

CLAIMS

1. A chimeric protein or protein complex comprising:

(a) a modified IL-2 signaling agent, wherein the modified IL-2 signaling agent has one or more mutations or modifications relative to a wild type signaling agent having SEQ ID NO: 1 that confer improved safety and reduced affinity or bioactivity of the modified IL-2 signaling agent for IL-2R $\alpha\beta\gamma$ and/or IL-2R β and/or IL-2R γ and/or IL-2R α , relative to the wild type IL-2 signaling agent; and

(b) one or more targeting moieties, said targeting moieties comprising recognition domains which specifically bind to antigens or receptors of interest,

wherein the modified IL-2, and the one or more targeting moieties are optionally connected with one or more linkers,

wherein the modified IL-2 signaling agent comprises:

(i) a mutation selected from D20E, D20V, D20F, D20G, D20H, D20I, D20K, and D20L; or

(ii) a mutation selected from N88G, N88E, N88K, N88Q, and N88V; or

(iii) a mutation selected from Q126G, Q126A, Q126E, Q126F, Q126H, Q126I, Q126K, Q126L, Q126N, Q126P, Q126R, Q126S, Q126T, Q126V, Q126W, and Q126Y; or

(iv) a mutation selected from (i) and (iii) or a mutation selected from (ii) and (iii); or

(v) one or more mutations selected from:

R38A/F42K/N88G/C125A,

F42K/C125A,

D20E/C125A,

D20F/C125A,

D20G/C125A,

D20H/C125A,

D20I/C125A,

D20K/C125A,

D20L/C125A,

D20N/C125A,

D20S/C125A,

D20T/C125A,

D20V/C125A,
N88A/C125A,
N88D/C125A,
N88G/C125A,
N88E/C125A,
N88H/C125A,
N88I/C125A,
N88K/C125A,
N88Q/C125A,
N88R/C125A,
N88T/C125A,
N88V/C125A,
D20E/R38A/F42K,
D20E/R38A/F42K/C125A,
D20V/R38A/F42K,
D20V/R38A/F42K/C125A,
R38A/F42Y/E62A/C125A,
R38A/F42Y/Y45A/E62A,
F42Y/Y45A/L72G,
R38A/F42Y/Y45A/E62A/C125A,
F42Y/Y45A/L72G/C125A,
R38A/F42K/N88G,
R38A/F42K/Q126G,
R38A/F42K/Q126I,
R38A/F42K/Q126Y,
R38A/F42K/Q126G/C125A,
R38A/F42K/Q126I/C125A,
R38A/F42K/Q126Y/C125A,
R38A/F42K/E62A/N88G, and

R38A/F42K/E62A/N88G/C125A.

2. The chimeric protein or protein complex of claim 1, wherein the modified IL-2-signaling agent further comprises a glycosylation mutation, wherein the mutation decreases or eliminates glycosylation of the modified IL-2 signaling agent,

optionally wherein the glycosylation mutation is a T3 substitution, wherein the mutation is one of T3A, T3F, T3H, T3L, T3V, and T3Y, or wherein the glycosylation mutation is a deletion of the first 3, 4, 5, 6, 7, or 8 residues of the modified IL-2.

3. A chimeric protein or protein complex comprising:

(a) a modified IL-2 signaling agent, wherein the modified IL-2 signaling agent has one or more mutations or modifications relative to a wild type signaling agent having SEQ ID NO: 1 that confer improved safety and reduced affinity or bioactivity of the modified IL-2 signaling agent for IL-2R $\alpha\beta\gamma$ and/or IL-2R β and/or IL-2R γ and/or IL-2R α , relative to the wild type IL-2 signaling agent; and

(b) one or more targeting moieties, said targeting moieties comprising recognition domains which specifically bind to antigens or receptors of interest,

wherein the modified IL-2, and the one or more targeting moieties are optionally connected with one or more linkers,

wherein the modified IL-2 signaling agent comprises a glycosylation mutation, wherein the mutation decreases or eliminates glycosylation of the modified IL-2 signaling agent,

optionally wherein the glycosylation mutation is a T3 substitution, optionally wherein the mutation is one of T3A, T3F, T3H, T3L, T3V, and T3Y, or wherein the glycosylation mutation is a deletion of the first 3, 4, 5, 6, 7, or 8 residues of the modified IL-2.

4. A chimeric protein or protein complex comprising:

(a) a modified IL-2 signaling agent, wherein the modified IL-2 signaling agent has one or more mutations or modifications relative to a neoleukin signaling agent having SEQ ID NO: 2 that confer improved safety and reduced affinity or bioactivity of the modified IL-2 signaling agent for IL-2R $\alpha\beta\gamma$ and/or IL-2R β and/or IL-2R γ and/or IL-2R α , relative to the neoleukin signaling agent; and

(b) one or more targeting moieties, said targeting moieties comprising recognition domains which specifically bind to antigens or receptors of interest,

wherein the modified IL-2 signaling agent, and the one or more targeting moieties are optionally connected with one or more linkers,

wherein the modified IL-2 signaling agent comprises one or more mutations at a position selected from D15 and N40, optionally wherein the mutation is selected from D15T, D15H, N40I, N40G, and N40R.

5. The chimeric protein or protein complex of claim 1, wherein the modified IL-2 comprises one or more mutations that confer reduced affinity for an IL-2 receptor-chain,

optionally wherein the modified IL-2 exhibits reduced affinity for IL-2R α β γ , or wherein the modified IL-2 exhibits reduced affinity for IL-2R β , IL-2R γ , or a combination thereof, or wherein the modified IL-2 exhibits ablated affinity for IL-2R α , IL-2R β , IL2R γ or a combination thereof,

optionally wherein the modified IL-2 exhibits reduced affinity for:

IL-2R α and IL2R β , optionally wherein the modified IL-2 comprises one or more mutations selected from D20E/R38A/F42K, D20E/R38A/F42K/C125A, D20V/R38A/F42K, D20V/R38A/F42K/C125A, D20V/R38A/F42K/E62A, D20V/R38A/F42K/E62A/C125A, R38A/F42K/N88G, R38A/F42K/N88G/C125A, R38A/F42K/E62A/N88G, and R38A/F42K/E62A/N88G/C125A; or

