ACTIVATABLE CYTOKINE CONSTRUCTS AND COMBINATION METHODS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 63/253,893, filed October 8, 2021 and U.S. Provisional Application No. 63/328,525, filed April 7, 2022. The entire contents of the above-identified applications are hereby fully incorporated herein by reference.

REFERENCE TO AN ELECTRONIC SEQUENCE LISTING

The contents of the electronic sequence listing entitled "CYTX086PCT.xml"; Size: 907,197 bytes; and Date of Creation: October 3, 2022, are incorporated herein by reference in their entirety.

TECHNICAL FIELD

The present disclosure relates to the field of biotechnology, and more specifically, to activatable cytokine constructs, including activatable cytokine constructs for use in immuno-oncology therapy.

BACKGROUND

Antibody-based therapies have been used for treating various diseases with varying degrees of success and, in some cases, toxicities due to broad target expression have limited their therapeutic effectiveness. In addition, antibody-based therapeutics have exhibited other limitations such as rapid clearance from the circulation following administration. Combination therapies have also been used with antibody-based therapies, but are often limited by increases in toxicities from the respective active drugs.

Cytokines are a family of naturally-occurring small proteins and glycoproteins produced and secreted by most nucleated cells in response to viral infection and/or other antigenic stimuli. Interferons are a subclass of cytokines. Interferons are presently grouped into three major classes: interferon type I, interferon type II, and interferon type III. Interferons exert their cellular activities by binding to specific membrane receptors on a cell surface.

Interferon therapy has many clinical benefits. For example, interferons are known to up-regulate the immune system and also to have antiviral and anti-proliferative properties. These biological properties have led to the clinical use of interferons as therapeutic agents for the treatment of viral infections and malignancies. Further,

interferons are useful for recruiting a patient's innate immune system to identify and attack cancer cells. Accordingly, interferon therapy has been extensively used in cancer and antiviral therapy, including for the treatment of hepatitis, Kaposi sarcoma, hairy cell leukemia, chronic myeloid leukemia (CML), follicular lymphoma, renal cell cancer (RCC), melanoma, and other disease states. However, systemic administration of interferons is accompanied by dose-dependent toxicities, including strong flu-like symtpoms, neurological symptoms, hepatotoxicity, bone marrow suppression, and arrythmia, among others. In a melanoma patient study, the combination of Pembrolizumab and Pegylated IFNa led to an ORR of 60.5%. The combination treatment was also associated with 49% of G3/G4 adverse events which required dose reduction of Pegylated IFNa (Davar et al., J. Clin. Oncol., 2018). These undesired side-effects have limited the dosage of interferon therapies and sometimes leads to discontinuation or delay of interferon treatment.

Interleukins are another subclass of cytokines. Interleukins regulate cell growth, differentiation, and motility. They are particularly important in stimulating immune responses, such as inflammation. Interleukins have been used for treatment of cancer, autoimmune disorders, and other disorders. For example, interleukin-2 (IL2) is indicated for treatment of melamona, graft-versus-host disease (GVHD), neuroblastoma, renal cell cancer (RCC), and is also considered useful for conditions including acute coronary syndrome, acute myeloid syndrome, atopic dermatitis, autoimmune liver diseases, basal cell carcinoma, bladder cancer, breast cancer, candidiasis, colorectal cancer, cutaneous T-cell lymphoma, endometriomas, HIV invention, ischemic heart disease, rheumatoid arthritis, nasopharyngeal adenocarcimoa, non-small cell lung cancer (NSCLC), ovarian cancer, pancreatic cancer, systemic lupus erythematosus, tuberculosis, and other disorders. Other interleukins, such as IL-6, IL-7, IL-12, and IL-21, among others, are potential treatments for cancers and other disorders. Interleukin therapy is often accompanied by undesired side effects, including flu-like symptoms, nausea, vomiting, diarrhea, low blood pressure, and arrhythmia, among others.

Under conditions of chronic stimulation, T cells upregulate and sustain expression of the inhibitory receptor PD-1 to negatively regulate the quality and magnitude of T cell responses. The primary ligand for PD-1, PD-L1, is upregulated on many tumor cells and

has been associated with inhibition of anti-tumor T-cell immunity via its engagement of PD-1 on tumor-infiltrating T cells. Clinical trials have confirmed the capacity of antibody blockade of either PD-1 or PD-L1 to restore the activity of durable tumor-specific immunity in patients across multiple tumor types. (Herbst et al, 2014; Lipson et al, 2015). PD-1/PD-L1 monotherapy has drawbacks, however, including a substantial number of non-responsive patients and/or patients showing recurrences, tumor resistance, and side effects associated with the autoimmune response.

Thus, the need and desire for improved specificity and selectivity of cytokine therapy to the desired target is of great interest. Increased targeting of cytokine therapeutics to the disease site could reduce systemic mechanism-based toxicities and lead to broader therapeutic utility. A further need exists for combination therapies to improve efficacy of treatments directed at inducing immune responses against various targets with specificity and selectivity.

SUMMARY

The present disclosure provides combinations, compositions, kits, and methods for treating a subject by administering a combination of an activatable cytokine construct (ACC) and a PD-1/PD-L1 pathway inhibitor to the subject. In certain aspects, the combination increases efficacy in therapy. In certain aspects, the combination reduces toxicity of one or both of the combination components when administered to the subject. In certain aspects, the combination reduces or inhibits tumor growth, proliferation, and/or metastasis. In certain aspects, the combination treats a subject suffering from cancer or an infection. In certain aspects, the combination augments or potentiates therapeutic efficacy and/or therapeutic index relative to a conventional cytokine therapy and/or conventional PD-1/PD-L1 inhibitor therapy in the subject. In certain aspects, the combination augments or potentiates therapeutic efficacy and/or therapeutic index relative to a conventional cytokine and PD-1/PD-L1 inhibitor combination therapy in the subject. In certain aspects, the combination augments or potentiates therapeutic efficacy and/or therapeutic index relative to administering the ACC alone.

In one aspect, the ACC may include: (a) a first monomer comprising a first peptide mask (PM1), a first mature cytokine protein (CP1), a first and a third cleavable moieties (CM1 and CM3), and a first dimerization domain (DD1), wherein the CM1 is

positioned between the CP1 and the DD1, and the CM3 is positioned between the PM1 and the CP1; and (b) a second monomer comprising a second mature cytokine protein (CP2), a second cleavable moiety (CM2), and a second dimerization domain (DD2), wherein the CM2 is positioned between the CP2 and the DD2, where: the CM1, the CM2, and the CM3 function as a substrate for a protease; the DD1 and the DD2 bind to each other; and where the ACC is characterized by a reduction in at least one activity of the CP1 and/or CP2 as compared to a control level of the at least one activity of the CP1 and/or CP2. The protease(s) that cleave the CM1, CM2, and CM3 may be over-expressed in diseased tissue (e.g., tumor tissue) relative to healthy tissue. The ACC may be activated upon cleavage of the CM1, CM2, and/or CM3 so that the cytokine may exert its activity in the diseased tissue (e.g., in a tumor microenvironment) while the cytokine activity is attenuated in the context of healthy tissue. Thus, the ACCs provided herein may provide reduced toxicity relative to traditional cytokine therapeutics, enable higher effective dosages of cytokine, and/or increase the therapeutic window for the cytokine.

Provided herein are activatable cytokine constructs (ACC) that include a first monomer construct and a second monomer construct, wherein: (a) the first monomer construct comprises a first peptide mask (PM1), a first mature cytokine protein (CP1), a first and a third cleavable moieties (CM1 and CM3), and a first dimerization domain (DD1), wherein the CM1 is positioned between the CP1 and the DD1, and the CM3 is positioned between the PM1 and the CP1; and (b) the second monomer construct comprises a second mature cytokine protein (CP2), a second cleavable moiety (CM2), and a second dimerization domain (DD2), wherein the CM2 is positioned between the CP2 and the DD2; wherein the DD1 and the DD2 bind each other thereby forming a dimer of the first monomer construct and the second monomer construct; and wherein the ACC is characterized by having a reduced level of at least one CP1 and/or CP2 activity as compared to a control level of the at least one CP1 and/or CP2 activity.

In some embodiments, the second monomer construct further comprises a second peptide mask (PM2) and a fourth cleavable moiety (CM4), wherein the CM4 is positioned between the PM2 and the CP2. In some embodiments, the first monomer construct comprises a first polypeptide that comprises the PM1, the CM3, the CP1, the CM1, and the DD1. In some embodiments, the second monomer construct comprises a

second polypeptide that comprises the CP2, the CM2, and the DD2. In some embodiments, the second monomer construct comprises a second polypeptide that comprises the PM2, the CM4, the CP2, the CM2, and the DD2.

In some embodiments, the PM1 comprises a sequence selected from the group consisting of SEQ ID NOs: 297, 298, 292, and 299-336, and the CP1 is an interferon; the PM1 comprises a sequence selected from the group consisting of SEQ ID NOs: 297, 298, 292, and 299-332, and the CP1 is an interferon α; the PM1 comprises a sequence selected from the group consisting of SEQ ID NOs: 299-328, and 330-332, and the CP1 is an interferon β; the PM1 comprises a sequence selected from the group consisting of SEQ ID NOs: 299-328, and 333-336, and the CP1 is an interferon γ; the PM1 comprises a sequence selected from the group consisting of SEQ ID NOs: 337-341, and the CP1 is an IL-12; the PM1 comprises a sequence selected from the group consisting of SEQ ID NOs: 342-349, 436-444, and 445, and the CP1 is an IL-15; the PM1 comprises a sequence selected from the group consisting of SEQ ID NOs: 350-435, and 436-445, and the CP1 is an IL-2; or the PM1 comprises a sequence selected from the group consisting of SEQ ID NOs: 445 and 446, and the CP1 is an IL-21. In some embodiments, the PM2 comprises a sequence selected from the group consisting of SEQ ID NOs: 297, 298, 292, and 299-336, and the CP2 is an interferon; the PM2 comprises a sequence selected from the group consisting of SEQ ID NOs: 297, 298, 292, and 299-364, and the CP2 is an interferon α; the PM2 comprises a sequence selected from the group consisting of SEQ ID NOs: 299-328, and 330-332, and the CP2 is an interferon β; the PM2 comprises a sequence selected from the group consisting of SEQ ID NOs: 299-328, and 333-336, and the CP2 is an interferon γ; the PM2 comprises a sequence selected from the group consisting of SEQ ID NOs: 337-341, and the CP2 is an IL-12; the PM2 comprises a sequence selected from the group consisting of SEQ ID NOs: 342-349, 436-444, and 445, and the CP2 is an IL-15; the PM2 comprises a sequence selected from the group consisting of SEQ ID NOs: 350-435, 436-445, and the CP2 is an IL-2; or the PM2 comprises a sequence selected from the group consisting of SEQ ID NOs: 445 and 446, and the CP2 is an IL-21. In some embodiments, the PM1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 297, 298, 292, and 299-

446. In some embodiments, the PM2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 297, 298, 292, and 299-446.

In some embodiments, the DD1 and the DD2 are a pair selected from the group consisting of: a pair of Fc domains, a sushi domain from an alpha chain of human IL-15 receptor (IL15Rα) and a soluble IL-15; barnase and barnstar; a protein kinase A (PKA) and an A-kinase anchoring protein (AKAP); adapter/docking tag modules based on mutated RNase I fragments; an epitope and single domain antibody (sdAb); an epitope and single chain variable fragment (scFv); and soluble N-ethyl-maleimide sensitive factor attachment protein receptors (SNARE) modules based on interactions of the proteins syntaxin, synaptotagmin, synaptobrevin, and SNAP25, an antigen-binding domain and an epitope.

