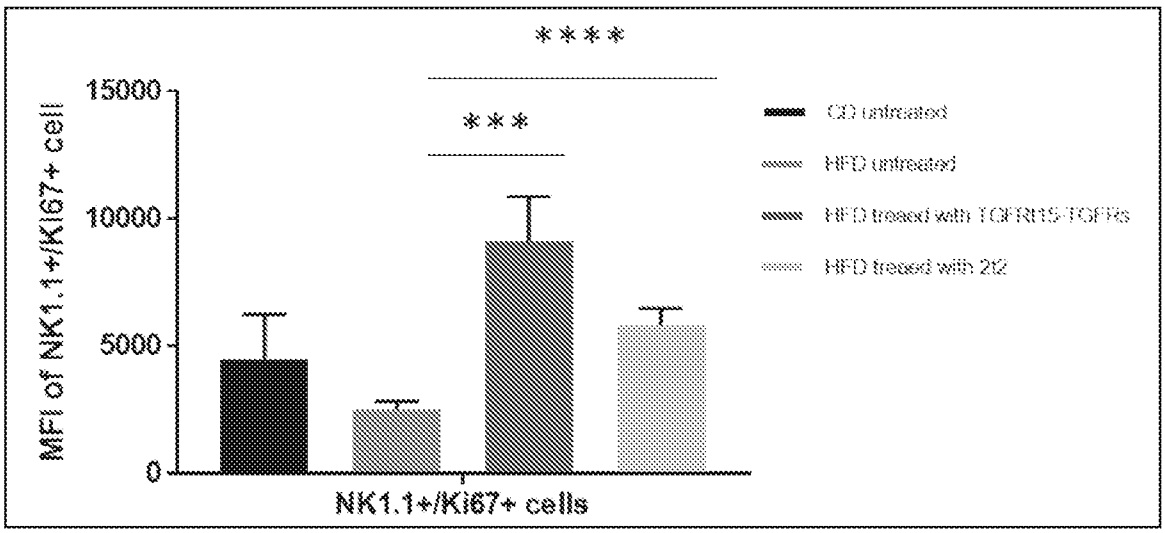


Figure 130A

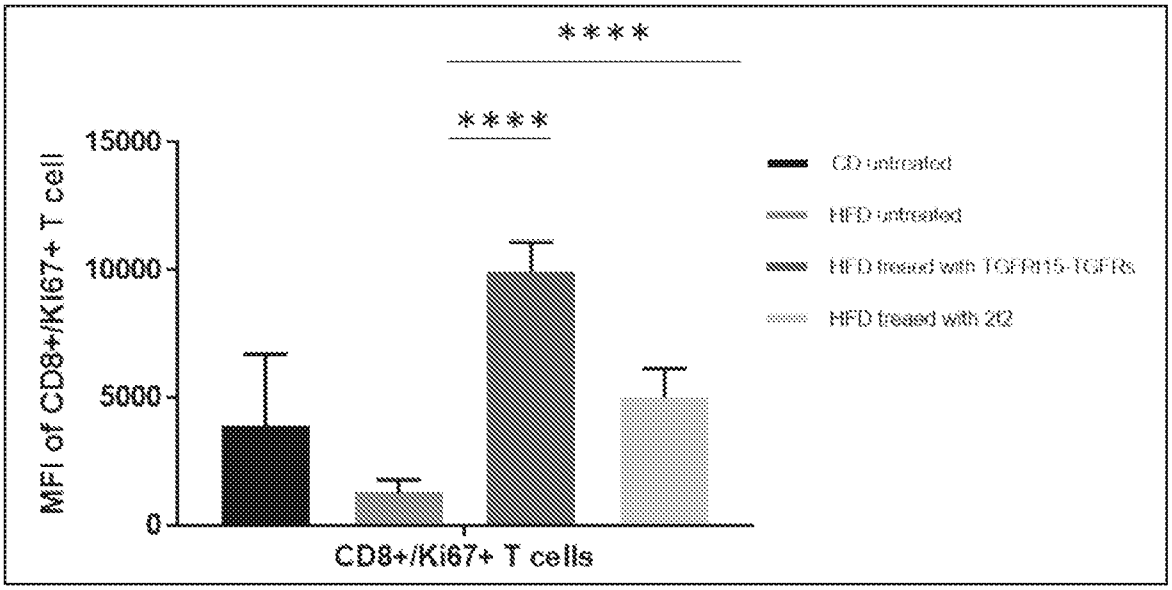


Figure 130B

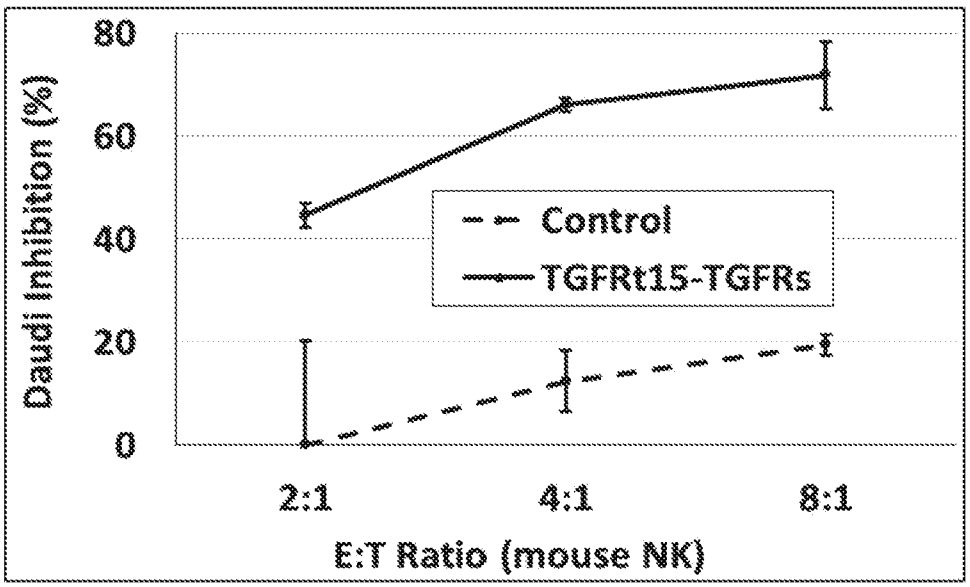


Figure 131A

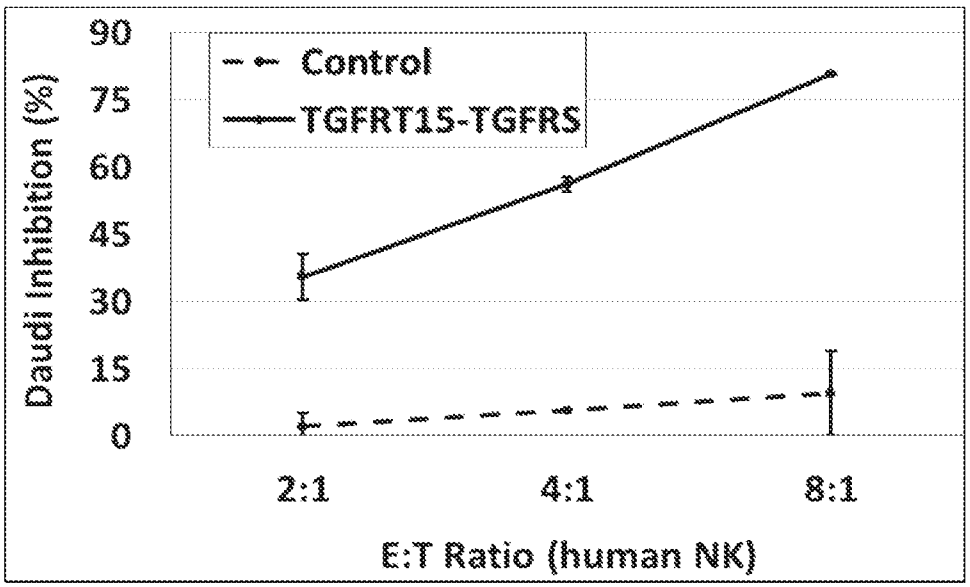