IL-2R α and IL-2R γ , optionally wherein the modified IL-2 comprises one or more mutations selected from R38A/F42K/Q126G, R38A/F42K/Q126I, and R38A/F42K/Q126Y; or

IL-2R β , optionally wherein the modified IL-2 comprises one or more mutations selected from D20E, D20F, D20G, D20H, D20I, D20K, D20L, D20V, N88G, N88E, N88K, N88Q, N88V, D20E/C125A, D20F/C125A, D20G/C125A, D20H/C125A, D20I/C125A, D20L/C125A, D20K/C125A, D20N/C125A, D20S/C125A, D20T/C125A, D20V/C125A, N88A/C125A, N88D/C125A, N88G/C125A, N88E/C125A, N88H/C125A, N88I/C125A, N88K/C125A, N88Q/C125A, N88R/C125A, N88T/C125A, and N88V/C125A; or

IL-2R γ , optionally wherein the modified IL-2 comprises one or more mutations selected from Q126A, Q126E, Q126F, Q126G, Q126H, Q126I, Q126K, Q126L, Q126N, Q126P, Q126R, Q126S, Q126T, Q126V, Q126W, and Q126Y, or a combination thereof.

6. The chimeric protein or protein complex of claim 1, wherein the modified IL-2 exhibits reduced affinity for IL-2R β γ , optionally wherein the modified IL-2 comprises one or more mutations selected from D20E/Q126A, D20E/Q126D, D20E/Q126E, D20E/Q126F, D20E/Q126G, D20E/Q126H, D20E/Q126I, D20E/Q126K, D20E/Q126L, D20E/Q126M, D20E/Q126N, D20E/Q126P, D20E/Q126R, D20E/Q126S, D20E/Q126T, D20E/Q126V, D20E/Q126W, D20E/Q126Y, D20V/Q126A, D20V/Q126D, D20V/Q126E, D20V/Q126F, D20V/Q126G, D20V/Q126H, D20V/Q126I, D20V/Q126K, D20V/Q126L, D20V/Q126M, D20V/Q126N, D20V/Q126P, D20V/Q126R, D20V/Q126S, D20V/Q126T, D20V/Q126V, D20V/Q126W, D20V/Q126Y, N88A/Q126A, N88A/Q126D, N88A/Q126E, N88A/Q126F, N88A/Q126G, N88A/Q126H, N88A/Q126I, N88A/Q126K, N88A/Q126L, N88A/Q126M, N88A/Q126N, N88A/Q126P, N88A/Q126R, N88A/Q126S, N88A/Q126T, N88A/Q126V, N88A/Q126W, N88A/Q126Y, N88G/Q126A, N88G/Q126D, N88G/Q126E, N88G/Q126F, N88G/Q126G, N88G/Q126H, N88G/Q126I, N88G/Q126K, N88G/Q126L, N88G/Q126M, N88G/Q126N, N88G/Q126P, N88G/Q126R, N88G/Q126S, N88G/Q126T, N88G/Q126V, N88G/Q126W, and N88G/Q126Y,

optionally wherein the one or more mutations in the IL-2 signaling agent confers reduced affinity or bioactivity that is restorable by attachment to one or more targeting moieties,

optionally wherein the one or more targeting moieties are directed against a tumor cell, endothelial cell, epithelial cell, mesenchymal cell, tumor stroma or stromal cell, and/or ECM,

optionally wherein the one or more targeting moieties are directed against an immune cell and/or organ cells, and/or tissue cells,

optionally wherein the immune cell is selected from a T cell, a Treg, a cytotoxic T lymphocyte, a T helper cell, a B cell, a dendritic cell, an anti-tumor or tumor-associated macrophage (e.g., a M1 or M2 macrophage), a neutrophil, myeloid derived suppressor cell, a natural killer (NK) cell, and a natural killer T (NKT) cell, optionally, the immune cell is a T cell and the targeting moiety targets CD8, or optionally wherein the immune cell is a Treg and the targeting moiety targets CTLA4, or optionally wherein the immune cell is an NK cell and the targeting moiety is Nkp46.

7. The chimeric protein or protein complex of claim 1, wherein the targeting moiety comprises a recognition domain that is a full-length antibody, a single-domain antibody, a recombinant heavy-chain-only antibody (VHH), a single-chain antibody (scFv), a shark heavy-chain-only antibody (VNAR), a microprotein (e.g. cysteine knot protein, knottin), a darpin, an anticalin, an adnectin, an aptamer, a Fv, a Fab, a Fab', a F(ab')₂, a peptide mimetic molecule, a natural ligand for a receptor, or a synthetic molecule,

optionally wherein the recognition domain is a single-domain antibody, optionally wherein the recognition domain is a VHH or humanized VHH,

optionally wherein the recognition domain functionally modulates the antigen or receptor of interest, or wherein the recognition domain binds but does not functionally modulate the antigen or receptor of interest,

optionally wherein the chimeric protein or protein complex of claim 1 comprises two or more targeting moieties, optionally wherein the targeting moieties binds to one or more of the following targets: CD8, CTLA4, CD3, CD4, DNAM-1, Nrp1 (neurophilin), TNFR1, TNFR2, GITR, ICOS, CD20, CD70, Clec9a, Nkp46, PD-1, PD-L1, PD-L2, SIRP1α, FAP, XCR1, tenascin, or ECM proteins.

8. The chimeric protein or protein complex of claim 1, further comprising one or more additional modified signaling agents, optionally wherein the chimeric protein comprises two signaling agents and one targeting moiety or two targeting moieties and one signaling agent or two of both,

optionally wherein the chimeric protein comprises three signaling agents or three targeting moieties or three of both,

optionally wherein the additional modified signaling agent comprises one or more mutations conferring reduced affinity or activity for a receptor relative to an unmutated signaling agent, optionally wherein the one or more mutations allow for attenuation of activity, optionally wherein agonistic or antagonistic activity is attenuated.