In some embodiments, the DD1 and the DD2 are a pair of Fc domains. In some embodiments, the pair of Fc domains is a pair of human Fc domains. In some embodiments, the human Fc domains are human IgG1 Fc domains, human IgG2 Fc domains, human IgG3 Fc domains, or human IgG4 Fc domains. In some embodiments, the human Fc domains are human IgG4 Fc domains. In some embodiments, the human Fc domains each comprise a sequence that is at least 80% identical to SEQ ID NO: 3. In some embodiments, the human Fc domains each comprise a sequence that is at least 90%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 3. In some embodiments, the human Fc domains comprise SEQ ID NO: 3. In some embodiments, the DD1 and the DD2 comprise SEQ ID NOs: 287 and 288, respectively. In some embodiments, the DD1 and the DD2 are the same. In some embodiments, the human Fc domains include mutations to eliminate glycosylation and/or to reduce Fc-gamma receptor binding. In some embodiments, the human Fc domains comprise the mutation N297Q, N297A, or N297G; in some embodiments the human Fc domains comprise a mutation at postion 234 and/or 235, for example L235E, or L234A and L235A (in IgG1), or F234A and L235A (in IgG4); in some embodiments the human Fc domains are IgG2 Fc domains that comprise the mutations V234A, G237A, P238S, H268Q/A, V309L, A330S, or P331S, or a combination thereof (all according to EU numbering).

Additional examples of engineered human Fc domains are known to those skilled in the art. Examples of Ig heavy chain constant region amino acids in which mutations

in at least one amino acid leads to reduced Fc function include, but are not limited to, mutations in amino acid 228, 233, 234, 235, 236, 237, 239, 252, 254, 256, 265, 270, 297, 318, 320, 322, 327, 329, 330, and 331 of the heavy constant region (according to EU numbering). Examples of combinations of mutated amino acids are also known in the art, such as, but not limited to a combination of mutations in amino acids 234, 235, and 331, such as L234F, L235E, and P331S or a combination of amino acids 318, 320, and 322, such as E318A, K320A, and K322A.

Further examples of engineered Fc domains include F243L/R292P/Y300L/V305I/P396 IgG1; S239D/I332E IgG1; S239D/I332E/A330L IgG1; S298A/E333A/K334A; in one heavy chain, L234Y/L235Q/G236W/S239M/H268D/D270E/S298A IgG1, and in the opposing heavy chain, D270E/K326D, A330M/K334E IgG; G236A/S239D/I332E IgG1; K326W/E333S IgG1; S267E/H268F/S324T IgG1; E345R/E430G/S440Y IgG1; N297A or N297Q or N297G IgG1; L235E IgG1; L234A/L235A IgG1; F234A/L235A IgG4; H268Q/V309L/A330S/P331S IgG2; V234A/G237A/P238S/H268A/V309L/A330S/P331S IgG2; M252Y/S254T/T256E IgG1; M428L/N434S IgG1; S267E/L328F IgG1; N325S/L328F IgG1, and the like. In some embodiments, the engineered Fc domain comprises one or more substitutions selected from the group consisting of N297A IgG1, N297Q IgG1, and S228P IgG4.

In some embodiments, the DD1 comprises an antigen-binding domain and the DD2 comprises a corresponding epitope. In some embodiments, the antigen-binding domain is an anti-His tag antigen-binding domain and wherein the DD2 comprises a His tag. In some embodiments, the antigen-binding domain is a single chain variable fragment (scFv). In some embodiments, the antigen-binding domain is a single domain antibody (sdAb). In some embodiments, at least one of the DD1 and the DD2 comprises a dimerization domain substituent selected from the group consisting of a non-polypeptide polymer and a small molecule. In some embodiments, the DD1 and the DD2 comprise non-polypeptide polymers covalently bound to each other. In some embodiments, the non-polypeptide polymer is a sulfur-containing polyethylene glycol, and wherein the DD1 and the DD2 are covalently bound to each other via one or more disulfide bonds. In some embodiments, at least one of the DD1 and the DD2 comprises a small molecule. In

some embodiments, the small molecule is biotin. In some embodiments, the DD1 comprises biotin and the DD2 comprises an avidin.

In some embodiments, the CP1 and the CP2 are mature cytokines. In some embodiments, each of the CP1 and the CP2 comprise a mature cytokine sequence and further comprise a signal peptide. A signal peptide is also referred to herein as a "signal sequence." In some embodiments, the CP1 and/or the CP2 is/are each individually selected from the group consisting of: an interferon, an interleukin, GM-CSF, G-CSF, LIF, OSM, CD154, LT-β, TNF-α, TNF-β, 4-1BBL, APRIL, CD70, CD153, CD178, GITRL, LIGHT, OX40L, TALL-1, TRAIL, TWEAK, TRANCE, TGF-β1, TGF-β1, TGF-β3, Epo, Tpo, Flt-3L, SCF, M-CSF, and MSP, optionally wherein the CP1 and/or the CP2 is independently selected from IL-2, IL-7, IL-8, IL-10, IL-12, IL-15, IL-21, an IFN-alpha, an IFN beta, an IFN gamma, GM-CSF, TGF-beta, LIGHT, GITR-L, CD40L, CD27L, 4-1BB-L, OX40, and OX40L. In some embodiments, the CP1 and the CP2 are the same. In some embodiments, the CP1 and the CP2 are different. In some embodiments, the CP1 and/or the CP2 is/are an interferon. In some embodiments, the CP1 and the CP2 both are an interferon. In some embodiments, the CP1 and the CP2 are different interferons. In some embodiments, the CP1 and the CP2 are the same interferon. In some embodiments, one of the CP1 or the CP2 is an interferon, and the other of CP1 or CP2 is a cytokine other than an interferon. In some aspects, one or both cytokines are monomeric cytokines. In some aspects, one or both interferons are monomeric inteferons. In some aspects, either CP1 or CP2 is a monomeric interferon and the other CP1 or CP2 is a different cytokine. In some aspects, the CP1 and/or the CP2 include a mutant cytokine sequence. In some aspects, the CP1 and/or the CP2 include a universal cytokine sequence. In some aspects, the CP1 and/or the CP2 include a truncated sequence that retains cytokine activity.

In some embodiments, the interferon(s) is/are a human wildtype mature interferon. In some embodiments, the interferon(s) may be type I and type II interferons, for example including, but not limited to interferon-alpha, interferon-beta, interferon-gamma, interferon-omega, and interferon-tau. In some embodiments, the interferons is/are an interferon-alpha. In some embodiments, the interferon(s) is/are selected from the group consisting of: interferon alpha-2a, interferon alpha-2b, and interferon alpha-n3. In

some embodiments, the interferon(s) is/are interferon alpha-2b. In some embodiments, the interferon(s) is/are a mutant interferon. In some embodiments, the interferon(s) is/are a mutant interferon wherein an endogenous protease cleavage site has been rendered disfunctional by substitution, deletion, or insertion of one or more amino acids. In some embodiments, the interferon(s) is/are a universal cytokine molecule, e.g., having a hybrid sequence of different cytokine subtypes or a chimeric cytokine sequence or a humanized cytokine sequence. In some embodiments, the interferon(s) is/are a universal interferon molecule. In some embodiments, the interferon(s) is/are a universal interferon alpha, e.g., a hybrid of interferon alpha 1 and interferon alpha 2a. In some embodiments, the CP1 and/or the CP2 comprises a sequence that is at least 80% identical to SEQ ID NO: 1. In some embodiments, the CP1 and/or the CP2 comprises a sequence that is at least 90%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 1. In some embodiments, the CP1 and/or the CP2 comprises a sequence of SEQ ID NO: 1. In some embodiments, the interferon is an interferon beta. In some embodiments, the interferon beta is selected from the group consisting of interferon beta-1a, and interferon beta-1b. In some embodiments, the CP1 and/or the CP2 comprises an IFab domain. In some embodiments, the CP1 and/or the CP2 comprises an interleukin. In some embodiments, the interleukin is selected from the group consisting of IL-1α, IL-1β, IL-1RA, IL-18, IL-2, IL-4, IL-7, IL-9, IL-13, IL-15, IL-3, IL-5, IL-6, IL-11, IL-12, IL-10, IL-20, IL-14, IL-16, and IL-17.

In some embodiments, the CM1 and/or the CM2 comprise a total of about 3 amino acids to about 15 amino acids. In some embodiments, the CM1 and the CM2 comprise substrates for different proteases. In some embodiments, wherein the CM1 and the CM2 comprise substrates for the same protease. In some embodiments, the protease(s) is/are selected from the group consisting of: ADAM8, ADAM9, ADAM10, ADAM12, ADAM15, ADAM17/TACE, ADAMDEC1, ADAMTS1, ADAMTS4, ADAMTS5, BACE, Renin, Cathepsin D, Cathepsin E, Caspase 1, Caspase 2, Caspase 3, Caspase 4, Caspase 5, Caspase 6, Caspase 7, Caspase 8, Caspase 9, Caspase 10, Caspase 14, Cathepsin B, Cathepsin C, Cathepsin K, Cathespin L, Cathepsin S, Cathepsin V/L2, Cathepsin X/Z/P, Cruzipain, Legumain, Otubain-2, KLK4, KLK5, KLK6, KLK7, KLK8, KLK10, KLK11, KLK13, KLK14, Meprin, Neprilysin, PSMA, BMP-1, matrix metalloproteinases (e.g., MMP-1, MMP-2, MMP-3, MMP-7, MMP-9, MMP-10, MMP-

11, MMP-12, MMP-13, MMP-14, MMP-15, MMP-16, MMP-17, MMP-19, MMP-20, MMP-23, MMP-24, MMP-26, MMP-27), activated protein C, cathepsin A, cathepsin G, Chymase, FVIIa, FIXa, FXa, FXIa, FXIIa, Elastase, Granzyme B, Guanidinobenzoatase, HtrA1, human neutrophil lyase, lactoferrin, marapsin, NS3/4A, PACE4, Plasmin, PSA, tPA, thrombin, tryptase, uPA, DESC1, DPP-4, FAP, Hepsin, Matriptase-2, MT-SP1/Matripase, TMPRSS2, TMPRSS3, and TMPRSS4. In some embodiments, the protease(s) is/are selected from the group consisting of: uPA, legumain, MT-SP1, ADAM17, BMP-1, TMPRSS3, TMPRSS4, MMP-2, MMP-9, MMP-12, MMP-13, and MMP-14.