Figure 131B

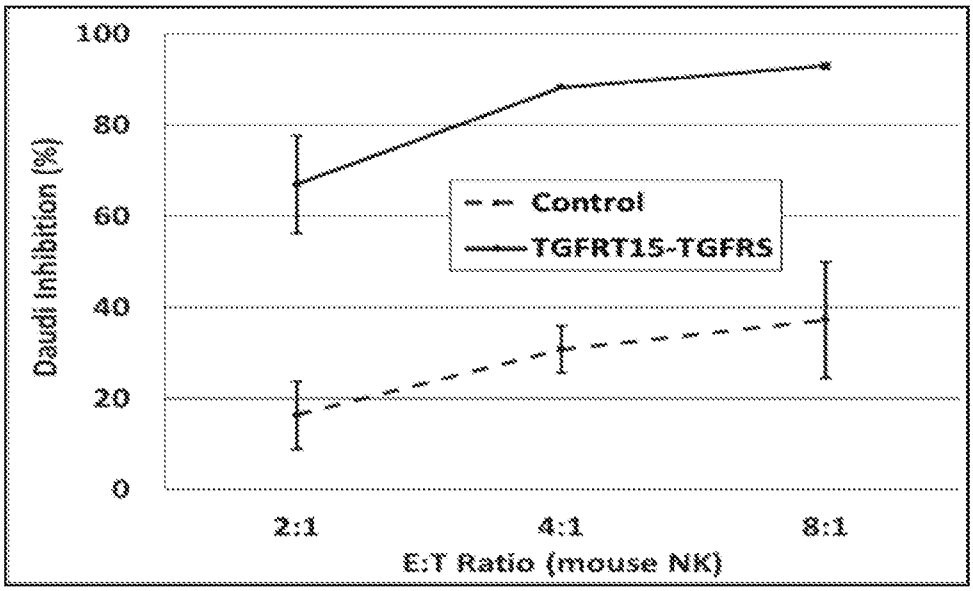


Figure 132A

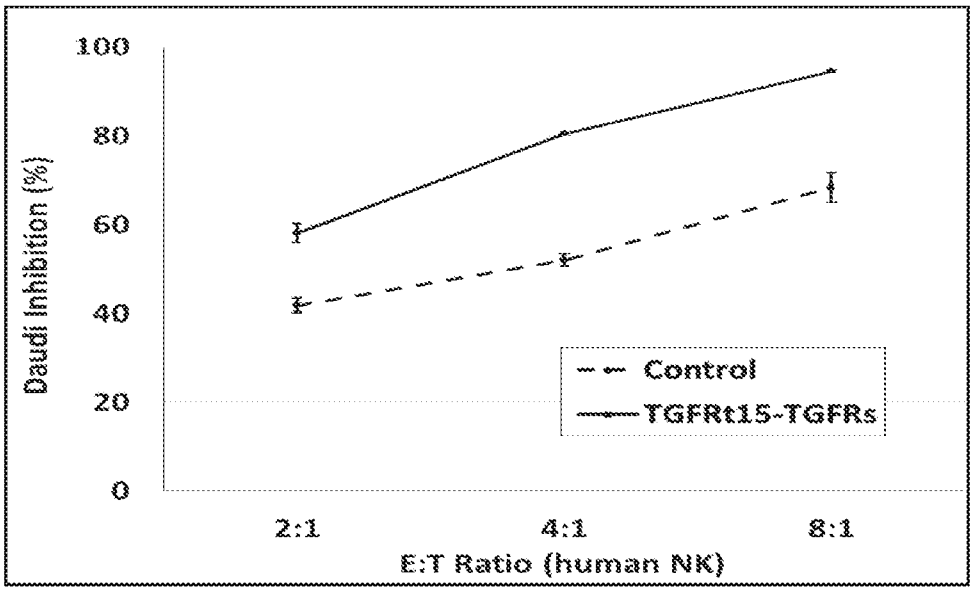
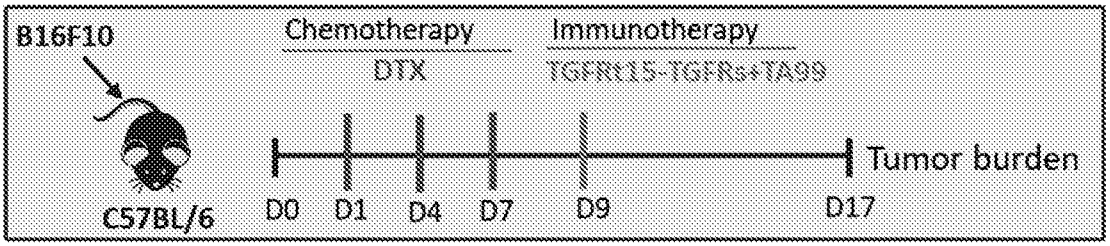


Figure 132B



DTX (10 mg/kg), TGFRt15-TGFRs (3mg/kg), TA99 (200 μg)