9. Use of the chimeric protein or protein complex of claim 1 in the manufacture of a medicament for the treatment of one or more of: cancer, infections, immune disorders, autoimmune diseases, cardiovascular diseases, wound, ischemia-related diseases, neurodegenerative diseases, and/or metabolic diseases.

10. A recombinant nucleic acid composition encoding one or more chimeric proteins or protein complexes of any one of claims 1-8.

11. A host cell comprising the recombinant nucleic acid of claim 10.

12. Use of an effective amount of the chimeric protein or protein complex of any one of claims 1-8 in the manufacture of a medicament for the treatment of cancer or an autoimmune disease,

optionally wherein the cancer is selected from one or more of basal cell carcinoma, biliary tract cancer; bladder cancer; bone cancer; brain and central nervous system cancer; breast cancer; cancer of the peritoneum; cervical cancer; choriocarcinoma; colon and rectum cancer; connective tissue cancer; cancer of the digestive system; endometrial cancer; esophageal cancer; eye cancer; cancer of the head and neck; gastric cancer (including gastrointestinal cancer); glioblastoma; hepatic carcinoma; hepatoma; intra-epithelial neoplasm; kidney or renal cancer; larynx cancer; leukemia; liver cancer; lung cancer (e.g., small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, and squamous carcinoma of the lung); melanoma; myeloma; neuroblastoma; oral cavity cancer (lip, tongue, mouth, and pharynx); ovarian cancer; pancreatic cancer; prostate cancer; retinoblastoma; rhabdomyosarcoma; rectal cancer; cancer of the respiratory system; salivary gland carcinoma; sarcoma (e.g., Kaposi's sarcoma); skin cancer; squamous cell cancer; stomach cancer; testicular cancer; thyroid cancer; uterine or endometrial cancer; cancer of the urinary system; vulval cancer; lymphoma including Hodgkin's and non-Hodgkin's lymphoma, as well as B-cell lymphoma (including low grade/follicular non-Hodgkin's lymphoma (NHL); small lymphocytic (SL) NHL; intermediate grade/follicular NHL; intermediate grade diffuse NHL; high grade immunoblastic NHL; high grade lymphoblastic NHL; high grade small non-cleaved cell NHL; bulky disease NHL; mantle cell lymphoma; AIDS-related lymphoma; and Waldenstrom's Macroglobulinemia; chronic lymphocytic leukemia (CLL); acute lymphoblastic leukemia (ALL); Hairy cell leukemia; chronic myeloblastic leukemia; as well as other carcinomas and sarcomas; and post-transplant lymphoproliferative disorder (PTLD), as well as abnormal vascular proliferation associated with phakomatoses, edema (e.g. that associated with brain tumors), and Meigs' syndrome.

13. A Fc-based chimeric protein complex comprising:

(a) a modified IL-2 signaling agent, wherein the modified IL-2 signaling agent has one or more mutations or modifications relative to a wild type signaling agent having SEQ ID NO: 1 that confer improved safety and reduced affinity or bioactivity of the modified IL-2 signaling agent for IL-2R $\alpha\beta\gamma$ and/or IL-2R β and/or IL-2R γ and/or IL-2R α , relative to the wild type IL-2 signaling agent; and

(b) one or more targeting moieties, said targeting moieties comprising recognition domains which specifically bind to antigens or receptors of interest; and

(c) a Fc domain, the Fc domain optionally having one or more mutations that reduces or eliminates one or more effector functions of the Fc domain, promotes Fc chain pairing in the Fc domain, and/or stabilizes a hinge region in the Fc domain,

wherein the modified IL-2 signaling agent comprises:

- (i) a mutation selected from D20E, D20V, D20F, D20G, D20H, D20I, D20K, and D20L; or
- (ii) a mutation selected from N88G, N88E, N88K, N88Q, and N88V; or
- (iii) a mutation selected from Q126G, Q126A, Q126E, Q126F, Q126H, Q126I, Q126K, Q126L, Q126N, Q126P, Q126R, Q126S, Q126T, Q126V, Q126W, and Q126Y; or
- (iv) a mutation selected from (i) and (iii) or a mutation selected from (ii) and (iii); or
- (v) one or more mutations selected from:

R38A/F42K/N88G/C125A,

F42K/C125A,

D20E/C125A,

D20F/C125A,

D20G/C125A,

D20H/C125A,

D20I/C125A,

D20K/C125A,

D20L/C125A,

D20N/C125A,

D20S/C125A,

D20T/C125A,

D20V/C125A,

N88A/C125A,

N88D/C125A,

N88G/C125A,

N88E/C125A,

N88H/C125A,

N88I/C125A,

N88K/C125A,

N88Q/C125A,

N88R/C125A,

N88T/C125A,

N88V/C125A,
 D20E/R38A/F42K,
 D20E/R38A/F42K/C125A,
 D20V/R38A/F42K,
 D20V/R38A/F42K/C125A,
 R38A/F42Y/E62A/C125A,
 R38A/F42Y/Y45A/E62A,
 F42Y/Y45A/L72G,
 R38A/F42Y/Y45A/E62A/C125A,
 F42Y/Y45A/L72G/C125A,
 R38A/F42K/N88G,
 R38A/F42K/Q126G,
 R38A/F42K/Q126I,
 R38A/F42K/Q126Y,
 R38A/F42K/Q126G/C125A,
 R38A/F42K/Q126I/C125A,
 R38A/F42K/Q126Y/C125A,
 R38A/F42K/E62A/N88G, and
 R38A/F42K/E62A/N88G/C125A.

14. The Fc-based chimeric protein complex of claim 13, wherein the modified IL-2-signaling agent further comprises a glycosylation mutation, wherein the mutation decreases or eliminates glycosylation of the modified IL-2 signaling agent, optionally wherein the glycosylation mutation is a T3 substitution, wherein the mutation is one of T3A, T3F, T3H, T3L, T3V, and T3Y, or wherein the glycosylation mutation is a deletion of the first 3, 4, 5, 6, 7, or 8 residues of the modified IL-2.