Suitable cleavable moieties have been disclosed in WO 2010/081173, WO 2015/048329, WO 2015/116933, WO 2016/118629, and WO 2020/118109, the disclosures of which are incorporated herein by reference in their entireties.

In some embodiments, the CM1 and/or the CM2 comprise a sequence selected from the group consisting of: LSGRSDNH (SEQ ID NO: 5), TGRGPSWV (SEQ ID NO: 6), PLTGRSGG (SEQ ID NO: 7), TARGPSFK (SEQ ID NO: 8), NTLSGRSENHSG (SEQ ID NO: 9), NTLSGRSGNHGS (SEQ ID NO: 10), TSTSGRSANPRG (SEQ ID NO: 11), TSGRSANP (SEQ ID NO: 12), VHMPLGFLGP (SEQ ID NO: 13), AVGLLAPP (SEQ ID NO: 14), AQNLLGMV (SEQ ID NO: 15), QNQALRMA (SEQ ID NO: 16), LAAPLGLL (SEQ ID NO: 17), STFPFGMF (SEQ ID NO: 18), ISSGLLSS (SEQ ID NO: 19), PAGLWLDP (SEQ ID NO: 20), VAGRSMRP (SEQ ID NO: 21), VVPEGRRS (SEQ ID NO: 22), ILPRSPAF (SEQ ID NO: 23), MVLGRSLL (SEQ ID NO: 24), QGRAITFI (SEQ ID NO: 25), SPRSIMLA (SEQ ID NO: 26), SMLRSMPL (SEQ ID NO: 27), ISSGLLSGRSDNH (SEQ ID NO: 28), AVGLLAPPGGLSGRSDNH (SEQ ID NO: 29), ISSGLLSSGGSGGSLSGRSDNH (SEQ ID NO: 30), LSGRSGNH (SEQ ID NO: 31), SGRSANPRG (SEQ ID NO: 32), LSGRSDDH (SEQ ID NO: 33), LSGRSDIH (SEQ ID NO: 34), LSGRSDQH (SEQ ID NO: 35), LSGRSDTH (SEQ ID NO: 36), LSGRSDYH (SEQ ID NO: 37), LSGRSDNP (SEQ ID NO: 38), LSGRSANP (SEQ ID NO: 39), LSGRSANI (SEQ ID NO: 40), LSGRSDNI (SEQ ID NO: 41), MIAPVAYR (SEQ ID NO: 42), RPSPMWAY (SEQ ID NO: 43), WATPRPMR (SEQ ID NO: 44), FRLLDWQW (SEQ ID NO: 45), ISSGL (SEQ ID NO: 46), ISSGLLS (SEQ ID NO: 47), ISSGLL (SEQ ID NO: 48), ISSGLLSGRSANPRG (SEQ ID NO: 49),

AVGLLAPPTSGRSANPRG (SEQ ID NO: 50), AVGLLAPPSGRSANPRG (SEQ ID NO: 51), ISSGLLSGRSDDH (SEQ ID NO: 52), ISSGLLSGRSDIH (SEQ ID NO: 53), ISSGLLSGRSDQH (SEQ ID NO: 54), ISSGLLSGRSDTH (SEQ ID NO: 55), ISSGLLSGRSDYH (SEQ ID NO: 56), ISSGLLSGRSDNP (SEQ ID NO: 57), ISSGLLSGRSANP (SEQ ID NO: 58), ISSGLLSGRSANI (SEQ ID NO: 59), AVGLLAPPGGLSGRSDDH (SEQ ID NO: 60), AVGLLAPPGGLSGRSDIH (SEQ ID NO: 61), AVGLLAPPGGLSGRSDQH (SEQ ID NO: 62), AVGLLAPPGGLSGRSDTH (SEQ ID NO: 63), AVGLLAPPGGLSGRSDYH (SEQ ID NO: 64), AVGLLAPPGGLSGRSDNP (SEQ ID NO: 65), AVGLLAPPGGLSGRSANP (SEQ ID NO: 66), AVGLLAPPGGLSGRSANI (SEQ ID NO: 67), ISSGLLSGRSDNI (SEQ ID NO: 68), AVGLLAPPGGLSGRSDNI (SEQ ID NO: 69), GLSGRSDNHGGAVGLLAPP (SEQ ID NO: 70), GLSGRSDNHGGVHMPLGFLGP (SEQ ID NO: 71), LSGRSDNHGGVHMPLGFLGP (SEQ ID NO: 72), ISSGLSS (SEQ ID NO: 73), PVGYTSSL (SEQ ID NO: 74), DWLYWPGI (SEQ ID NO: 75), LKAAPRWA (SEQ ID NO: 76), GPSHLVLT (SEQ ID NO: 77), LPGGLSPW (SEQ ID NO: 78), MGLFSEAG (SEQ ID NO: 79), SPLPLRVP (SEQ ID NO: 80), RMHLRSLG (SEQ ID NO: 81), LLAPSHRA (SEQ ID NO: 82), GPRSFGL (SEQ ID NO: 83), GPRSFG (SEQ ID NO: 84), SARGPSRW (SEQ ID NO: 85), GGWHTGRN (SEQ ID NO: 86), HTGRSGAL (SEQ ID NO: 87), AARGPAIH (SEQ ID NO: 88), RGPAFNPM (SEQ ID NO: 89), SSRGPAYL (SEQ ID NO: 90), RGPATPIM (SEQ ID NO: 91), RGPA (SEQ ID NO: 92), GGQPSGMWGW (SEQ ID NO: 93), FPRPLGITGL (SEQ ID NO: 94), SPLTGRSG (SEQ ID NO: 95), SAGFSLPA (SEQ ID NO: 96), LAPLGLQRR (SEQ ID NO: 97), SGGPLGVR (SEQ ID NO: 98), PLGL (SEQ ID NO: 99), and SGRSDNI (SEQ ID NO: 100). In some embodiments, the CM comprises a sequence selected from the group consisting of: ISSGLLSGRSDNH (SEQ ID NO: 28), LSGRSDDH (SEQ ID NO: 33), ISSGLLSGRSDQH (SEQ ID NO: 54), SGRSDNI (SEQ ID NO: 100), and ISSGLLSGRSDNI (SEQ ID NO: 68). In some embodiments, the protease(s) is/are produced by a tumor in the subject, e.g., the protease(s) are produced in greater amounts in the tumor than in healthy tissues of the subject. In some embodiments, the subject has been diagnosed or identified as having a cancer.

In some embodiments, the CP1 and the CM1 directly abut each other in the first monomer construct. In some embodiments, the CM1 and the DD1 directly abut each other in the first monomer construct. In some embodiments, the CP2 and the CM2 directly abut each other in the second monomer construct. In some embodiments, the CM2 and the DD2 directly abut each other in the second monomer construct. In some embodiments, the first monomer contruct comprises the CP1 directly abutting the CM1, and the CM1 directly abutting the DD1, wherein the CM1 comprises a sequence that is selected from the group consisting of SEQ ID Nos 5-100. In some embodiments, the second monomer contruct comprises the CP2 directly abutting the CM2, and the CM2 directly abutting the DD2, wherein the CM2 comprises a sequence that is selected from the group consisting of SEQ ID Nos 5-100. In some embodiments, the first monomer contruct comprises the CP1 directly abutting the CM1, and the CM1 directly abutting the DD1, wherein the CM1 comprises a sequence that is no more than 13, 12, 11, 10, 9, 8, 7, 6, 5 or 4 amino acids in length. In some embodiments, the second monomer contruct comprises the CP2 directly abutting the CM2, and the CM2 directly abutting the DD2, wherein the CM2 comprises a sequence that is no more than 13, 12, 11, 10, 9, 8, 7, 6, 5 or 4 amino acids in length. In some embodiments, the first and second monomer construct each are configured such that the cytokine (CM1 and CM2, respectively) directly abuts a cleavable moiety (CM1 and CM2, respectively) that is no more than 10, 9, 8, 7, 6, 5, or 4 amino acids in length, and the cleavable moiety directly abuts a dimerization domain (DD1 and DD2, respectively) that is the Fc region of a human IgG, wherein the N-terminus of the Fc region is the first cysteine residue (reading in the N- to C- direction) in the hinge region that participates in a disulfide linkage with a second Fc domain (e.g., Cysteine 226 of human IgG1, using EU numbering). In some aspects, the dimerization domain is an IgG Fc region wherein the upper hinge residues have been deleted. For example, the Fc is a variant wherein N-terminal sequences EPKSCDKTHT (SEQ ID NO: 522), ERK, ELKTPLGDTTHT (SEQ ID NO: 523), or ESKYGPP (SEQ ID NO: 524 have been deleted.

In some embodiments, the first monomer construct comprises at least one linker. In some embodiments, the at least one linker is a linker L1 disposed between the PM1 and the CM3 and/or a linker L2 disposed between the CM3 and the CP1. In some

embodiments, the second monomer construct comprises at least one linker. In some embodiments, the at least one linker is a linker L3 disposed between the PM2 and the CM4 and/or a linker L4 disposed between the CM4 and the CP2. In some embodiments, the first monomer construct comprises a linker L1 and the second monomer construct comprises a linker L3. In some embodiments, L1 and L3 are the same. In some embodiments, the first monomer construct comprises a linker L2 and the second monomer construct comprises a linker L4. In some embodiments, L2 and L4 are the same. In some embodiments, the first monomer construct comprises a linker between the CP1 and CM1 and/or a linker between the CM1 and the DD1. In some embodiments, the second monomer construct comprises a linker between the CP2 and the CM2 and/or a linker between the CM2 and the DD2. In some embodiments, each linker has a total length of 1 amino acid to about 15 amino acids. In some embodiments, each linker has a total length of at least 5 amino acids.