Figure 133A

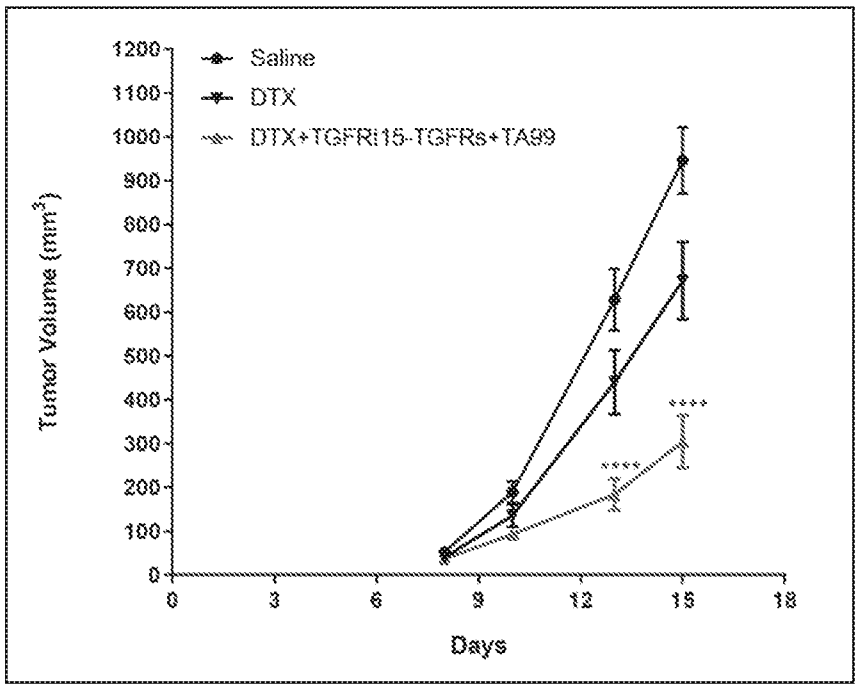


Figure 133B

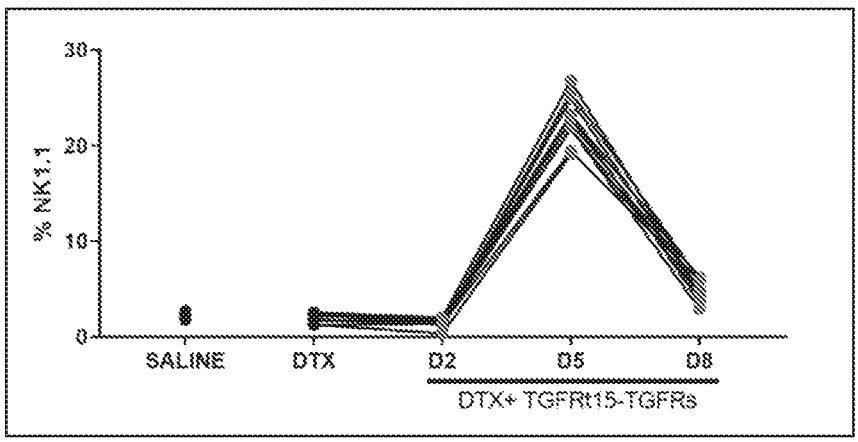


Figure 133C

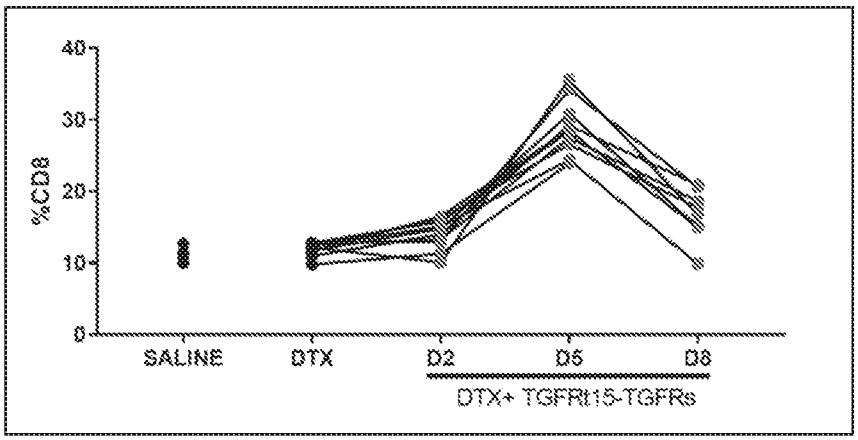


Figure 133D

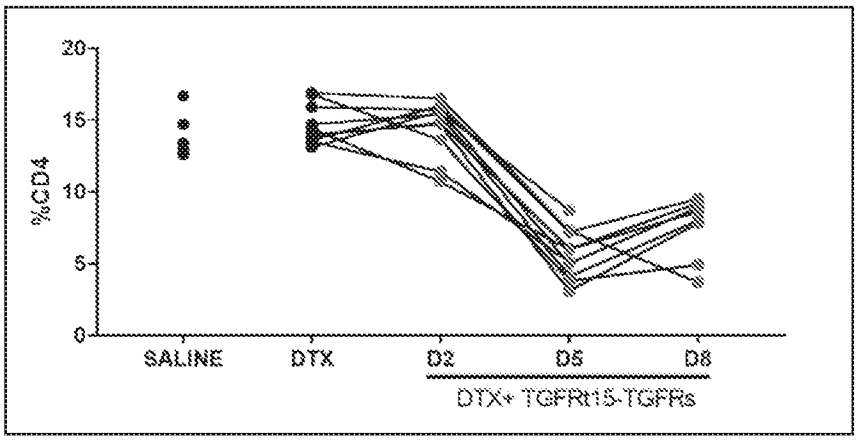


Figure 133E

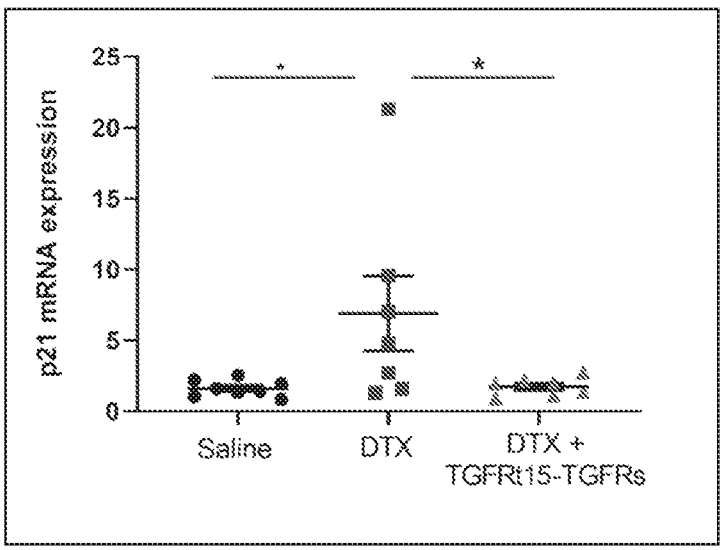


Figure 133F

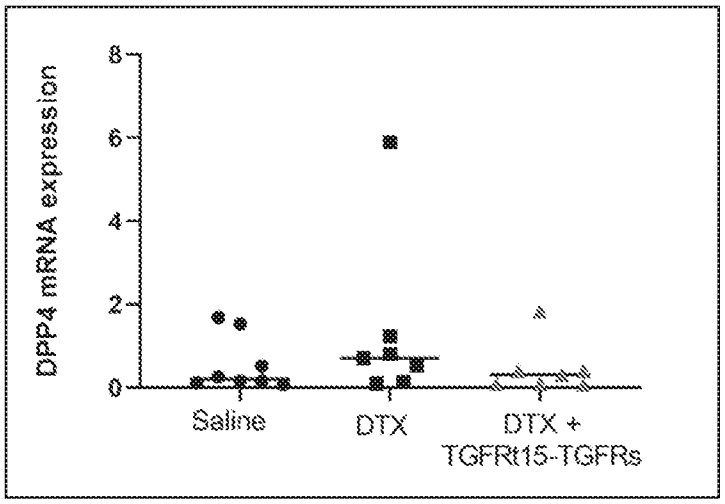


Figure 133G

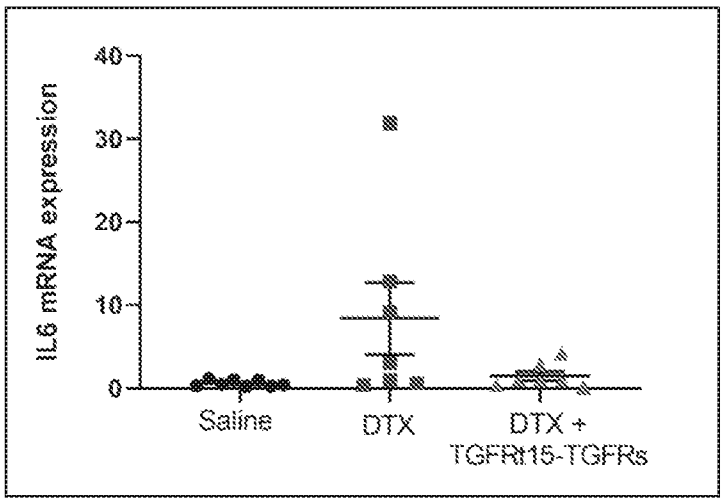


Figure 133H

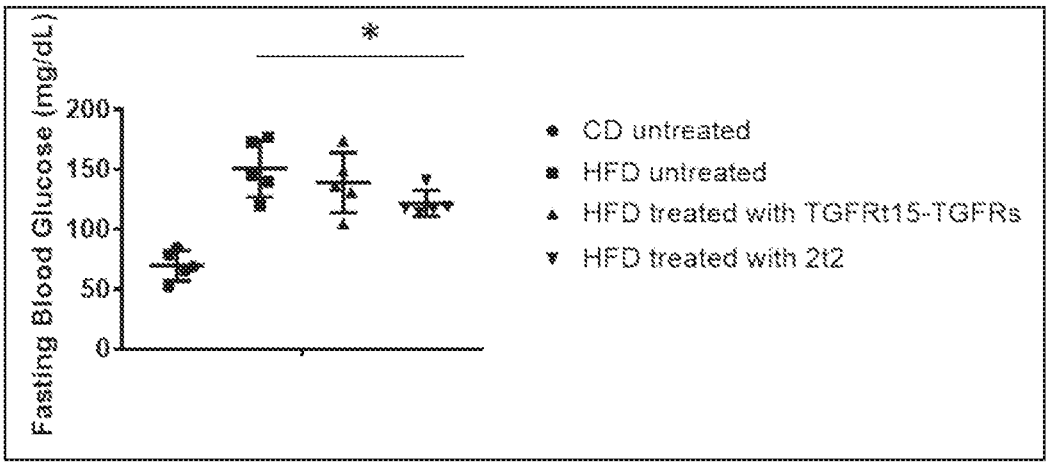


Figure 134A