15. A Fc-based chimeric protein complex comprising:

(a) a modified IL-2 signaling agent, wherein the modified IL-2 signaling agent has one or more mutations or modifications relative to a wild type signaling agent having SEQ ID NO: 1 that confer improved safety and reduced affinity or bioactivity of the modified IL-2 signaling agent for IL-2R $\alpha\beta\gamma$ and/or IL-2R β and/or IL-2R γ and/or IL-2R α , relative to the wild type IL-2 signaling agent; and

(b) one or more targeting moieties, said targeting moieties comprising recognition domains which specifically bind to antigens or receptors of interest; and

(c) a Fc domain, the Fc domain optionally having one or more mutations that reduces or eliminates one or more effector functions of the Fc domain, promotes Fc chain pairing in the Fc domain, and/or stabilizes a hinge region in the Fc domain,

wherein the modified IL-2 signaling agent comprises a glycosylation mutation, wherein the mutation decreases or eliminates glycosylation of the modified IL-2 signaling agent,

optionally wherein the glycosylation mutation is a T3 substitution, optionally wherein the mutation is one of T3A, T3F, T3H, T3L, T3V, and T3Y, or wherein the glycosylation mutation is a deletion of the first 3, 4, 5, 6, 7, or 8 residues of the modified IL-2.

16. A Fc-based chimeric protein complex comprising:

(a) a modified IL-2 signaling agent, wherein the modified IL-2 signaling agent has one or more mutations or modifications relative to a neoleukin signaling agent having SEQ ID NO: 2 that confer improved safety and reduced affinity or bioactivity of the modified IL-2 signaling agent for IL-2R $\alpha\beta\gamma$ and/or IL-2R β and/or IL-2R γ and/or IL-2R α , relative to the neoleukin signaling agent; and

(b) one or more targeting moieties, said targeting moieties comprising recognition domains which specifically bind to antigens or receptors of interest,

wherein the modified IL-2 signaling agent, and the one or more targeting moieties are optionally connected with one or more linkers,

wherein the modified IL-2 signaling agent comprises one or more mutations at a position selected from D15 and N40, optionally wherein the mutation is selected from D15T, D15H, N40I, N40G, and N40R.

17. The Fc-based chimeric protein complex of claim 13, wherein the modified IL-2 comprises one or more mutations that confer reduced affinity for an IL-2 receptor,

optionally wherein the modified IL-2 exhibits reduced affinity for IL-2R $\alpha\beta\gamma$, or wherein the modified IL-2 exhibits reduced affinity for IL-2R β , IL-2R γ , or a combination thereof, or wherein the modified IL-2 exhibits ablated affinity for IL-2R α , IL-2R $\alpha\beta$, IL-2R γ , or a combination thereof,

optionally wherein the modified IL-2 exhibits reduced affinity for:

IL-2R α and IL-2R β , optionally wherein the modified IL-2 comprises one or more mutations selected from D20E/R38A/F42K, D20E/R38A/F42K/C125A, D20V/R38A/F42K, D20V/R38A/F42K/C125A, D20V/R38A/F42K/E62A, D20V/R38A/F42K/E62A/C125A, R38A/F42K/N88G, R38A/F42K/N88G/C125A, R38A/F42K/E62A/N88G, and R38A/F42K/E62A/N88G/C125A; or

IL-2R α and IL-2R γ , optionally wherein the modified IL-2 comprises one or more mutations selected from R38A/F42K/Q126G, R38A/F42K/Q126I, and R38A/F42K/Q126Y; or

IL-2R β , optionally wherein the modified IL-2 comprises one or more mutations selected from D20E, D20V, N88G, D20F, D20G, D20H, D20I, D20K, D20L, N88E, N88K, N88Q, N88V, D20E/C125A, D20F/C125A, D20G/C125A, D20H/C125A, D20I/C125A, D20L/C125A, D20K/C125A, D20N/C125A, D20S/C125A, D20T/C125A, D20V/C125A, N88A/C125A, N88D/C125A, N88G/C125A, N88E/C125A, N88H/C125A, N88I/C125A, N88K/C125A, N88Q/C125A, N88R/C125A, N88T/C125A, and N88V/C125A; or

IL-2R γ , optionally wherein the modified IL-2 comprises one or more mutations selected from Q126A, Q126E, Q126F, Q126G, Q126H, Q126I, Q126K, Q126L, Q126N, Q126P, Q126R, Q126S, Q126T, Q126V, Q126W, and Q126Y, or a combination thereof, or

optionally wherein the modified IL-2 exhibits reduced affinity for IL-2R $\beta\gamma$, optionally wherein the modified IL-2 comprises one or more mutations selected from D20E/Q126A, D20E/Q126D, D20E/Q126E, D20E/Q126F, D20E/Q126G, D20E/Q126H, D20E/Q126I, D20E/Q126K, D20E/Q126L, D20E/Q126M, D20E/Q126N, D20E/Q126P, D20E/Q126R, D20E/Q126S, D20E/Q126T, D20E/Q126V, D20E/Q126W, D20E/Q126Y, D20V/Q126A, D20V/Q126D, D20V/Q126E, D20V/Q126F, D20V/Q126G, D20V/Q126H, D20V/Q126I, D20V/Q126K, D20V/Q126L, D20V/Q126M, D20V/Q126N, D20V/Q126P, D20V/Q126R, D20V/Q126S, D20V/Q126T, D20V/Q126V, D20V/Q126W, D20V/Q126Y, N88A/Q126A, N88A/Q126D, N88A/Q126E, N88A/Q126F, N88A/Q126G, N88A/Q126H, N88A/Q126I, N88A/Q126K, N88A/Q126L, N88A/Q126M, N88A/Q126N, N88A/Q126P, N88A/Q126R, N88A/Q126S, N88A/Q126T, N88A/Q126V, N88A/Q126W, N88A/Q126Y, N88G/Q126A, N88G/Q126D, N88G/Q126E, N88G/Q126F, N88G/Q126G, N88G/Q126H, N88G/Q126I, N88G/Q126K, N88G/Q126L, N88G/Q126M, N88G/Q126N, N88G/Q126P, N88G/Q126R, N88G/Q126S, N88G/Q126T, N88G/Q126V, N88G/Q126W, and N88G/Q126Y.