In some embodiments, the first monomer construct comprises at least one linker, wherein each linker is independently selected from from the group consisting of GSSGGSGGSGG (SEQ ID NO: 210); GGGS (SEQ ID NO: 2); GGGSGGGS (SEQ ID NO: 211); GGGSGGGSGGGS (SEQ ID NO: 212); GGGGSGGGGSGGGGS (SEQ ID NO: 213); GGGGSGGGGSGGGGSGGGGSGGGGS (SEQ ID NO: 214); GGGGSGGGGS (SEQ ID NO: 215); GGGGS (SEQ ID NO: 216); GS; GGGGSGS (SEQ ID NO: 217); GGGGSGGGGSGGGGSGS (SEQ ID NO: 218); GGSLDPKGGGGS (SEQ ID NO: 219); PKSCDKTHTCPPCPAPELLG (SEQ ID NO: 220); SKYGPPCPPCPAPEFLG (SEQ ID NO: 221); GKSSGSGSESKS (SEQ ID NO: 222); GSTSGSGKSSEGKG (SEQ ID NO: 223); GSTSGSGKSSEGSGSTKG (SEQ ID NO: 224); GSTSGSGKPGSGEGSTKG (SEQ ID NO: 225); GSTSGSGKPGSSEGST (SEQ ID NO: 226); (GS)n, (GGS)n, (GSGGS)n (SEQ ID NO: 227), (GGGS)n (SEQ ID NO: 228), (GGGGS)n (SEQ ID NO: 216), wherein each n is an integer of at least one; GGSG (SEQ ID NO: 229); GGSGG (SEQ ID NO: 230); GSGSG (SEQ ID NO: 231; GSGGG (SEQ ID NO: 232); GGGSG (SEQ ID NO: 233); GSSSG (SEQ ID NO: 234); GGGGSGGGGSGGGGS (SEQ ID NO: 213); GGGGSGGGGSGGGGSGGGGS (SEQ ID NO: 214); and GSTSGSGKPGSSEGST (SEQ ID NO: 226). In some embodiments, the linker comprises a sequence of GGGS (SEQ ID NO: 2).

In some embodiments, the first monomer construct, comprises in an N- to C-terminal direction, the PM1, the CM3, the CP1, the CM1, and, linked directly or indirectly to the C-terminus of the CM1, the DD1. In some embodiments, the first polypeptide comprises in a C- to N-terminal direction, the PM1, the CM3, the CP1, the CM1, and, linked directly or indirectly to the N-terminus of the CM1, the DD1. In some embodiments, the second polypeptide comprises in a N- to C-terminal direction, the PM2, the CM4, the CP2, the CM2, and, linked directly or indirectly to the C-terminus of the CM2, the DD2. In some embodiments, the second polypeptide comprises in a C- to N-terminal direction, the PM2, the CM4, the CP2, the CM2, and, linked directly or indirectly to the CM2, the DD2.

In some embodiments, the first monomer construct comprises in an N- to C-terminal direction, the CP1, an optional linker, the CM1, an optional linker, and the DD1, wherein DD1 is an Fc region of an IgG, wherein the N-terminus of the Fc region is the first cysteine residue (reading in the N- to C- direction) in the hinge region that participates in a disulfide linkage with a second Fc domain (e.g., Cysteine 226 of human IgG1 or IgG4, using EU numbering), and wherein the CM1 and any linker(s) interposed between the CP1 and the N-terminal cysteine of DD1 (the "linking region" or "LR") have a combined total length of no more than 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, or 4 amino acids, preferably no more than 10 amino acids, especially preferably no more than 7 amino acids. In some such embodiments, the first monomer construct further comprises, in an N- to C- terminal direction, the PM1, an optional linker, the CM3, and an optional linker attached to the N-terminus of the CP1. In some embodiments, the second monomer construct comprises in an N- to C- terminal direction, the CP2, an optional linker, the CM2, an optional linker, and the DD2, wherein DD2 is an Fc region of an IgG, wherein the N-terminus of the Fc region is the first cysteine residue (reading in the N- to C- direction) in the hinge region that participates in a disulfide linkage with a second Fc domain (e.g., Cysteine 226 of human IgG1 or IgG4, using EU numbering), and wherein the CM2 and any linker(s) interposed between the CP2 and the N-terminal cysteine of the DD2 (the "linking region" or "LR") have a combined total length of no more than 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, or 4 amino acids, preferably no more than 10 amino acids, especially preferably no more than 7 amino acids. In some

such embodiments, the second monomer construct further comprises, in an N- to C-terminal direction, the PM2, an optional linker, the CM4, and an optional linker attached to the N-terminus of the CP2. In some aspects, there is no linker or spacer between a peptide mask and a cleavable moiety. In some aspects, there is no linker or spacer between a cytokine protein and a cleavable moiety. In some aspects, there is no linker or spacer between a cleavable moiety and a dimerization domain.

In some embodiments, the ACC is a homodimer in which the first monomer construct and the second monomer construct are identical and comprise the amino acid sequence of SEQ ID NO: 290. In some embodiments, the first monomer construct and the second monomer construct each comprise an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 290. In some embodiments, the ACC is a homodimer in which the first monomer construct and the second monomer construct are identical and comprise the amino acid sequence of SEQ ID NO: 290 without the N-terminal spacer sequence (QSGQ). In some embodiments, the first monomer construct and the second monomer construct each comprise, in an N- to C-terminal direction, SEQ ID NO: 292; an optional flexible linker of zero to 10 amino acids; a CM comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 41, SEQ ID NO: 68, and SEQ ID NO: 100; an optional flexible linker of zero to 10 amino acids; SEQ ID NO:1; a second CM comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 41, SEQ ID NO: 68, and SEQ ID NO: 100; and a dimerization domain.

In some embodiments, the at least one CP1 and/or CP2 activity is a binding affinity of the CP1 and/or the CP2 for its cognate receptor as determined using surface plasmon resonance. For example, where the CP1 or CP2 is an interferon, the cognate receptor may be the interferon-alpha/beta receptor (IFNAR). In some embodiments, the at least one CP1 and/or CP2 activity is a level of proliferation of lymphoma cells. In some embodiments, the at least one CP1and/or CP2 activity is the level of JAK/STAT/ISGF3 pathway activation in a lymphoma cell. In some embodiments, the at least one activity is a level of secreted alkaline phosphatase (SEAP) production in a lymphoma cell. In some embodiments, the ACC is characterized by at least a 2-fold reduction in at least one of the CP1 and the CP2 activity as compared to the control level.

In some embodiments, the ACC is characterized by at least a 5-fold, 10-fold, 20-fold, 50-fold, 100-fold, 200-fold, 300-fold, 400-fold, 500-fold, 600-fold, 700-fold, 800-fold, 900-fold, 1000-fold, 1100-fold, 1200-fold, 1300-fold, 1400-fold, 1500-fold, 1600-fold, 1700-fold, 1800-fold, 1900-fold, 2000-fold, 3000-fold, or 4000-fold reduction in at least one CP1 and/or the CP2 activity as compared to the control level. In some embodiments, the ACC is characterized by at least a 5000-fold reduction in at least one activity of the CP1 and/or the CP2 as compared to the control level. In some embodiments, the control level of the at least one activity of the CP1 and/or CP2, is the activity of the CP1 and/or the CP2 in the ACC following exposure of the ACC to the protease(s). In some embodiments, the control level of the at least one CP1 and/or the CP2, is the corresponding the CP1 and/or the CP2 activity of a corresponding wildtype mature cytokine.

In some embodiments, the ACC is characterized by generating a cleavage product following exposure to the protease(s), wherein the cleavage product comprises the at least one activity of the CP1 and/or the CP2. In some embodiments, the at least one activity of the CP1 and/or the CP2 is anti-proliferation activity. In some embodiments, the control level is an EC50 value of the wildtype mature cytokine, and wherein ratio of EC50 (cleavage product) to EC50 (wildtype control level) is less than about 10, or less than about 9, or less than about 8, or less than about 7, or less than about 6, or less than about 5, or less than about 4, or less than about 3, or less than about 2, or less than about 1.5, or equal to about 1. In some embodiments, the EC50 of the cleavage product is approximately the same as the EC50 of the wildtype mature cytokine, demonstrating that the following cleavage, the activity of the CP1 and/or CP2 is fully recovered, or nearly fully recovered.

In some aspects, the ACCs include: (a) a first monomer comprising a first mature cytokine protein (CP1), a first cleavable moiety (CM1), and a first dimerization domain (DD1), wherein the CM1 is positioned between the CP1 and the DD1; and (b) a second monomer comprising a second mature cytokine protein (CP2), a second cleavable moiety (CM2), and a second dimerization domain (DD2), wherein the CM2 is positioned between the CP2 and the DD2, where: the CM1 and the CM2 function as a substrate for a protease; the DD1 and the DD2 bind each other; and where the ACC is characterized by a

reduction in at least one activity of the CP1 and/or CP2 as compared to a control level of the at least one activity of the CP1 and/or CP2. The protease(s) that cleave the CM1 and CM2 may be over-expressed in diseased tissue (e.g., tumor tissue) relative to healthy tissue. The ACC may be activated upon cleavage of the CM1 and/or CM2 so that the cytokine may exert its activity in the diseased tissue (e.g., in a tumor microenvironment) while the cytokine activity is attenuated in the context of healthy tissue.

Provided herein are activatable cytokine constructs (ACC) that include a first monomer construct and a second monomer construct, wherein: (a) the first monomer construct comprises a first mature cytokine protein (CP1), a first cleavable moiety (CM1), and a first dimerization domain (DD1), wherein the CM1 is positioned between the CP1 and the DD1; and (b) the second monomer construct comprises a second mature cytokine protein (CP2), a second cleavable moiety (CM2), and a second dimerization domain (DD2), wherein the CM2 is positioned between the CP2 and the DD2; wherein the DD1 and the DD2 bind each other thereby forming a dimer of the first monomer construct and the second monomer construct; and wherein the ACC is characterized by having a reduced level of at least one CP1 and/or CP2 activity as compared to a control level of the at least one CP1 and/or CP2 activity.

The present disclosure provides activatable cytokine constructs (ACCs) that include: (a) a first monomer comprising a first mature cytokine protein (CP1), a first dimerization domain (DD1); and (b) a second monomer comprising a second mature cytokine protein (CP2), a cleavable moiety (CM), and a second dimerization domain (DD2), wherein the CM is positioned between the CP2 and the DD2, where: the CM functions as a substrate for a protease; the DD1 and the DD2 bind each other; and where the ACC is characterized by a reduction in at least one activity of the CP1 and/or CP2 as compared to a control level of the at least one activity of the CP1 and/or CP2.

The present disclosure provides activatable cytokine constructs (ACCs) that include: (a) a first monomer comprising a first mature cytokine protein (CP1), a cleavable moiety (CM), and a first dimerization domain (DD1), wherein the CM is positioned between the CP1 and the DD1; and (b) a second monomer comprising a second mature cytokine protein (CP2), and a second dimerization domain (DD2), where: the CM functions as a substrate for a protease; the DD1 and the DD2 bind each other; and where

the ACC is characterized by a reduction in at least one activity of the CP1 and/or CP2 as compared to a control level of the at least one activity of the CP1 and/or CP2.