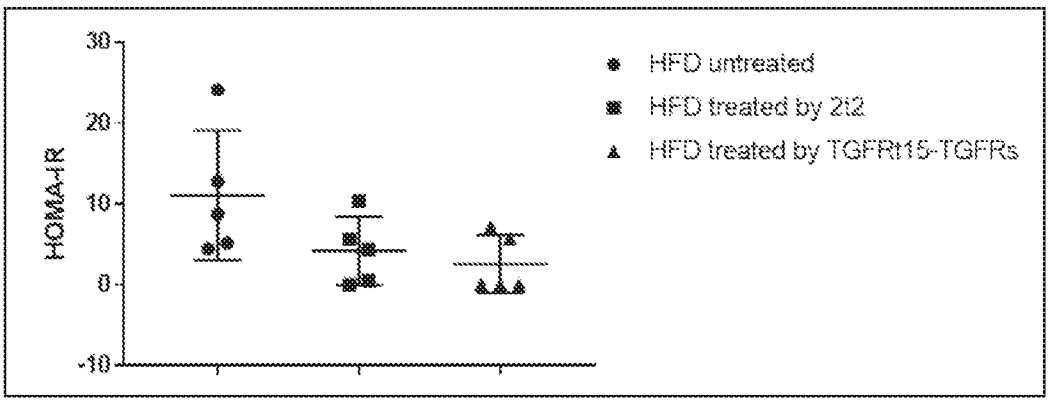


Figure 134B

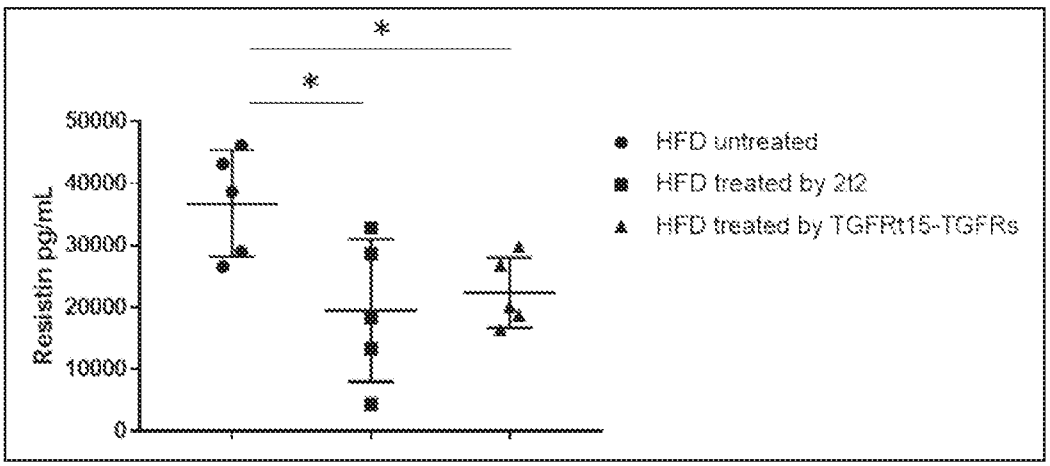


Figure 134C

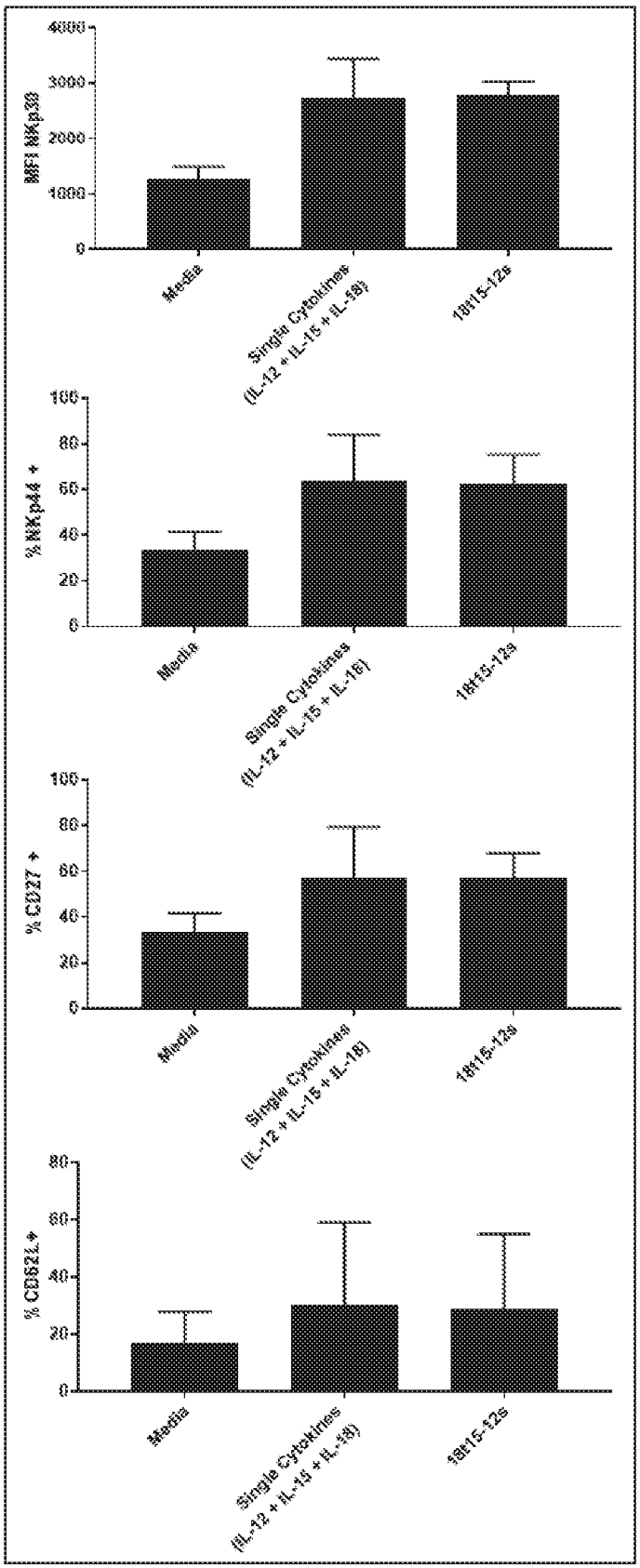

MFI NKp30
4000
3000
2000
1000
0
Media
Single Cytokines (IL-12 + IL-15 + IL-18)
18t15-12s
% NKp44 +
100
80
60
40
20
0
Media
Single Cytokines (IL-12 + IL-15 + IL-18)
18t15-12s
% CD27 +
100
80
60
40
20
0
Media
Single Cytokines (IL-12 + IL-15 + IL-18)
18t15-12s
% CD62L +
80
60
40
20
0
Media
Single Cytokines (IL-12 + IL-15 + IL-18)
18t15-12s