18. The Fc-based chimeric protein complex of claim 13, wherein the one or more mutations in the IL-2 signaling agent confers reduced affinity or bioactivity that is restorable by attachment to one or more targeting moieties or upon inclusion in the Fc-based chimeric protein complex,

optionally wherein the one or more targeting moieties are directed against a tumor cell, endothelial cell, epithelial cell, mesenchymal cell, tumor stroma or stromal cell, and/or ECM,

optionally wherein the one or more targeting moieties are directed against an immune cell and/or organ cells, and/or tissue cells, optionally wherein the immune cell is selected from a T cell, a B cell, a dendritic cell, a macrophage, a neutrophil, a mast cell, a monocyte, a red blood cell, myeloid cell, myeloid derived suppressor cell, a NKT cell, and a NK cell, or derivatives thereof, optionally, wherein the immune cell is a T cell and the targeting moiety targets CD8, or optionally wherein the immune cell is a Treg and the targeting moiety targets CTLA4, or optionally wherein the immune cell is an NK cell and the targeting moiety is Nkp46.

19. The Fc-based chimeric protein complex of claim 13, wherein the targeting moiety comprises a recognition domain that is a full-length antibody, a single-domain antibody, a recombinant heavy-chain-only antibody (VHH), a single-chain antibody (scFv), a shark heavy-chain-only antibody (VNAR), a microprotein (e.g. cysteine knot protein,

knottin), a darpin, an anticalin, an adnectin, an aptamer, a Fv, a Fab, a Fab', a F(ab')₂, a peptide mimetic molecule, a natural ligand for a receptor, or a synthetic molecule,

optionally wherein the recognition domain is a single-domain antibody, optionally wherein the recognition domain is a V_{HH} or humanized V_{HH},

optionally wherein the recognition domain functionally modulates the antigen or receptor of interest, or wherein the recognition domain binds but does not functionally modulate the antigen or receptor of interest,

optionally wherein the Fc-based chimeric protein complex comprises two or more targeting moieties,

wherein the targeting moieties binds to one or more of the following targets: CD8, CTLA4, CD3, CD4, DNAM-1, Nrp1 (neuropilin), TNFR1, TNFR2, GITR, ICOS, CD20, CD70, Clec9a, NKp46, PD-1, PD-L1, PD-L2, SIRP1 α , FAP, XCR1, tenascin, or ECM proteins,

optionally further comprising one or more additional modified signaling agents, optionally wherein the chimeric protein comprises two signaling agents or two targeting moieties or two of both, optionally wherein the chimeric protein comprises three signaling agents or three targeting moieties or three of both,

optionally wherein the additional modified signaling agent comprises one or more mutations conferring reduced affinity or activity for a receptor relative to an unmutated signaling agent,

optionally wherein the one or more mutations allow for attenuation of activity, optionally wherein agonistic or antagonistic activity is attenuated.

20. A recombinant nucleic acid composition encoding one or more Fc-based chimeric protein complexes of any one of claims 13-19, or a constituent polypeptide thereof.

21. A host cell comprising the recombinant nucleic acid of claim 20.

22. Use of the (i) Fc-based chimeric protein complex of any one of claims 13-19 to a patient in need thereof; ii) the recombinant nucleic acid of claim 20 to a patient in need thereof; or iii) the host cell of claim 21 in the manufacture of a medicament for the treatment of cancer or an autoimmune disease, optionally wherein the cancer is selected from one or more of basal cell carcinoma, biliary tract cancer; bladder cancer; bone cancer; brain and central nervous system cancer; breast cancer; cancer of the peritoneum; cervical cancer; choriocarcinoma; colon and rectum cancer; connective tissue cancer; cancer of the digestive system; endometrial cancer; esophageal cancer; eye cancer; cancer of the head and neck; gastric cancer (including gastrointestinal cancer); glioblastoma; hepatic carcinoma; hepatoma; intra-epithelial neoplasm; kidney or renal cancer; larynx cancer; leukemia; liver cancer; lung cancer (e.g., small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, and squamous carcinoma of the lung); melanoma; myeloma; neuroblastoma; oral cavity cancer (lip, tongue, mouth, and pharynx); ovarian cancer; pancreatic cancer; prostate cancer; retinoblastoma; rhabdomyosarcoma; rectal cancer; cancer of the respiratory system; salivary gland carcinoma; sarcoma (e.g., Kaposi's sarcoma); skin cancer; squamous cell cancer; stomach cancer; testicular cancer;

thyroid cancer; uterine or endometrial cancer; cancer of the urinary system; vulval cancer; lymphoma including Hodgkin's and non-Hodgkin's lymphoma, as well as B-cell lymphoma (including low grade/follicular non-Hodgkin's lymphoma (NHL); small lymphocytic (SL) NHL; intermediate grade/follicular NHL; intermediate grade diffuse NHL; high grade immunoblastic NHL; high grade lymphoblastic NHL; high grade small non-cleaved cell NHL; bulky disease NHL; mantle cell lymphoma; AIDS-related lymphoma; and Waldenstrom's Macroglobulinemia; chronic lymphocytic leukemia (CLL); acute lymphoblastic leukemia (ALL); Hairy cell leukemia; chronic myeloblastic leukemia; as well as other carcinomas and sarcomas; and post-transplant lymphoproliferative disorder (PTLD), as well as abnormal vascular proliferation associated with phakomatoses, edema (e.g. that associated with brain tumors), and Meigs' syndrome.