The present disclosure provides activatable cytokine constructs (ACCs) that include: (a) a first monomer comprising a first mature cytokine protein (CP1), and a first dimerization domain (DD1); and (b) a second monomer comprising a second mature cytokine protein (CP2), and a second dimerization domain (DD2), wherein the CP1, the CP2, or both CP1 and CP2 include(s) an amino acid sequence that functions as a substrate for a protease; the DD1 and the DD2 bind each other; and where the ACC is characterized by a reduction in at least one activity of the CP1 and/or CP2 as compared to a control level of the at least one activity of the CP1 and/or CP2.

Thus, the ACCs of the present disclosure do not require that CP1 and CP2 are connected to peptide masks, for example, affinity masking moieties; such peptide masks are an optional feature of certain ACCs of the present disclosure.

In some embodiments, the ACC is administered in combination with a PD-1/PD-L1 pathway inhibitor. The disclosure provides inhibitors that specifically bind programmed cell death protein 1 (PD-1), also known as CD279, SLEB2, and/or hSLE1, and inhibitors that specifically bind programmed death-ligand 1, also known as cluster of differentiation 274 or B7 homolog 1 and/or B7-H1. The use of the term "PD-1" or "PD-L1" is intended to cover any variation thereof, such as, by way of non-limiting example, PD1 and/or PD-1 and PDL1 and/or PD-L1, all variations are used herein interchangeably.

In some embodiments, the ACC that is administered in combination with the PD-1/PD-L1 pathway inhibitor comprises a CP1 and/or the CP2 that is/are each individually selected from the group consisting of: an interferon, an interleukin, GM-CSF, G-CSF, LIF, OSM, CD154, LT-β, TNF-α, TNF-β, 4-1BBL, APRIL, CD70, CD153, CD178, GITRL, LIGHT, OX40L, TALL-1, TRAIL, TWEAK, TRANCE, TGF-β1, TGF-β1, TGF-β3, Epo, Tpo, Flt-3L, SCF, M-CSF, and MSP, optionally wherein the CP1 and/or the CP2 is independently selected from IL-2, IL-7, IL-8, IL-10, IL-12, IL-15, IL-21, an IFN-alpha, an IFN beta, an IFN gamma, GM-CSF, TGF-beta, LIGHT, GITR-L, CD40L, CD27L, 4-1BB-L, OX40, and OX40L. In preferred embodiments, CP1 and/or the CP2 is/are each individually selected from an interferon as described above. In more preferred

embodiments, the ACC that is administered in combination with the PD-1/PD-L1 pathway inhibitor comprises a CP1 and CP2 that are each interferon alpha-2b.

In some embodiments, the PD-1/PD-L1 pathway inhibitor is an antibody or antigen-binding fragment thereof that specifically binds PD-1 or PD-L1. In some embodiments, the antibody or antigen-binding fragment thereof that binds PD-1 or PD-L1 is a monoclonal antibody, domain antibody, single chain, Fab fragment, a $F(ab')_2$ fragment, a scFv, a scAb, a dAb, a single domain heavy chain antibody, or a single domain light chain antibody. In some embodiments, such an antibody or antigen-binding fragment thereof that binds PD-1 or PD-L1 is a mouse, other rodent, chimeric, humanized or fully human monoclonal antibody. In some embodiments, the antibody includes an isolated antibody or antigen binding fragment thereof (AB) that specifically binds to mammalian PD-1 or PD-L1, wherein the AB has one or more of the characteristics selected from the group consisting of: (a) the AB inhibits binding of mammalian PD-1 to mammalian PDL1. In some embodiments, the PD-1/PD-L1 pathway inhibitor is an activatable antibody.

In some embodiments, the antibody includes an isolated antibody or antigen binding fragment thereof (AB) that specifically binds to mammalian PD-1 or PD-L1, wherein the AB has one or more of the characteristics selected from the group consisting of: (a) the AB inhibits binding of mammalian PD-1 to mammalian PDL1 with an EC50 value less than 5 nM; (b) the AB inhibits binding of mammalian PD-1 to mammalian PDL2 with an EC50 value less than 5 nM; and (c) the AB specifically binds to human PD-1 and cynomolgus monkey PD-1.

In some embodiments, the antibody specifically binds to the mammalian PD-1 or PD-L1 with a dissociation constant of 0.01 nM to 5 nM, 0.05 nM to 5 nM, 0.1 nM to 5 nM, 0.2 nM to 5 nM, 0.3 nM to 5 nM, 0.4 nM to 5 nM, 0.5 nM to 5 nM, 0.75 nM to 5 nM, 1 nM to 5 nM, 2 nM to 5 nM, 0.01 nM to 2 nM, 0.05 nM to 2 nM, 0.1 nM to 2 nM, 0.2 nM to 2 nM, 0.3 nM to 2 nM, 0.4 nM to 2 nM, 0.5 nM to 2 nM, 0.75 nM to 1 nM, 1 nM to 2 nM, 0.01 nM to 1 nM, 0.05 nM to 1 nM, 0.1 nM to 1 nM, 0.2 nM to 1 nM, 0.3 nM to 1 nM, 0.4 nM to 1 nM, 0.5 nM to 1 nM, 0.75 nM to 1 nM, 0.01 nM to 0.75 nM, 0.05 nM to 0.75 nM, 0.1 nM to 0.75 nM, 0.2 nM to 0.75 nM, 0.3 nM to 0.75 nM, 0.4 nM to 0.75 nM, 0.5 nM to 0.75 nM, 0.01 nM to 0.5 nM, 0.05 nM to 0.5 nM, 0.1 nM to 0.5

nM, 0.2 nM to 0.5 nM, 0.3 nM to 0.5 nM, 0.4 nM to 0.5 nM, 0.01 nM to 0.4 nM, 0.05 nM to 0.4 nM, 0.1 nM to 0.4 nM, 0.2 nM to 0.4 nM, 0.3 nM to 0.4 nM, 0.01 nM to 0.3 nM, 0.05 nM to 0.3 nM, 0.1 nM to 0.3 nM, 0.2 nM to 0.3 nM, 0.01 nM to 0.2 nM, 0.05 nM to 0.2 nM, 0.1 nM to 0.2 nM, 0.01 nM to 0.1 nM, 0.05 nM to 0.1 nM, or 0.01 nM to 0.05 nM.

In some embodiments, the mammalian PD-1/PD-L1 is selected from the group consisting of a human PD-1/PD-L1 and a cynomolgus monkey PD-1/PD-L1. In some embodiments, the mammalian PD-1/PD-L1 is a murine PD-1/PD-L1. In some embodiments, the antibody specifically binds to human PD-1/PD-L1 or cynomolgus monkey PD-1/PD-L1 with a dissociation constant of less than or equal to 1 nM. In some embodiments, the mammalian PD-1/PD-L1 is a human PD-1/PD-L1.

In some embodiments, the antibody or antigen binding fragment thereof specifically binds to the mammalian PD-1 or PD-L1with a dissociation constant is less than or equal to 0.01 nM, less than or equal to 0.05 nM, less than or equal to 0.1 nM, less than or equal to 0.2 nM, less than or equal to 0.3 nM, less than or equal to 0.4 nM, less than or equal to 0.5 nM, less than or equal to 0.75 nM, and less than or equal to 1 nM.

In some embodiments, the antibody has one or more of the characteristics selected from the group consisting of: (a) the AB specifically binds human PD-1 or PD-L1 and cynomolgus monkey PD-1 or PD-L1; (b) the AB inhibits binding of human PDL1 and human PDL2 to human PD-1; (c) the AB inhibits binding of cynomolgus monkey PDL1 and cynomolgus monkey PDL2 to cynomolgus monkey PD-1; (d) the AB specifically binds to murine PD-1; and (e) the AB inhibits binding of murine PDL1 and murine PDL2 to murine PD-1.

In some embodiments, the antibody blocks the ability of a natural ligand to bind to the mammalian PDL1 with an EC50 of 0.1 nM to 10 nM, 0.1 nM to 5 nM, 0.1 nM to 3 nM, 0.1 nM to 2 nM, 0.1 nM to 1 nM, 0.1 nM to 0.5 nM, 0.1 nM to 0.25 nM, 0.25 nM to 10 nM, 0.25 nM to 5 nM, 0.25 nM to 3 nM, 0.25 nM to 2 nM, 0.25 nM to 1 nM, 0.25 nM to 0.5 nM, 0.5 nM to 10 nM, 0.5 nM to 5 nM, 0.5 nM to 3 nM, 0.5 nM to 2 nM, 0.5 nM to 1 nM, 1 nM to 10 nM, 1 nM to 5 nM, 1 nM to 3 nM, 1 nM to 2 nM, 2 nM to 10 nM, 2 nM to 5 nM, 2 nM to 3 nM, 3 nM to 10 nM, 3 nM to 5 nM, or 5 nM to 10 nM. In some embodiments, the natural ligand is a mammalian PDL1 or a mammalian PDL2. In some

embodiments, the natural ligand is selected from the group consisting of: a human PDL1, a human PDL2, a cynomolgus monkey PDL1, and a cynomolgus monkey PDL2. In some embodiments, the natural ligand is a murine PDL1 or a murine PDL2.

In some embodiments, the antibody blocks the ability of a natural ligand to bind to the mammalian PDL1 with an EC50 of less than or equal to 0.1 nM, less than or equal to 0.25 nM, less than or equal to 0.5 nM, less than or equal to 1 nM, less than or equal to 2 nM, less than or equal to 3 nM, less than or equal to 4 nM, less than or equal to 5 nM or less than or equal to 10 nM.

In some embodiments, the anti-PD-1 antibody includes a heavy chain that comprises or is derived from an amino acid sequence selected from the group consisting of SEQ ID NOs: 610-614 and 620-628, and a light chain that comprises or is derived from an amino acid sequence selected from the group consisting of SEQ ID NOs: 615-619 and 629-639.

In some embodiments, the anti-PD-1 antibody comprises a heavy chain amino acid sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 610-614 and 620-628 and comprises a light chain amino acid sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 615-619 and 629-639.

In some embodiments, the anti-PD-1 antibody includes: (a) a variable heavy chain complementarity determining region 1 (VH CDR1) comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 487 and 642-645; (b) a variable heavy chain complementarity determining region 2 (VH CDR2) comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 488 and 646-650; (c) a variable heavy chain complementarity determining region 3 (VH CDR3) comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 489 and 652-655; (d) a variable light chain complementarity determining region 1 (VL CDR1) comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 656-663; (e) a variable light chain complementarity determining region 2 (VL CDR2) comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 491 and 664-666; and (f) variable light chain complementarity determining region 3 (VL

CDR3) comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 492 and 667-670.

In some embodiments, the anti-PD-1 antibody includes a combination of a variable heavy chain complementarity determining region 1 (VH CDR1, also referred to herein as CDRH1) sequence, a variable heavy chain complementarity determining region 2 (VH CDR2, also referred to herein as CDRH2) sequence, and a variable heavy chain complementarity determining region 3 (VH CDR3, also referred to herein as CDRH3) sequence, wherein the VH CDR1 sequence comprises GITFSNSG (SEQ ID NO: 525); the VH CDR2 sequence comprises IWYDGSKR (SEQ ID NO: 526); and the VH CDR3 sequence comprises TNDDY (SEQ ID NO: 527).