Figure 135

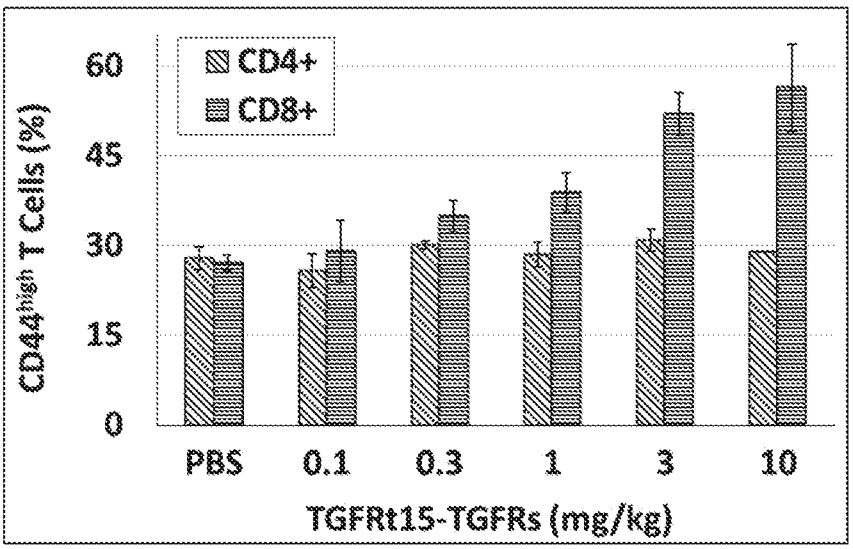


Figure 136

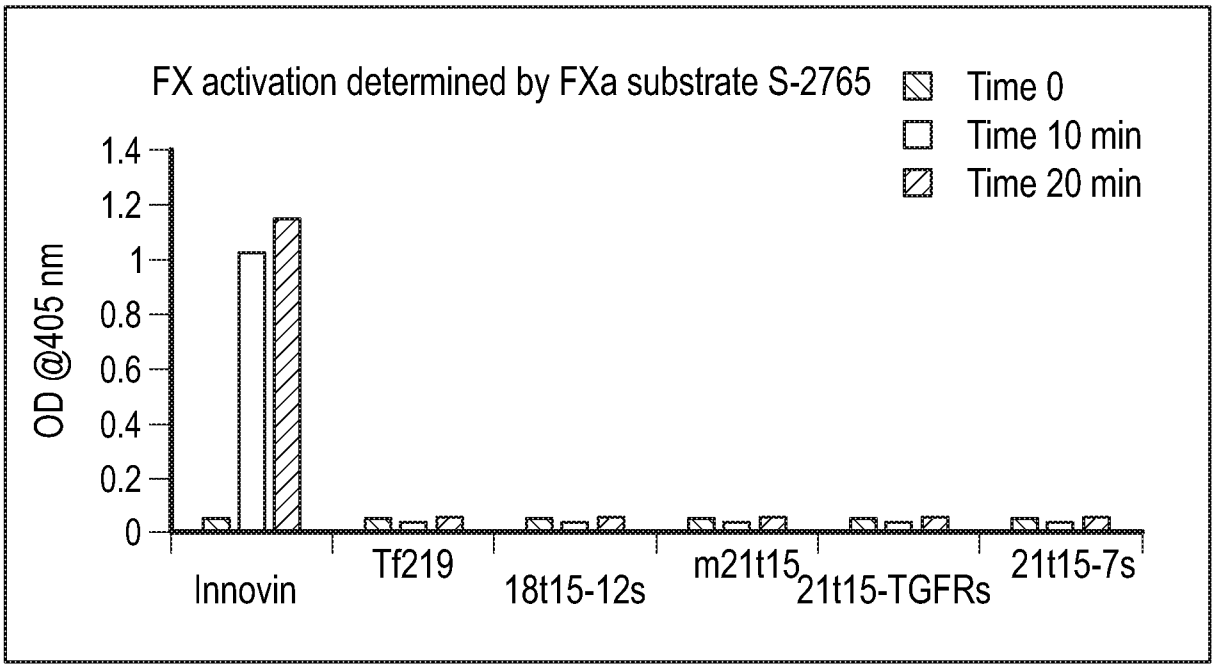


Figure 137

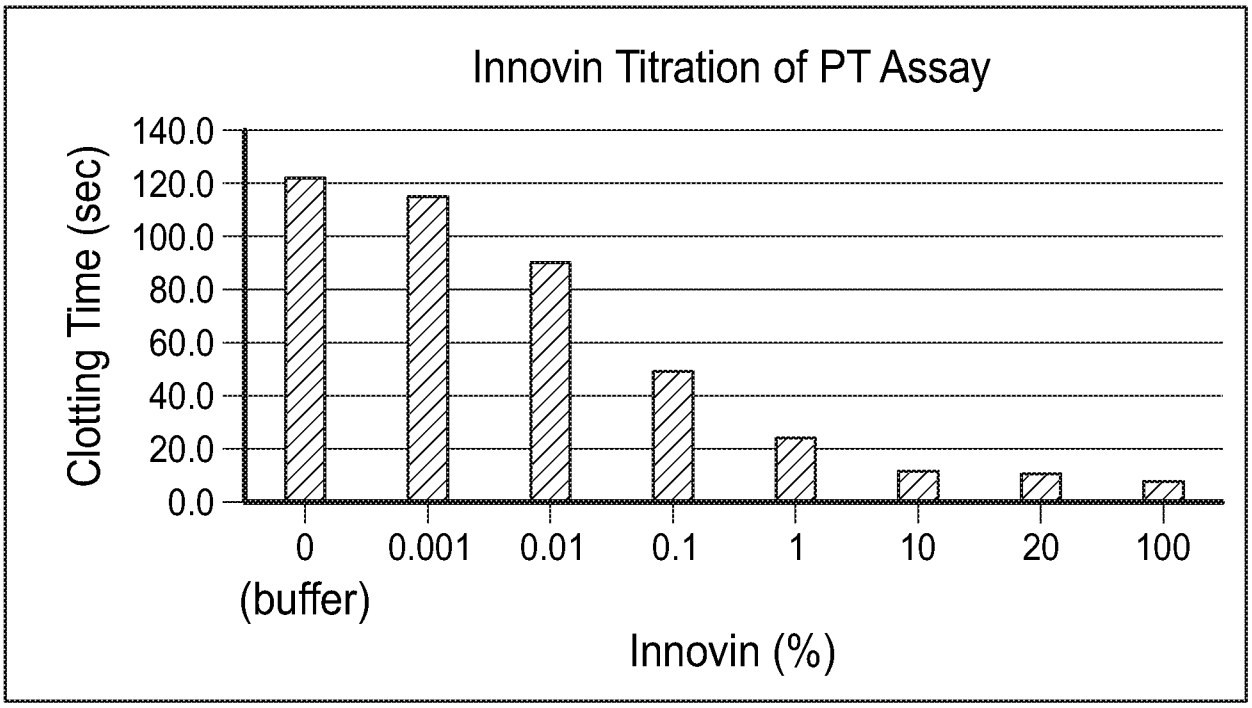


Figure 138

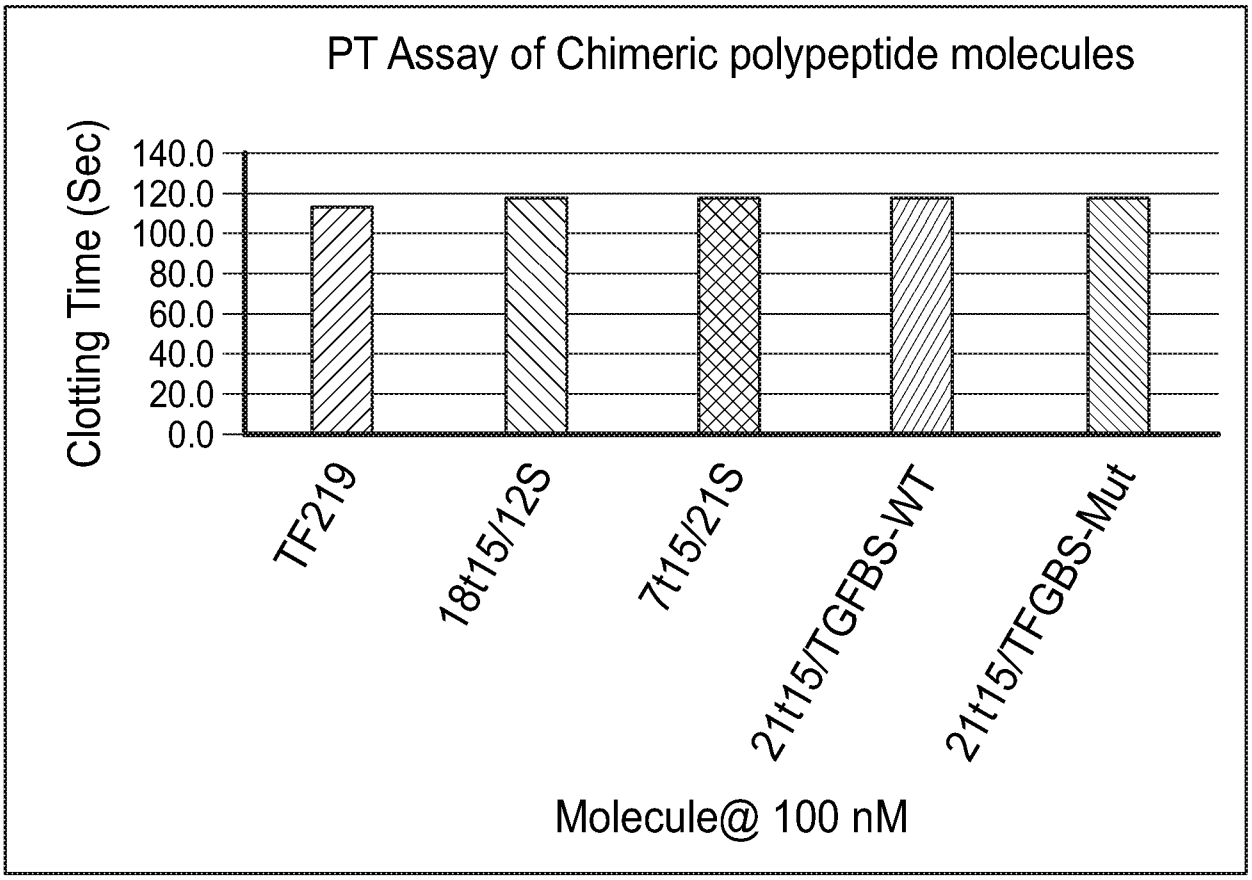