23. The Fc-based chimeric protein complex of any one of claims 13-19, wherein the Fc domain is from IgG, IgA, IgD, IgM or IgE, optionally human IgG, IgA, IgD, IgM or IgE, optionally wherein the IgG is selected from IgG1, IgG2, IgG3, or IgG4, optionally human IgG1, IgG2, IgG3, or IgG4,

optionally wherein the Fc chain pairing is promoted by ionic pairing and/or a knob-in-hole pairing, optionally wherein the one or more mutations to the Fc domain results in an ionic pairing between the Fc chains in the Fc domain, optionally wherein the one or more mutations to the Fc domain results in a knob-in-hole pairing in the Fc domain, optionally wherein the one or more mutations to the Fc domain results in the reduction or elimination of an effector function of the Fc domain,

optionally wherein the Fc-based chimeric protein complex is a heterodimer and has a trans orientation/configuration, as relates to any targeting moiety and signaling agent, relative to each other, or any targeting moieties relative to each other, or any signaling agents relative to each other, or optionally wherein the Fc-based chimeric protein complex is a heterodimer and has a cis orientation, as relates to any targeting moiety and signaling agent, relative to each other, or any targeting moieties relative to each other, or any signaling agents relative to each other,

optionally wherein the Fc comprises L234A, L235A, and K322Q substitutions in human IgG1 (according to EU numbering), optionally wherein the Fc is human IgG1, and optionally contains one or more mutations of L234, L235, K322, D265, P329, and P331 (according to EU numbering), optionally wherein the Fc-based chimeric protein complex has an orientation and/or configuration of any one of FIGs. 1A-F, 2A-H, 3A-H, 4A-D, 5A-F, 6A-J, 7A-D, 8A-F, 9A-J, 10A-F, 11A-L, 12A-L, 13A-F, 14A-L, 15A-L, 16A-J, 17A-J, 18A-F, 19A-F, 31, and 32,

optionally wherein the Fc-based chimeric protein complex comprises a polypeptide having an amino acid sequence having at least 90%, or at least 95%, or at least 96%, or at least 97%, or at least 98%, or at least 99% identity with any one of SEQ ID NOs: 292, 293, 294, 299, 301, 310, 311, 312, 315, 316, 319, 320, 325, 328, 332, 333, and 335, optionally wherein the chimeric protein or Fc-based chimeric protein complex comprises a polypeptide having an amino acid sequence having at least 90%, or at least 95%, or at least 96%, or at least 97%, or at least 98%, or at least 99% identity with any one of SEQ ID NOs: 292, 290-291, 293-449, 478-495, or 501-531.

24. A chimeric protein or protein complex comprising:

(a) a modified IL-2 signaling agent, wherein the modified IL-2 signaling agent has a single mutation relative to a wild type signaling agent having SEQ ID NO: 1 that confers improved safety and reduced affinity or bioactivity of the modified IL-2 signaling agent for IL-2R β , relative to the wild type IL-2 signaling agent; and

(b) one or more targeting moieties, said targeting moieties comprising recognition domains which specifically bind to antigens or receptors of interest,

wherein the modified IL-2, and the one or more targeting moieties are optionally connected with one or more linkers,

wherein the single mutation is selected from D20E, D20F, D20G, D20H, D20I, D20K, D20L, D20N, D20V, N88G, N88E, N88I, N88K, N88Q, N88R and N88V, and

wherein the modified IL-2 signaling agent does not comprise a mutation that confers reduced affinity or bioactivity for IL-2R α ,

optionally wherein the modified IL-2-signaling agent further comprises a glycosylation mutation, wherein the mutation decreases or eliminates glycosylation of the modified IL-2 signaling agent, optionally wherein the glycosylation mutation is a T3 substitution, wherein the mutation is one of T3A, T3F, T3H, T3L, T3V, and T3Y, or wherein the glycosylation mutation is a deletion of the first 3, 4, 5, 6, 7, or 8 residues of the modified IL-2,

optionally wherein the one or more mutations in the IL-2 signaling agent confers reduced affinity or bioactivity that is restorable by attachment to one or more targeting moieties,

optionally wherein the one or more targeting moieties are directed against a tumor cell, endothelial cell, epithelial cell, mesenchymal cell, tumor stroma or stromal cell, and/or ECM, or wherein the one or more targeting moieties are directed against an immune cell and/or organ cells, and/or tissue cells, optionally wherein the immune cell is selected from a T cell, a Treg, a cytotoxic T lymphocyte, a T helper cell, a B cell, a dendritic cell, an anti-tumor or tumor-associated macrophage (e.g., a M1 or M2 macrophage), a neutrophil, myeloid derived suppressor cell, a natural killer (NK) cell, and a natural killer T (NKT) cell, optionally, the immune cell is a T cell and the targeting moiety targets CD8, or optionally wherein the immune cell is a Treg and the targeting moiety targets CTLA4, or optionally wherein the immune cell is an NK cell and the targeting moiety is Nkp46.

25. The chimeric protein or protein complex of claim 24, wherein the targeting moiety comprises a recognition domain that is a full-length antibody, a single-domain antibody, a recombinant heavy-chain-only antibody (VHH), a single-chain antibody (scFv), a shark heavy-chain-only antibody (VNAR), a microprotein (e.g. cysteine knot protein, knottin), a darpin, an anticalin, an adnectin, an aptamer, a Fv, a Fab, a Fab', a F(ab')₂, a peptide mimetic molecule, a natural ligand for a receptor, or a synthetic molecule, optionally wherein the recognition domain is a single-domain antibody, optionally wherein the recognition domain is a VHH or humanized VHH, optionally wherein the recognition

domain functionally modulates the antigen or receptor of interest, or wherein the recognition domain binds but does not functionally modulate the antigen or receptor of interest,

optionally wherein the chimeric protein or protein complex comprises two or more targeting moieties,

optionally wherein the targeting moieties binds to one or more of the following targets: CD8, CTLA4, CD3, CD4, DNAM-1, Nrp1 (neurophilin), TNFR1, TNFR2, GTR, ICOS, CD20, CD70, Clec9a, NKp46, PD-1, PD-L1, PD-L2, SIRP1 α , FAP, XCR1, tenascin, or ECM proteins,

optionally wherein the chimeric protein or protein complex further comprises one or more additional modified signaling agents, optionally wherein the chimeric protein comprises two signaling agents and one targeting moiety or two targeting moieties and one signaling agent or two of both, optionally wherein the chimeric protein comprises three signaling agents or three targeting moieties or three of both,

optionally wherein the additional modified signaling agent comprises one or more mutations conferring reduced affinity or activity for a receptor relative to an unmutated signaling agent, optionally wherein the one or more mutations allow for attenuation of activity, optionally wherein agonistic or antagonistic activity is attenuated.