In some embodiments, the anti-PD-1 antibody includes a combination of a variable light chain complementarity determining region 1 (VL CDR1, also referred to herein as CDRL1) sequence, a variable light chain complementarity determining region 2 (VL CDR2, also referred to herein as CDRL2) sequence, and a variable light chain complementarity determining region 3 (VL CDR3, also referred to herein as CDRL3) sequence, wherein the VL CDR1 sequence comprises QSVSSY (SEQ ID NO: 528); the VL CDR2 sequence comprises DAS; and the VL CDR3 sequence comprises QQSSNWPRT (SEQ ID NO: 529).

In some embodiments, the anti-PD-1 antibody includes a combination of a variable heavy chain complementarity determining region 1 (VH CDR1, also referred to herein as CDRH1) sequence, a variable heavy chain complementarity determining region 2 (VH CDR2, also referred to herein as CDRH2) sequence, and a variable heavy chain complementarity determining region 3 (VH CDR3, also referred to herein as CDRH3) sequence, wherein the VH CDR1 sequence comprises GYTFTNYY (SEQ ID NO: 530); the VH CDR2 sequence comprises INPSNGGT (SEQ ID NO: 531); and the VH CDR3 sequence comprises RRDYRFDMGFDY (SEQ ID NO: 532).

In some embodiments, the anti-PD-1 antibody includes a combination of a variable light chain complementarity determining region 1 (VL CDR1, also referred to herein as CDRL1) sequence, a variable light chain complementarity determining region 2 (VL CDR2, also referred to herein as CDRL2) sequence, and a variable light chain complementarity determining region 3 (VL CDR3, also referred to herein as CDRL3)

sequence, wherein the VL CDR1 sequence comprises KGVSTSGYSY (SEQ ID NO: 533); the VL CDR2 sequence comprises LAS; and the VL CDR3 sequence comprises QHSRDLPLT (SEQ ID NO: 534).

In some embodiments, the anti-PD-L1 antibody a heavy chain that comprises or is derived from an amino acid sequence selected from the group consisting of SEQ ID NOs: 673-694 and a light chain that comprises or is derived from an amino acid sequence selected from the group consisting of SEQ ID NO: 671 or SEQ ID NO: 672.

In some embodiments, the anti-PD-L1 antibody comprises a heavy chain amino acid sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 673-694 and comprises a light chain amino acid sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to an amino acid sequence selected from the group consisting of SEQ ID NO: 671 or SEQ ID NO: 672.

In some embodiments, the anti-PD-L1 antibody comprises a combination of a VH CDRl sequence, a VH CDR2 sequence, a VH CDR3 sequence, a VL CDRl sequence, a VL CDR2 sequence, and a VL CDR3 sequence, wherein at least one CDR sequence is selected from the group consisting of a VL CDRl sequence comprising RASQSISSYLN (SEQ ID NO: 535); a VL CDR2 sequence comprising AASSLQS (SEQ ID NO: 536); a VL CDR3 sequence comprising DNGYPST (SEQ ID NO: 537); a VH CDRl sequence comprising SYAMS (SEQ ID NO: 538); a VH CDR2 sequence comprising SSIWRNGIVTVYADS (SEQ ID NO: 539); and a VH CDR3 sequence comprising WSAAFDY (SEQ ID NO: 540).

In some embodiments, the PD-1/PD-L1 pathway inhibitor is selected from the group consisting of nivolumab, pembrolizumab, tislelizumab, spartalizumab, camrelizumab, cetrelimab, cemiplimab, Balstilimab, Dostarlimab, Prolgolimab, Sasanlimab, zimberelimab, Atezolizumab, Avelumab, Durvalumab, adebrelimab, Lodapolimab, Envafolimab, Cosibelimab, budigalimab, ezabenlimab, finotonlimab, geptanolimab, lodapolimab, penpulimab, pimivalimab, pucotenlimab, serplulimab, Sintilimab, toripalimab, zeluvalimab, iparomlimab, nofazinlimab, rulonilimab, garivulimab, manelimab, opucolimab, pacmilimab (CX-072), sudubrilimab, sugemalimab, socazolimab, and tagitanlimab.

In some embodiments, the PD1/PD-L1 pathway inhibitor comprises pacmilimab (CX-072 (SEQ ID NO: 485-HC, SEQ ID NO: 496-LC); CX-075 (SEQ ID NO: 485-HC, SEQ ID NO: 497-LC), CX-171 (SEQ ID NOs: 504 or 505– HC, SEQ ID NO: 506– LC), or CX-188 (SEQ ID NO: 483-HC, SEQ ID NO: 484-LC).

The disclosure also provides activatable antibodies that include an antibody or antigen-binding fragment thereof that specifically binds PD-1 or PD-L1 coupled to a masking moiety (MM), such that coupling of the MM reduces the ability of the antibody or antigen-binding fragment thereof to bind PD-1 or PD-L1. In some embodiments, the MM is coupled via a cleavable moiety (CM) that includes sequence that functions as a substrate for a protease. The activatable anti-PD- 1 or anti-PD-L1 antibodies of the disclosure are activated when the cleavable moiety is cleaved by a protease. For example, the protease is produced by a tumor that is in proximity to T cells that express PD- 1 or PD-L1. In some embodiments, the protease is produced by a tumor that is co-localized with T cells that express PD-1 or PD-L1.

The activatable anti-PD-1 or anti-PD-L1 antibodies provided herein, also referred to herein as anti-PD-1 or anti-PD-L1 activatable antibodies or PD-1 and anti-PD-L1 activatable antibodies, are stable in circulation, activated at intended sites of therapy and/or diagnosis but not in normal, e.g., healthy tissue or other tissue not targeted for treatment and/or diagnosis, and, when activated, exhibit binding to PD-1 or PD-L1 that is at least comparable to the corresponding, unmodified antibody.

The invention also provides methods of treating, preventing and/or delaying the onset or progression of, or alleviating a symptom associated with aberrant expression and/or activity of PD-1 or PD-L1 in a subject using antibodies or activatable antibodies that bind PD-1 or PD-L1, particularly activatable antibodies that bind and neutralize or otherwise inhibit at least one biological activity of PD-1 or PD-L1, alone or in combination with an activatable cytokine such as an activatable interferon.

In some embodiments, the activatable anti-PD-1 or anti-PD-L1 antibody comprises an activatable antibody that, in an activated state, specifically binds to mammalian PD-1 or PD-L1, wherein said activatable antibody comprises: an antibody or an antigen binding fragment thereof (AB) that specifically binds to mammalian PD-1 or anti-PD-L1; a masking moiety (MM) that inhibits the binding of the AB to mammalian

PD-1 or PD-L1 when the activatable antibody is in an uncleaved state; and a cleavable moiety (CM) coupled to the AB, wherein the CM is a polypeptide that functions as a substrate for a protease.

In some embodiments, the activatable anti-PD-1 or anti-PD-L1 antibody comprises an activatable antibody that, in an activated state, (a) specifically binds to mammalian PD-1 or PD-L1; and (b) specifically blocks a natural ligand of PD-1 from binding to the mammalian PD-1, wherein the activatable antibody comprises: an antibody or an antigen binding fragment thereof (AB) that specifically binds to mammalian PD-1 or PD-L1; a masking moiety (MM) that inhibits the binding of the AB to mammalian PD-1 or PD-L1 when the activatable antibody is in an uncleaved state; and a cleavable moiety (CM) coupled to the AB, wherein the CM is a polypeptide that functions as a substrate for a protease.

In some embodiments, the activatable antibody in an uncleaved state specifically binds to the mammalian PD-1 or PD-L1 with a dissociation constant of 0.5 nM to 1 nM, 0.5 nM to 2 nM, 0.5 nM to 5 nM, 0.5 nM to 10 nM, 0.5 nM to 15 nM, 0.5 nM to 20 nM, 0.5 nM to 25 nM, 0.5 nM to 50 nM, 0.5 nM to 75 nM, 0.5 nM to 100 nM, 0.5 nM to 150 nM, 0.5 nM to 200 nM, 0.5 nM to 300 nM, 0.5 nM to 400 nM, 1 nM to 2 nM, 1 nM to 5 nM, 1 nM to 10 nM, 1 nM to 15 nM, 1 nM to 20 nM, 1 nM to 25 nM, 1 nM to 50 nM, 1 nM to 75 nM, 1 nM to 100 nM, 1 nM to 150 nM, 1 nM to 200 nM, 1 nM to 300 nM, 1 nM to 400 nM, 2 nM to 5 nM, 2 nM to 10 nM, 2 nM to 15 nM, 2 nM to 20 nM, 2 nM to 25 nM, 2 nM to 50 nM, 2 nM to 75 nM, 2 nM to 100 nM, 2 nM to 150 nM, 2 nM to 200 nM, 2 nM to 300 nM, 2 nM to 400 nM, 5 nM to 10 nM, 5 nM to 15 nM, 5 nM to 20 nM, 5 nM to 25 nM, 5 nM to 50 nM, 5 nM to 75 nM, 5 nM to 100 nM, 5 nM to 150 nM, 5 nM to 200 nM, 5 nM to 300 nM, 5 nM to 400 nM, 10 nM to 15 nM, 10 nM to 20 nM, 10 nM to 25 nM, 10 nM to 50 nM, 10 nM to 75 nM, 10 nM to 100 nM, 10 nM to 150 nM, 10 nM to 200 nM, 10 nM to 300 nM, 10 nM to 400 nM, 15 nM to 20 nM, 15 nM to 25 nM, 15 nM to 50 nM, 15 nM to 75 nM, 15 nM to 100 nM, 15 nM to 150 nM, 15 nM to 200 nM, 15 nM to 300 nM, 15 nM to 400 nM, 20 nM to 25 nM, 20 nM to 50 nM, 20 nM to 75 nM, 20 nM to 100 nM, 20 nM to 150 nM, 20 nM to 200 nM, 20 nM to 300 nM, 20 nM to 400 nM, 25 nM to 50 nM, 25 nM to 75 nM, 25 nM to 100 nM, 25 nM to 150 nM, 25 nM to 200 nM, 25 nM to 300 nM, 25 nM to 400 nM, 50 nM to 75 nM, 50 nM to 100

nM, 50 nM to 150 nM, 50 nM to 200 nM, 50 nM to 300 nM, 50 nM to 400 nM, 75 nM to 100 nM, 75 nM to 150 nM, 75 nM to 200 nM, 75 nM to 300 nM, 75 nM to 400 nM, 100 nM to 150 nM, 100 nM to 200 nM, 100 nM to 300 nM, 100 nM to 400 nM, 150 nM to 200 nM, 150 nM to 300 nM, 150 nM to 400 nM, 200 nM to 300 nM, 200 nM to 400 nM, or 300 nM to 400 nM.