Figure 139

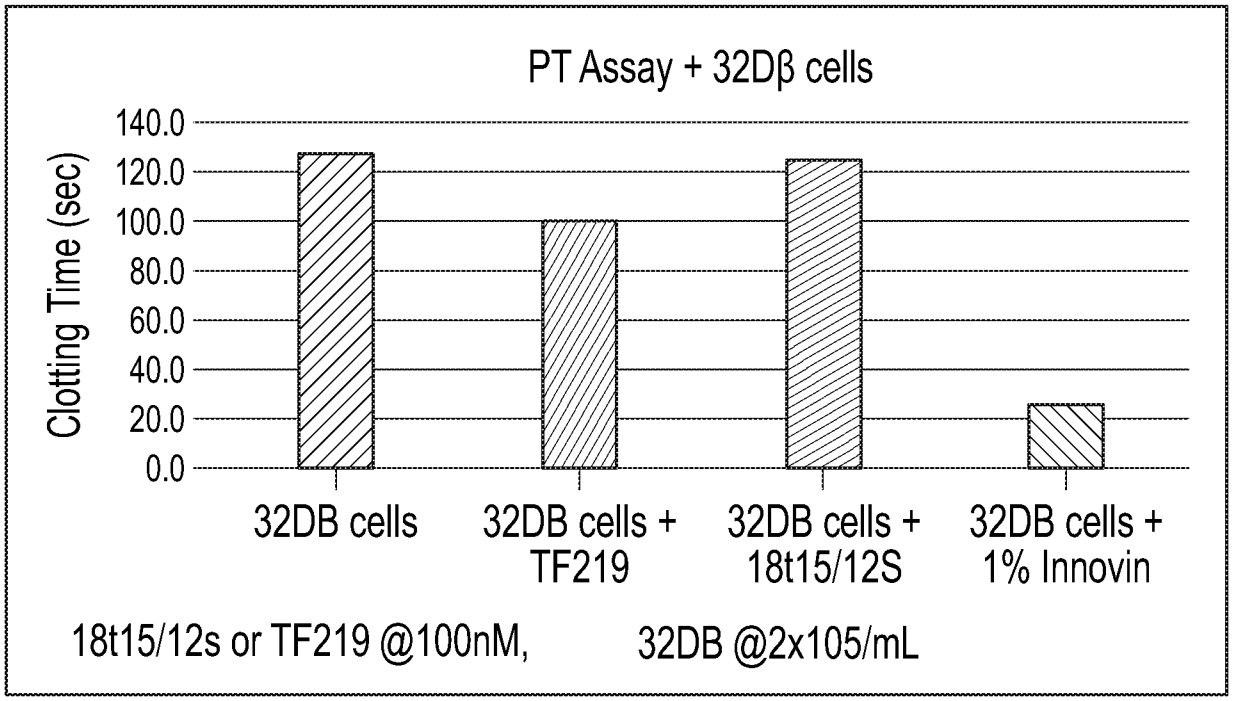


Figure 140

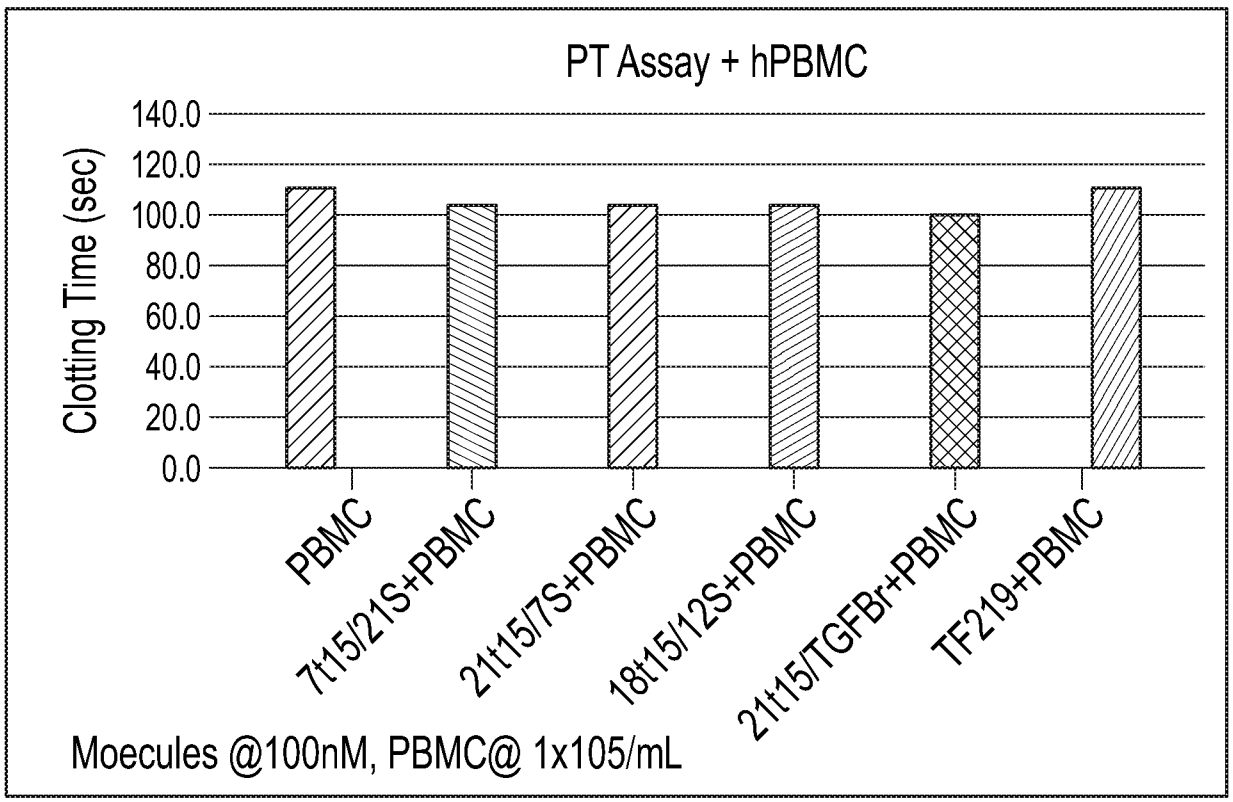


Figure 141

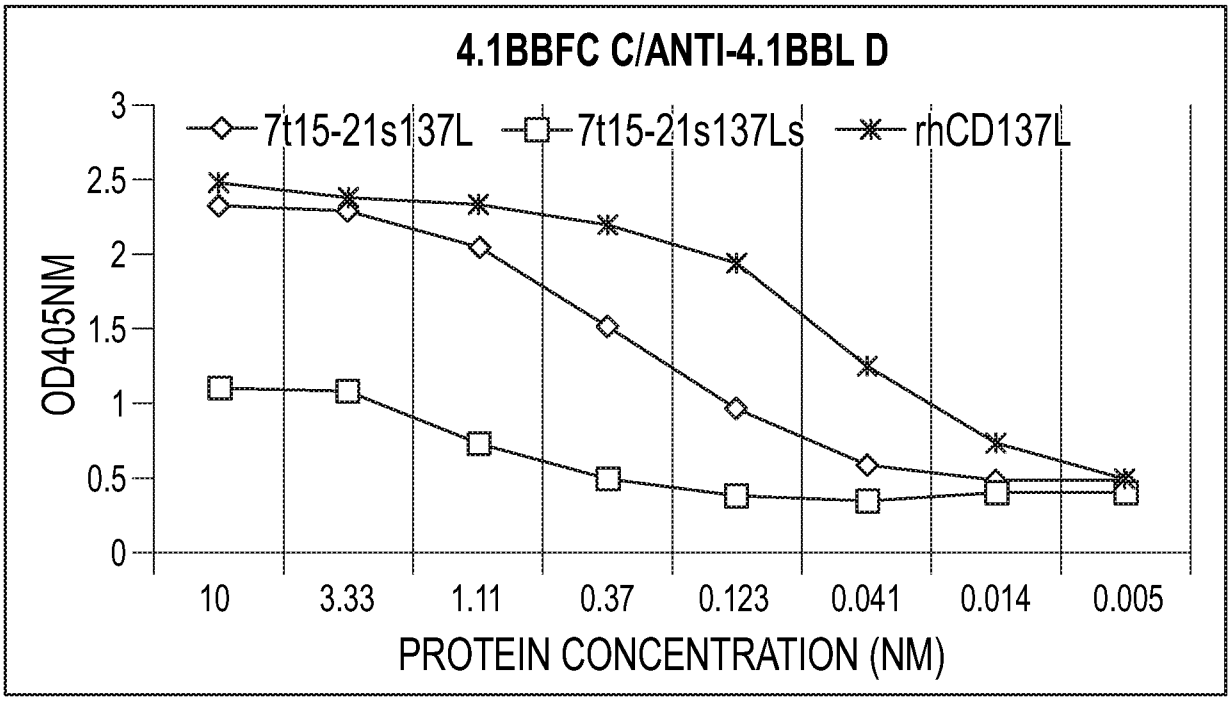


Figure 142