26. A recombinant nucleic acid composition encoding one or more chimeric proteins or protein complexes of claim 24 or 25.

27. A host cell comprising the recombinant nucleic acid of claim 26.

28. Use of the chimeric protein or protein complex of any one of claims 24 to 27 in the manufacture of a medicament for the treatment of cancer or an autoimmune disease, optionally wherein the cancer is selected from one or more of basal cell carcinoma, biliary tract cancer; bladder cancer; bone cancer; brain and central nervous system cancer; breast cancer; cancer of the peritoneum; cervical cancer; choriocarcinoma; colon and rectum cancer; connective tissue cancer; cancer of the digestive system; endometrial cancer; esophageal cancer; eye cancer; cancer of the head and neck; gastric cancer (including gastrointestinal cancer); glioblastoma; hepatic carcinoma; hepatoma; intra-epithelial neoplasm; kidney or renal cancer; larynx cancer; leukemia; liver cancer; lung cancer (*e.g.*, small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, and squamous carcinoma of the lung); melanoma; myeloma; neuroblastoma; oral cavity cancer (lip, tongue, mouth, and pharynx); ovarian cancer; pancreatic cancer; prostate cancer; retinoblastoma; rhabdomyosarcoma; rectal cancer; cancer of the respiratory system; salivary gland carcinoma; sarcoma (*e.g.*, Kaposi's sarcoma); skin cancer; squamous cell cancer; stomach cancer; testicular cancer; thyroid cancer; uterine or endometrial cancer; cancer of the urinary system; vulval cancer; lymphoma including Hodgkin's and non-Hodgkin's lymphoma, as well as B-cell lymphoma (including low grade/follicular non-Hodgkin's lymphoma (NHL); small lymphocytic (SL) NHL; intermediate grade/follicular NHL; intermediate grade diffuse NHL; high grade immunoblastic NHL; high grade lymphoblastic NHL; high grade small non-cleaved cell NHL; bulky disease NHL; mantle cell lymphoma; AIDS-related lymphoma; and Waldenstrom's Macroglobulinemia; chronic lymphocytic leukemia (CLL); acute lymphoblastic leukemia (ALL); Hairy cell leukemia; chronic myeloblastic leukemia; as well as other

carcinomas and sarcomas; and post-transplant lymphoproliferative disorder (PTLD), as well as abnormal vascular proliferation associated with phakomatoses, edema (e.g. that associated with brain tumors), and Meigs' syndrome.

29. A Fc-based chimeric protein complex comprising:

(a) a modified IL-2 signaling agent, wherein the modified IL-2 signaling agent has a single mutation relative to a wild type signaling agent having SEQ ID NO: 1 that confers improved safety and reduced affinity or bioactivity of the modified IL-2 signaling agent for IL-2R β , relative to the wild type IL-2 signaling agent; and

(b) one or more targeting moieties, said targeting moieties comprising recognition domains which specifically bind to antigens or receptors of interest; and

(c) a Fc domain, the Fc domain optionally having one or more mutations that reduces or eliminates one or more effector functions of the Fc domain, promotes Fc chain pairing in the Fc domain, and/or stabilizes a hinge region in the Fc domain,

wherein the single mutation is selected from D20E, D20V, N88G, D20F, D20G, D20H, D20I, D20K, D20L, D20N, N88E, N88I, N88K, N88Q, N88R and N88V, and

wherein the modified IL-2 signaling agent does not comprise a mutation that confers reduced affinity or bioactivity for IL-2R α ,

optionally wherein the modified IL-2-signaling agent further comprises a glycosylation mutation, wherein the mutation decreases or eliminates glycosylation of the modified IL-2 signaling agent, optionally wherein the glycosylation mutation is a T3 substitution, wherein the mutation is one of T3A, T3F, T3H, T3L, T3V, and T3Y, or wherein the glycosylation mutation is a deletion of the first 3, 4, 5, 6, 7, or 8 residues of the modified IL-2,

optionally wherein the one or more mutations in the IL-2 signaling agent confers reduced affinity or bioactivity that is restorable by attachment to one or more targeting moieties or upon inclusion in the Fc-based chimeric protein complex,

optionally wherein the one or more targeting moieties are directed against a tumor cell, endothelial cell, epithelial cell, mesenchymal cell, tumor stroma or stromal cell, and/or ECM, or optionally wherein the one or more targeting moieties are directed against an immune cell and/or organ cells, and/or tissue cells,

optionally wherein the immune cell is selected from a T cell, a B cell, a dendritic cell, a macrophage, a neutrophil, a mast cell, a monocyte, a red blood cell, myeloid cell, myeloid derived suppressor cell, a NKT cell, and a NK cell, or derivatives thereof, optionally, wherein the immune cell is a T cell and the targeting moiety targets CD8, or optionally wherein the immune cell is a Treg and the targeting moiety targets CTLA4, or optionally wherein the immune cell is an NK cell and the targeting moiety is NKp46.

30. The Fc-based chimeric protein complex of claim 29, wherein the targeting moiety comprises a recognition domain that is a full-length antibody, a single-domain antibody, a recombinant heavy-chain-only antibody (VHH), a single-chain antibody (scFv), a shark heavy-chain-only antibody (VNAR), a microprotein (e.g. cysteine knot protein, knottin), a darpin, an anticalin, an adnectin, an aptamer, a Fv, a Fab, a Fab', a F(ab')₂, a peptide mimetic molecule, a natural ligand for a receptor, or a synthetic molecule, optionally wherein the recognition domain is a single-domain antibody, optionally wherein the recognition domain is a VHH or humanized VHH,

optionally wherein the recognition domain functionally modulates the antigen or receptor of interest, or wherein the recognition domain binds but does not functionally modulate the antigen or receptor of interest,

optionally wherein the Fc-based chimeric protein complex comprises two or more targeting moieties, optionally wherein the targeting moieties binds to one or more of the following targets: CD8, CTLA4, CD3, CD4, DNAM-1, Nrp1 (neurophilin), TNFR1, TNFR2, GTR, ICOS, CD20, CD70, Clec9a, NKp46, PD-1, PD-L1, PD-L2, SIRP1 α , FAP, XCR1, tenascin, or ECM proteins.