In some embodiments, the activatable antibody in an activated state specifically binds to the mammalian PD-1 or PD-L1 with a dissociation constant of 0.01 nM to 5 nM, 0.05 nM to 5 nM, 0.1 nM to 5 nM, 0.2 nM to 5 nM, 0.3 nM to 5 nM, 0.4 nM to 5 nM, 0.5 nM to 5 nM, 0.75 nM to 5 nM, 1 nM to 5 nM, 2 nM to 5 nM, 0.01 nM to 2 nM, 0.05 nM to 2 nM, 0.1 nM to 2 nM, 0.2 nM to 2 nM, 0.3 nM to 2 nM, 0.4 nM to 2 nM, 0.5 nM to 2 nM, 0.75 nM to 1 nM, 1 nM to 2 nM, 0.01 nM to 1 nM, 0.05 nM to 1 nM, 0.1 nM to 1 nM, 0.2 nM to 1 nM, 0.3 nM to 1 nM, 0.4 nM to 1 nM, 0.5 nM to 1 nM, 0.75 nM to 1 nM, 0.01 nM to 0.75 nM, 0.05 nM to 0.75 nM, 0.1 nM to 0.75 nM, 0.2 nM to 0.75 nM, 0.3 nM to 0.75 nM, 0.4 nM to 0.75 nM, 0.5 nM to 0.75 nM, 0.01 nM to 0.5 nM, 0.05 nM to 0.5 nM, 0.1 nM to 0.5 nM, 0.2 nM to 0.5 nM, 0.3 nM to 0.5 nM, 0.4 nM to 0.5 nM, 0.01 nM to 0.4 nM, 0.05 nM to 0.4 nM, 0.1 nM to 0.4 nM, 0.2 nM to 0.4 nM, 0.3 nM to 0.4 nM, 0.01 nM to 0.3 nM, 0.05 nM to 0.3 nM, 0.1 nM to 0.3 nM, 0.2 nM to 0.3 nM, 0.01 nM to 0.2 nM, 0.05 nM to 0.2 nM, 0.1 nM to 0.2 nM, 0.01 nM to 0.1 nM, 0.05 nM to 0.1 nM, or 0.01 nM to 0.05 nM.

In some embodiments, the activatable antibody comprises an AB that specifically binds to the mammalian PD-1 or PD-L1 with a dissociation constant of 0.01 nM to 5 nM, 0.05 nM to 5 nM, 0.1 nM to 5 nM, 0.2 nM to 5 nM, 0.3 nM to 5 nM, 0.4 nM to 5 nM, 0.5 nM to 5 nM, 0.75 nM to 5 nM, 1 nM to 5 nM, 2 nM to 5 nM, 0.01 nM to 2 nM, 0.05 nM to 2 nM, 0.1 nM to 2 nM, 0.2 nM to 2 nM, 0.3 nM to 2 nM, 0.4 nM to 2 nM, 0.5 nM to 2 nM, 0.75 nM to 1 nM, 1 nM to 2 nM, 0.01 nM to 1 nM, 0.05 nM to 1 nM, 0.1 nM to 1 nM, 0.2 nM to 1 nM, 0.3 nM to 1 nM, 0.4 nM to 1 nM, 0.5 nM to 1 nM, 0.75 nM to 1 nM, 0.01 nM to 0.75 nM, 0.05 nM to 0.75 nM, 0.1 nM to 0.75 nM, 0.2 nM to 0.75 nM, 0.3 nM to 0.75 nM, 0.4 nM to 0.75 nM, 0.5 nM to 0.75 nM, 0.01 nM to 0.5 nM, 0.05 nM to 0.5 nM, 0.1 nM to 0.5 nM, 0.2 nM to 0.5 nM, 0.3 nM to 0.5 nM, 0.4 nM to 0.5 nM, 0.01 nM to 0.4 nM, 0.05 nM to 0.4 nM, 0.1 nM to 0.4 nM, 0.2 nM to 0.4 nM, 0.3 nM to 0.4 nM, 0.01 nM to 0.3 nM, 0.05 nM to 0.3 nM, 0.1 nM to 0.3 nM, 0.2 nM to 0.3 nM,

0.01 nM to 0.2 nM, 0.05 nM to 0.2 nM, 0.1 nM to 0.2 nM, 0.01 nM to 0.1 nM, 0.05 nM to 0.1 nM, or 0.01 nM to 0.05 nM.

In some embodiments, the mammalian PD-1 or PD-L1 is selected from the group consisting of a human PD-1 or PD-L1 and a cynomolgus monkey PD-1 or PD-L1. In some embodiments, the AB specifically binds to human PD-1 or PD-L1 or cynomolgus monkey PD-1 or PD-L1 with a dissociation constant of less than or equal to 1 nM. In some embodiments, the mammalian PD-1 or PD-L1 is a human PD-1 or PD-L1. In some embodiments, the AB has one or more of the characteristics selected from the group consisting of: (a) the AB specifically binds human PD-1 or PD-L1 and cynomolgus monkey PD-1 or PD-L1; (b) the AB inhibits binding of human PDL1 and human PDL2 to human PD-1; and (c) the AB inhibits binding of cynomolgus monkey PDL1 and cynomolgus monkey PDL2 to cynomolgus monkey PD-1.

In some embodiments, the mammalian PD-1 or PD-L1 is mouse PD-1 or PD-L1. In some embodiments, the activatable antibody comprises an AB that specifically binds mouse PD-1 or PD-L1 or inhibits binding of mouse PDL1 and mouse PDL2 to mouse PD1.

In some embodiments, the activatable antibody in an uncleaved state specifically binds to the mammalian PD-1 or PD-L1 with a dissociation constant greater than or equal to 0.5 nM, greater than or equal to 1 nM, greater than or equal to 2 nM, greater than or equal to 3 nM, greater than or equal to 4 nM, greater than or equal to 5 nM, greater than or equal to 10 nM, greater than or equal to 15 nM, greater than or equal to 20 nM, greater than or equal to 25 nM, greater than or equal to 50 nM, greater than or equal to 75 nM, greater than or equal to 100 nM, greater than or equal to 150 nM, greater than or equal to 200 nM, greater than or equal to 300 nM and/or greater than or equal to 400 nM.

In some embodiments, the activatable antibody in an activated state specifically binds to the mammalian PD-1 or PD-L1 with a dissociation constant less than or equal to 0.01 nM, less than or equal to 0.05 nM, less than or equal to 0.1 nM, less than or equal to 0.2 nM, less than or equal to 0.3 nM, less than or equal to 0.4 nM, less than or equal to 0.5 nM, less than or equal to 0.75 nM, and less than or equal to 1 nM.

In some embodiments, the activatable antibody comprises an AB that specifically binds to the mammalian PD-1 or PD-L1 with a dissociation constant less than or equal to

0.01 nM, less than or equal to 0.05 nM, less than or equal to 0.1 nM, less than or equal to 0.2 nM, less than or equal to 0.3 nM, less than or equal to 0.4 nM, less than or equal to 0.5 nM, less than or equal to 0.75 nM, and less than or equal to 1 nM.

In some embodiments, the activatable antibody comprises an AB blocks the ability of a natural ligand to bind to the mammalian PDL1 with an EC_{50} of 0.1 nM to 10 nM, 0.1 nM to 5 nM, 0.1 nM to 3 nM, 0.1 nM to 2 nM, 0.1 nM to 1 nM, 0.1 nM to 0.5 nM, 0.1 nM to 0.25 nM, 0.25 nM to 10 nM, 0.25 nM to 5 nM, 0.25 nM to 3 nM, 0.25 nM to 2 nM, 0.25 nM to 1 nM, 0.25 nM to 0.5 nM, 0.5 nM to 10 nM, 0.5 nM to 5 nM, 0.5 nM to 3 nM, 0.5 nM to 2 nM, 0.5 nM to 1 nM, 1 nM to 10 nM, 1 nM to 5 nM, 1 nM to 3 nM, 1 nM to 2 nM, 2 nM to 10 nM, 2 nM to 5 nM, 2 nM to 3 nM, 3 nM to 10 nM, 3 nM to 5 nM, or 5 nM to 10 nM.

In some embodiments, the natural ligand is a mammalian PDL1 or a mammalian PDL2. In some embodiments, the natural ligand is selected from the group consisting of: a human PDL1, a human PDL2, a cynomolgus monkey PDL1, and a cynomolgus monkey PDL2.

The activatable antibodies in an activated state bind PD-1 or PD-L1 and include (i) an antibody or an antigen binding fragment thereof (AB) that specifically binds to PD-1 or PD-L1; (ii) a masking moiety (MM) that, when the activatable antibody is in an uncleaved state, inhibits the binding of the AB to PD-1 or PD-L1; and (c) a cleavable moiety (CM) coupled to the AB, wherein the CM is a polypeptide that functions as a substrate for a protease.

In some embodiments, the activatable PD-1 or PD-L1 antibody in the uncleaved state has the structural arrangement from N-terminus to C-terminus as follows: MM-CM-AB or AB-CM- MM.

In some embodiments, the activatable PD-1 or PD-L1 antibody comprises a linking peptide between the MM and the CM.

In some embodiments, the activatable PD-1 or PD-L1 antibody comprises a CM as defined herein. In some embodiments, the activatable PD-1 or PD-L1 antibody comprises a linking peptide between the CM and the AB.

In some embodiments, the activatable PD-1 or PD-L1 antibody comprises a first linking peptide (LP1) and a second linking peptide (LP2), and wherein the activatable

antibody in the uncleaved state has the structural arrangement from N-terminus to C-terminus as follows: MM-LP1-CM- LP2-AB or AB-LP2-CM-LP1-MM. In some embodiments, the two linking peptides need not be identical to each other. In some embodiments, each of LP1 and LP2 is a peptide of about 1 to 20 amino acids in length.

In some embodiments, at least one of LP1 or LP2 comprises an amino acid sequence selected from the group consisting of $(GS)_n$, $(GGS)_n$, $(GSGGS)_n$ (SEQ ID NO: 227) and $(GGGS)_n$ (SEQ ID NO: 228), where n is an integer of at least one.

In some embodiments, at least one of LP1 or LP2 comprises an amino acid sequence selected from the group consisting of GGSG (SEQ ID NO: 229), GGSGG (SEQ ID NO: 230), GSGSG (SEQ ID NO: 231), GSGGG (SEQ ID NO: 232), GGGSG (SEQ ID NO: 233), and GSSSG (SEQ ID NO: 234).