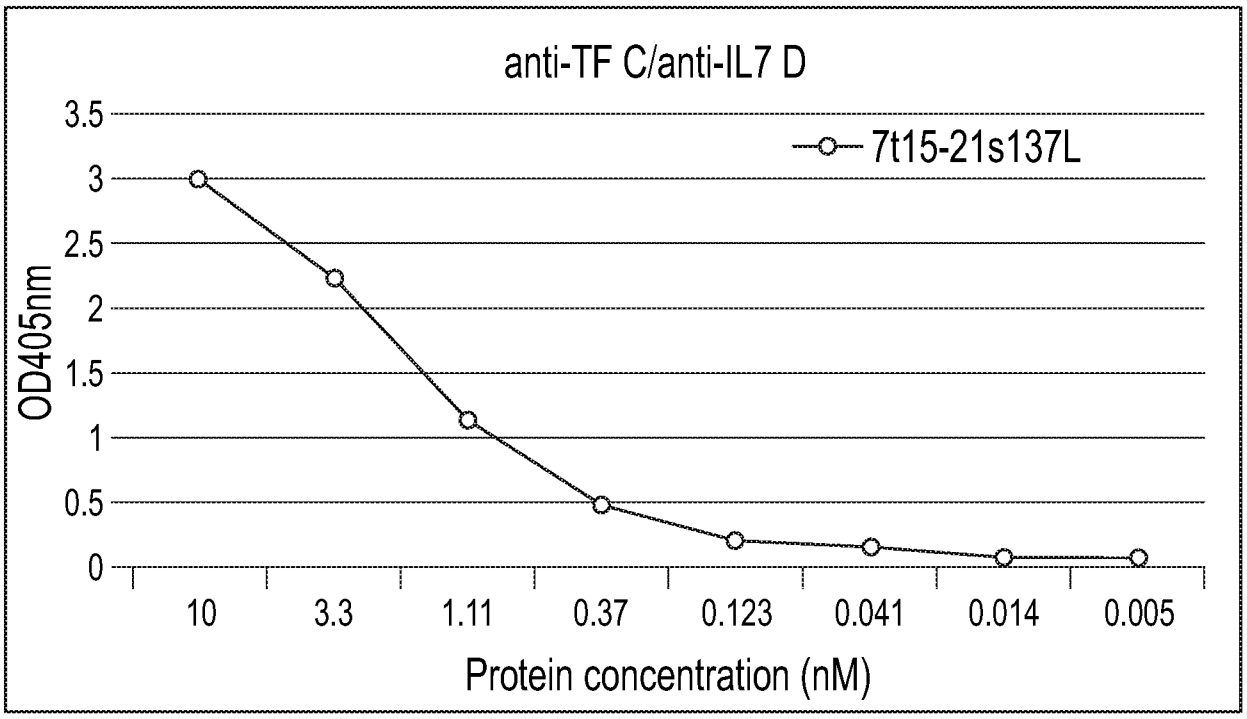


Figure 143A

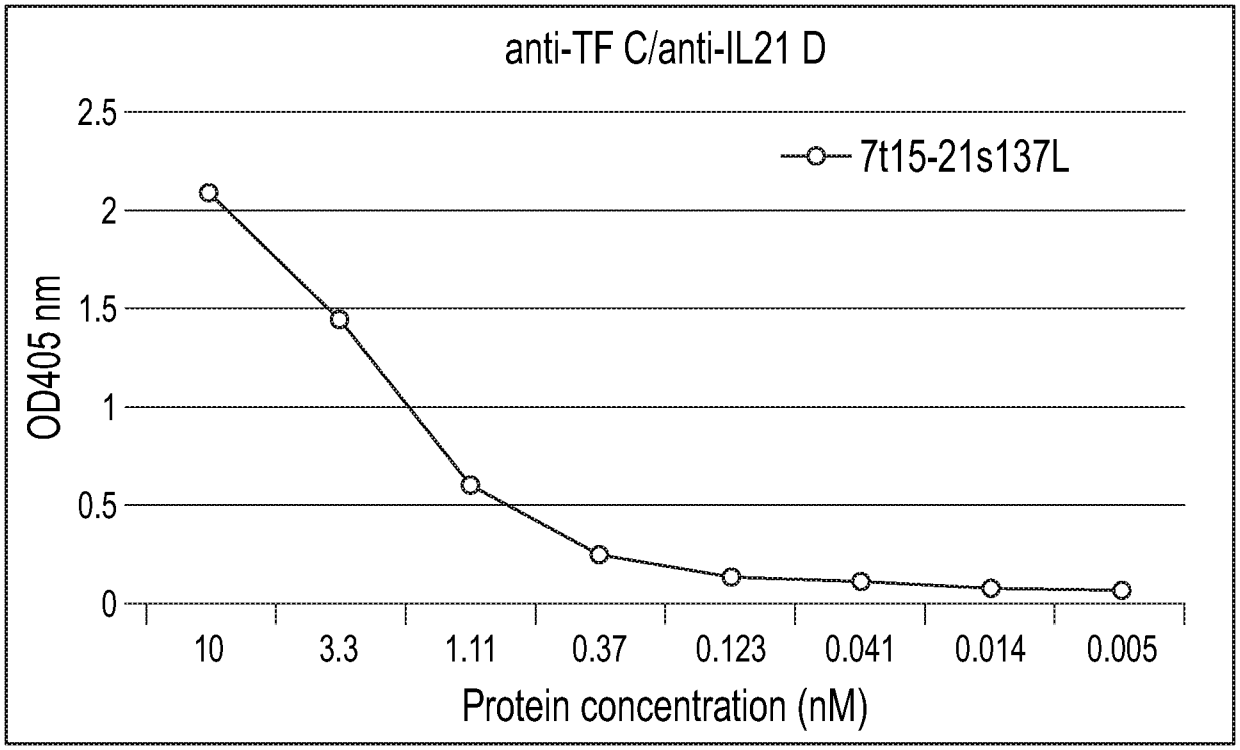


Figure 143B

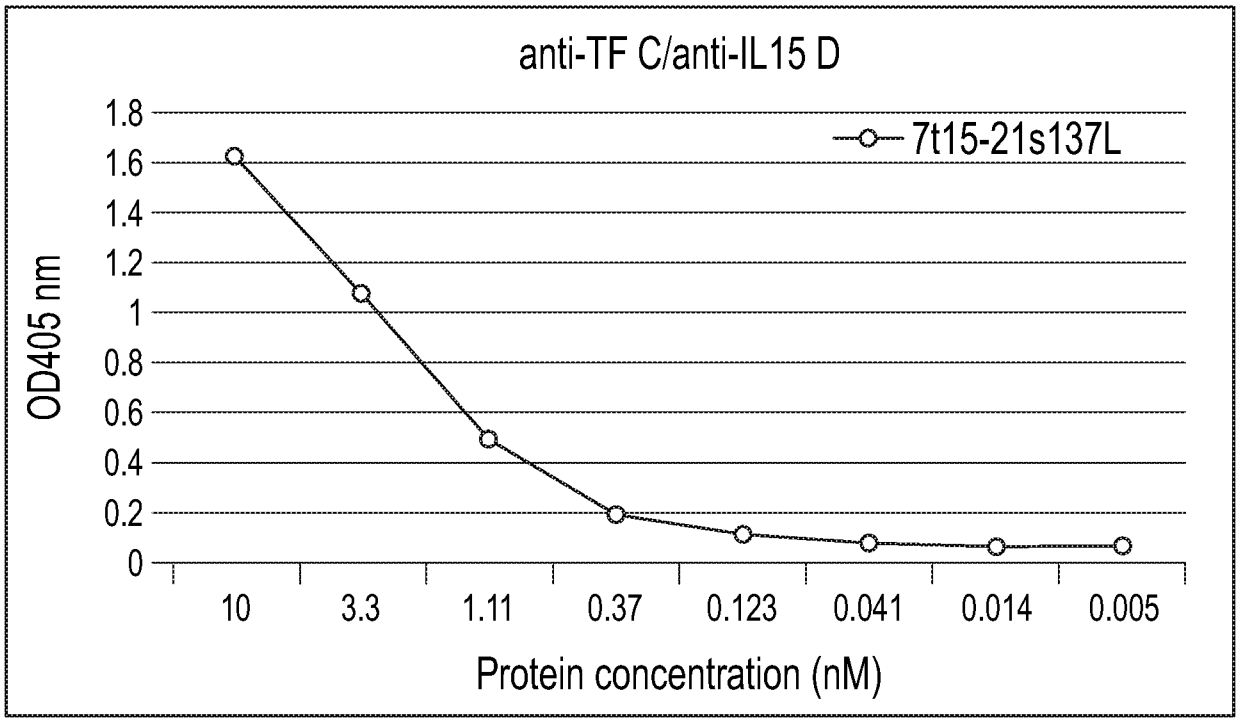


Figure 143C

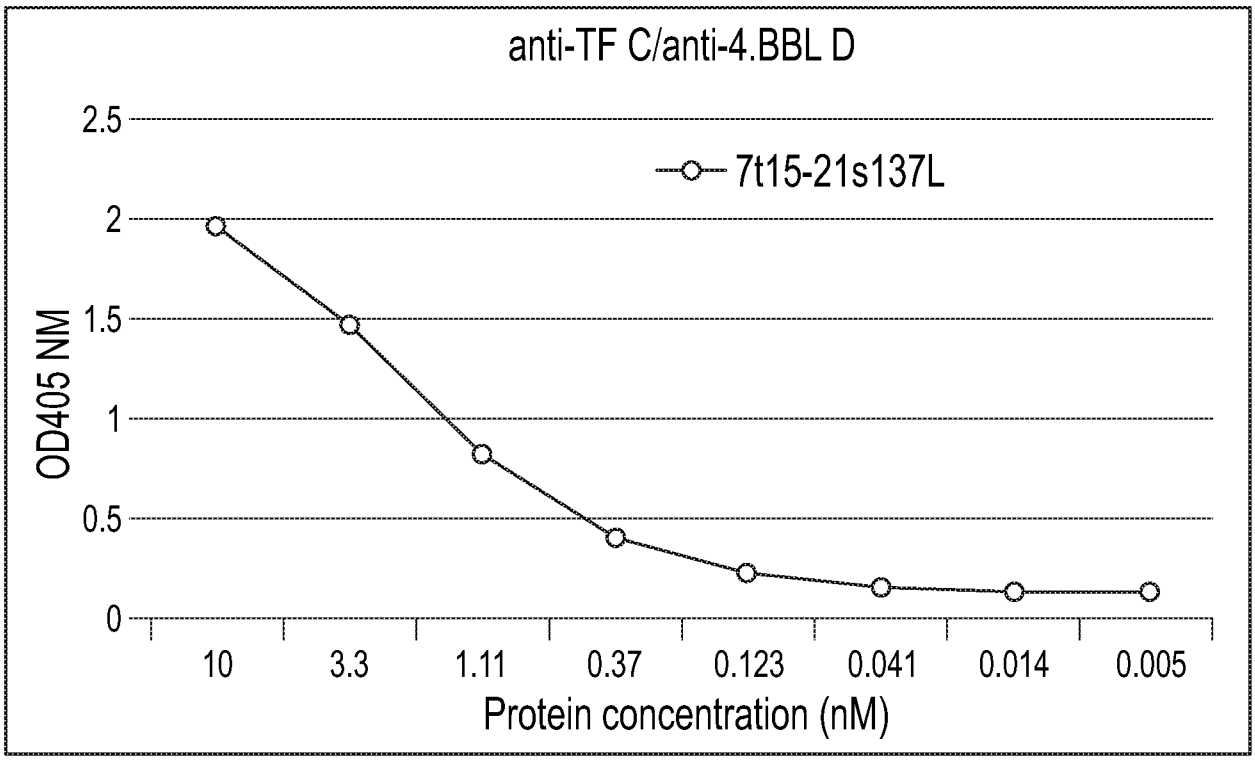