31. The Fc-based chimeric protein complex of claim 29, further comprising one or more additional modified signaling agents, optionally wherein the chimeric protein comprises two signaling agents or two targeting moieties or two of both, optionally wherein the chimeric protein comprises three signaling agents or three targeting moieties or three of both,

optionally wherein the additional modified signaling agent comprises one or more mutations conferring reduced affinity or activity for a receptor relative to an unmutated signaling agent, optionally wherein the one or more mutations allow for attenuation of activity, optionally wherein agonistic or antagonistic activity is attenuated.

32. A recombinant nucleic acid composition encoding one or more Fc-based chimeric protein complexes of any one of claims 29 to 31, or a constituent polypeptide thereof.

33. A host cell comprising the recombinant nucleic acid of claim 32.

34. Use of the (i) Fc-based chimeric protein complex of any one of claims 29 to 31 to a patient in need thereof; ii) the recombinant nucleic acid of claim 32 to a patient in need thereof; or iii) the host cell of claim 33 in the manufacture of a medicament for the treatment of cancer or an autoimmune disease, optionally wherein the cancer is selected from one or more of basal cell carcinoma, biliary tract cancer; bladder cancer; bone cancer; brain and central nervous system cancer; breast cancer; cancer of the peritoneum; cervical cancer; choriocarcinoma; colon and rectum cancer; connective tissue cancer; cancer of the digestive system; endometrial cancer; esophageal cancer; eye cancer; cancer of the head and neck; gastric cancer (including gastrointestinal cancer); glioblastoma; hepatic carcinoma; hepatoma; intra-epithelial neoplasm; kidney or renal cancer; larynx cancer; leukemia; liver cancer; lung cancer (e.g., small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, and squamous carcinoma of the lung); melanoma; myeloma; neuroblastoma; oral cavity cancer (lip, tongue, mouth, and pharynx); ovarian cancer; pancreatic cancer; prostate cancer; retinoblastoma; rhabdomyosarcoma; rectal cancer; cancer of the respiratory system; salivary gland

carcinoma; sarcoma (e.g., Kaposi's sarcoma); skin cancer; squamous cell cancer; stomach cancer; testicular cancer; thyroid cancer; uterine or endometrial cancer; cancer of the urinary system; vulval cancer; lymphoma including Hodgkin's and non-Hodgkin's lymphoma, as well as B-cell lymphoma (including low grade/follicular non-Hodgkin's lymphoma (NHL); small lymphocytic (SL) NHL; intermediate grade/follicular NHL; intermediate grade diffuse NHL; high grade immunoblastic NHL; high grade lymphoblastic NHL; high grade small non-cleaved cell NHL; bulky disease NHL; mantle cell lymphoma; AIDS-related lymphoma; and Waldenstrom's Macroglobulinemia; chronic lymphocytic leukemia (CLL); acute lymphoblastic leukemia (ALL); Hairy cell leukemia; chronic myeloblastic leukemia; as well as other carcinomas and sarcomas; and post-transplant lymphoproliferative disorder (PTLD), as well as abnormal vascular proliferation associated with phakomatoses, edema (e.g. that associated with brain tumors), and Meigs' syndrome.

35. The Fc-based chimeric protein complex of any one of claims 29 to 31, wherein the Fc domain is from IgG, IgA, IgD, IgM or IgE, optionally wherein the Fc domain is from human IgG, IgA, IgD, IgM or IgE, optionally wherein the IgG is selected from IgG1, IgG2, IgG3, or IgG4, optionally wherein the human IgG is selected from human IgG1, IgG2, IgG3, or IgG4.

36. The Fc-based chimeric protein complex of any one of claims 29 to 31, wherein the Fc chain pairing is promoted by ionic pairing and/or a knob-in-hole pairing, optionally wherein the one or more mutations to the Fc domain results in an ionic pairing between the Fc chains in the Fc domain, optionally wherein the one or more mutations to the Fc domain results in a knob-in-hole pairing in the Fc domain, optionally wherein the one or more mutations to the Fc domain results in the reduction or elimination of an effector function of the Fc domain,

optionally wherein the Fc-based chimeric protein complex is a heterodimer and has a trans orientation/configuration, as relates to any targeting moiety and signaling agent, relative to each other, or any targeting moieties relative to each other, or any signaling agents relative to each other, or optionally wherein the Fc-based chimeric protein complex is a heterodimer and has a cis orientation, as relates to any targeting moiety and signaling agent, relative to each other, or any targeting moieties relative to each other, or any signaling agents relative to each other,

optionally wherein the Fc comprises L234A, L235A, and K322Q substitutions in human IgG1 (according to EU numbering), optionally wherein the Fc is human IgG1, and optionally contains one or more mutations of L234, L235, K322, D265, P329, and P331 (according to EU numbering), optionally wherein the Fc-based chimeric protein complex has an orientation and/or configuration of any one of FIGs. 1A-F, 2A-H, 3A-H, 4A-D, 5A-F, 6A-J, 7A-D, 8A-F, 9A-J, 10A-F, 11A-L, 12A-L, 13A-F, 14A-L, 15A-L, 16A-J, 17A-J, 18A-F, 19A-F, 31, and 32,

optionally wherein the Fc-based chimeric protein complex comprises a polypeptide having an amino acid sequence having at least 90%, or at least 95%, or at least 96%, or at least 97%, or at least 98%, or at least 99% identity with any one of SEQ ID NOs: 292, 293, 294, 299, 301, 310, 311, 312, 315, 316, 319, 320, 325, 328, 332, 333, and 335, optionally wherein the chimeric protein or Fc-based chimeric protein complex comprises a polypeptide having an amino acid

sequence having at least 90%, or at least 95%, or at least 96%, or at least 97%, or at least 98%, or at least 99% identity with any one of SEQ ID NOs: 292, 290-291, 293-449, 478-495, or 501-531.