Figure 143D

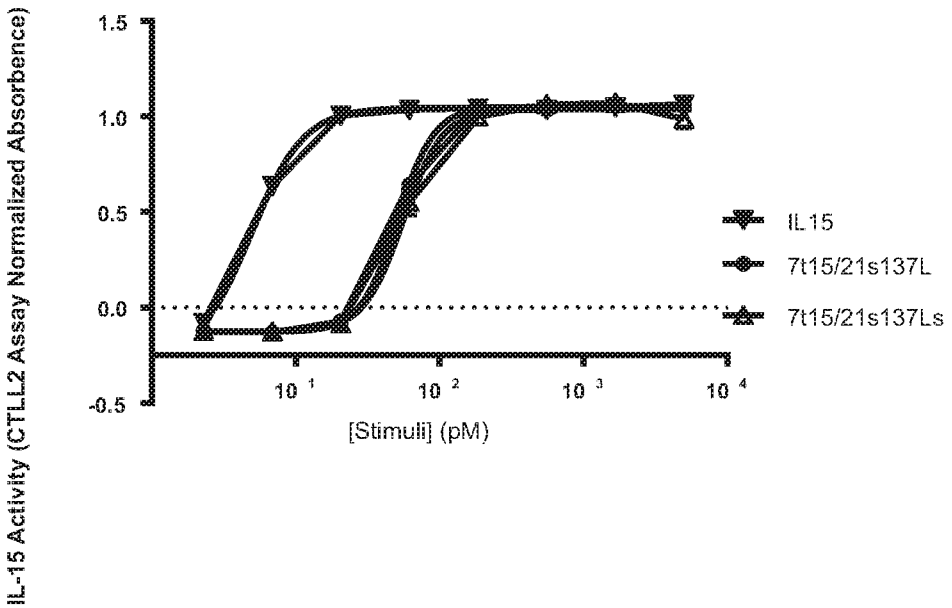


Figure 144

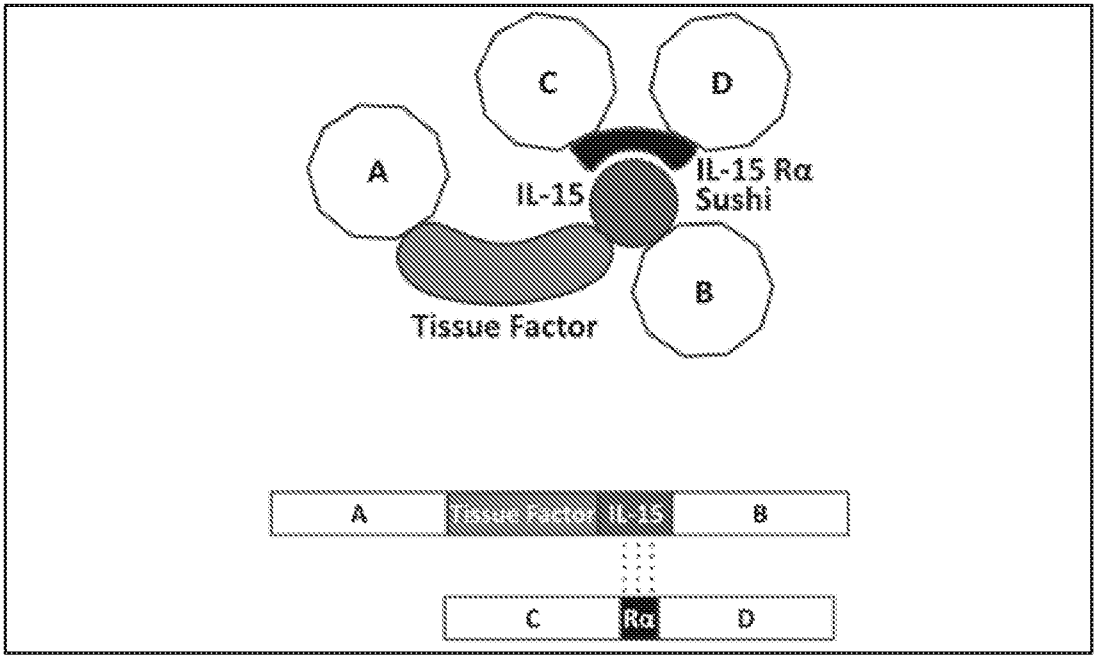

C
D
A
IL-15
IL-15 Rα
Sushi
B
Tissue Factor
A
Tissue Factor
IL-15
B
C
Rα
D

Figure 1