In some embodiments, LP1 comprises the amino acid sequence GSSGGSGGSGGSG (SEQ ID NO: 541), GSSGGSGGSGG (SEQ ID NO: 210), GSSGGSGGSGGS (SEQ ID NO: 542), GSSGGSGGSGGSGGGS (SEQ ID NO: 588), GSSGGSGGSG (SEQ ID NO: 543), GSSGGSGGSGS (SEQ ID NO: 544), GGGSSGGS (SEQ ID NO: 545), or GGGSSGG (SEQ ID NO: 546).

In some embodiments, LP2 comprises the amino acid sequence GSS, GGS, GGGS (SEQ ID NO: 2), GSSGT (SEQ ID NO: 548) or GSSG (SEQ ID NO: 549).

In some embodiments, the activatable antibody also includes a signal peptide. In some embodiments, the signal peptide is conjugated to the activatable antibody via a spacer. In some embodiments, the spacer is conjugated to the activatable antibody in the absence of a signal peptide. In some embodiments, the spacer is joined directly to the MM of the activatable antibody. In some embodiments, the spacer is joined directly to the MM of the activatable antibody in the structural arrangement from N-terminus to C-terminus of spacer-MM-CM-AB.

In some embodiments, the activatable anti-PD-1 antibody includes a heavy chain that comprises or is derived from an amino acid sequence selected from the group consisting of SEQ ID NOs: 610-614 and 620-628, and a light chain that comprises or is derived from an amino acid sequence selected from the group consisting of SEQ ID NOs: 615-619 and 629-639. In some aspects, the present disclosure includes an activatable

anti-PD-1 antibody disclosed in WO2017011580, which is incorporated herein by reference in its entirety.

In some embodiments, the activatable anti-PD-1 antibody comprises a masking moiety (MM) comprising an amino acid sequence selected from the group consisting of AMSGCSWSAFCPYLA (SEQ ID NO: 550), DVNCAIWYSVCITVP (SEQ ID NO: 551), LVCPLYALSSGVCMG (SEQ ID NO: 552), SVNCRIWSAVCAGYE (SEQ ID NO: 553), MLVCSLQPTAMCERV (SEQ ID NO: 554), APRCYMFASYCKSQY (SEQ ID NO: 555), VGPCELTPKPVCNTY (SEQ ID NO: 556), ETCNQYERSSGLCFA (SEQ ID NO: 557), APRTCYTYQCSSFYT (SEQ ID NO: 558), GLCSWYLSSSGLCVD (SEQ ID NO: 559), VPWCQLTPRVMCMWA (SEQ ID NO: 560), NWLDCQFYSECSVYG (SEQ ID NO: 561), SCPLYVMSSFGGCWD (SEQ ID NO: 562), MSHCWMFSSSCDGVK (SEQ ID NO: 563), VSYCTWLIEVICLRG (SEQ ID NO: 564), VLCAAYALSSGICGG (SEQ ID NO: 565), TTCNLYQQSSMFCNA (SEQ ID NO: 566), APRCYMFASYCKSQY (SEQ ID NO: 567), PCDQNPYFYPYVCHA (SEQ ID NO: 568), SVCPMYALSSMLCGA (SEQ ID NO: 569), LSVECYVFSRCSSLP (SEQ ID NO: 570), FYCTYLVSLTCHPQ (SEQ ID NO: 571), SMAGCQWSSFCVQRD (SEQ ID NO: 572), IYSCYMFASRCTSDK (SEQ ID NO: 573), SRCSVYEVSSGLCDW (SEQ ID NO: 574), GMCSAYAYSSKLCTI (SEQ ID NO: 575), MTTNTCNLLCQQFLT (SEQ ID NO: 576), FQPCLMFASSCFTSK (SEQ ID NO: 577), WNCHPAGVGPVFCEV (SEQ ID NO: 578), ALCSMYLASSGLCNK (SEQ ID NO: 579), NYLSCQFFQNCYETY (SEQ ID NO: 580), GWCLFSDMWLGLCSA (SEQ ID NO: 581), EFCARDWLPYQCSSF (SEQ ID NO: 582), TSYCSIEHYPCNTHH (SEQ ID NO: 583).

In some embodiments, the activatable anti-PD-1 antibody comprises a heavy chain amino acid sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 610-614 and 620-628 and comprises a light chain amino acid sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 615-619 and 629-639.

In some embodiments, the activatable anti-PD-1 antibody includes: (a) a variable heavy chain complementarity determining region 1 (VH CDR1) comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 487 and 642-645; (b) a variable heavy chain complementarity determining region 2 (VH CDR2) comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 488 and 646-650; (c) a variable heavy chain complementarity determining region 3 (VH CDR3) comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 489 and 652-655; (d) a variable light chain complementarity determining region 1 (VL CDR1) comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 656-663; (e) a variable light chain complementarity determining region 2 (VL CDR2) comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 491 and 664-666; and (f) variable light chain complementarity determining region 3 (VL CDR3) comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 683- 687.

In some embodiments, the activatable anti-PD-1 antibody includes a combination of a variable heavy chain complementarity determining region 1 (VH CDR1, also referred to herein as CDRH1) sequence, a variable heavy chain complementarity determining region 2 (VH CDR2, also referred to herein as CDRH2) sequence, and a variable heavy chain complementarity determining region 3 (VH CDR3, also referred to herein as CDRH3) sequence, wherein the VH CDR1 sequence comprises GITFSNSG (SEQ ID NO: 525); the VH CDR2 sequence comprises IWYDGSKR (SEQ ID NO: 526); and the VH CDR3 sequence comprises TNDDY (SEQ ID NO: 527).

In some embodiments, the activatable anti-PD-1 antibody includes a combination of a variable light chain complementarity determining region 1 (VL CDR1, also referred to herein as CDRL1) sequence, a variable light chain complementarity determining region 2 (VL CDR2, also referred to herein as CDRL2) sequence, and a variable light chain complementarity determining region 3 (VL CDR3, also referred to herein as CDRL3) sequence, wherein the VL CDR1 sequence comprises QSVSSY (SEQ ID NO: 528); the VL CDR2 sequence comprises DAS; and the VL CDR3 sequence comprises QQSSNWPRT (SEQ ID NO: 529).

In some embodiments, the activatable anti-PD-1 antibody includes a combination of a variable heavy chain complementarity determining region 1 (VH CDR1, also referred to herein as CDRH1) sequence, a variable heavy chain complementarity determining region 2 (VH CDR2, also referred to herein as CDRH2) sequence, and a variable heavy chain complementarity determining region 3 (VH CDR3, also referred to herein as CDRH3) sequence, wherein the VH CDR1 sequence comprises GYTFTNYY (SEQ ID NO: 530); the VH CDR2 sequence comprises INPSNGGT (SEQ ID NO: 531); and the VH CDR3 sequence comprises RRDYRFDMGFDY (SEQ ID NO: 532).

In some embodiments, the activatable anti-PD-1 antibody includes a combination of a variable light chain complementarity determining region 1 (VL CDR1, also referred to herein as CDRL1) sequence, a variable light chain complementarity determining region 2 (VL CDR2, also referred to herein as CDRL2) sequence, and a variable light chain complementarity determining region 3 (VL CDR3, also referred to herein as CDRL3) sequence, wherein the VL CDR1 sequence comprises KGVSTSGYSY (SEQ ID NO: 533); the VL CDR2 sequence comprises LAS; and the VL CDR3 sequence comprises QHSRDLPLT (SEQ ID NO: 534).

In some embodiments, the activatable anti-PD-L1 antibody a heavy chain that comprises or is derived from an amino acid sequence selected from the group consisting of SEQ ID NOs: 673-694 and a light chain that comprises or is derived from an amino acid sequence selected from the group consisting of SEQ ID NO: 671 or SEQ ID NO: 672. In some aspects, the present disclosure includes an activatable anti-PD-L1 antibody disclosed in WO2016/149201, which is incorporated herein by reference in its entirety.

In some embodiments, the activatable anti-PD-L1 antibody comprises a heavy chain amino acid sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 673-694 and comprises a light chain amino acid sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to an amino acid sequence selected from the group consisting of SEQ ID NO: 671 or SEQ ID NO: 672.

In some embodiments, the activatable anti-PD-L1 antibody comprises a combination of a VH CDRl sequence, a VH CDR2 sequence, a VH CDR3 sequence, a

VL CDRl sequence, a VL CDR2 sequence, and a VL CDR3 sequence, wherein at least one CDR sequence is selected from the group consisting of a VL CDRl sequence comprising RASQSISSYLN (SEQ ID NO: 535); a VL CDR2 sequence comprising AASSLQS (SEQ ID NO: 536); a VL CDR3 sequence comprising DNGYPST (SEQ ID NO: 537); a VH CDRl sequence comprising SYAMS (SEQ ID NO: 538); a VH CDR2 sequence comprising SSIWRNGIVTVYADS (SEQ ID NO: 539); and a VH CDR3 sequence comprising WSAAFDY (SEQ ID NO: 540).

In some embodiments, the activatable anti-PD-L1 antibody comprises a masking moiety (MM) comprising an amino acid sequence selected from the group consisting of YCEVSELFVLPWCMG (SEQ ID NO: 584), SCLMHPHYAHDYCYV (SEQ ID NO: 585), LCEVLMLLQHPWCMG (SEQ ID NO: 586), IACRHFMEQLPFCHH (SEQ ID NO: 587), FGPRCGEASTCVPYE (SEQ ID NO: 588), LYCDSWGAGCLTRP (SEQ ID NO: 589), GIALCPSHFCQLPQT (SEQ ID NO: 590), DGPRCFVSGECSPIG (SEQ ID NO: 591), LCYKLDYDDRSYCHI (SEQ ID NO: 592), PCHPHPYDARPYCNV (SEQ ID NO: 593), PCYWHPFFAYRYCNT (SEQ ID NO: 594), VCYYMDWLGRNWCSS (SEQ ID NO: 595), LCDLFKLREFPYCMG (SEQ ID NO: 596), YLPCHFVPIGACNNK (SEQ ID NO: 597), FCHMGVVVPQCANY (SEQ ID NO: 598), ACHPHPYDARPYCNV (SEQ ID NO: 599), PCHPAPYDARPYCNV (SEQ ID NO: 600), PCHPHAYDARPYCNV (SEQ ID NO: 601), PCHPHPADARPYCNV (SEQ ID NO: 602), PCHPHPYAARPYCNV (SEQ ID NO: 603), PCHPHPYDAAPYCNV (SEQ ID NO: 604), PCHPHPYDARPACNV (SEQ ID NO: 605), PCHPHPYDARPYCAV (SEQ ID NO: 606), PCHAHPYDARPYCNV (SEQ ID NO: 607), PCHPHPYDARAYCNV (SEQ ID NO: 608).

Provided herein are compositions comprising any one of the ACCs described herein. In some embodiments, the composition is a pharmaceutical composition. Also provided herein are kits comprising at least one dose of any one of the compositions described herein.

Provided herein are are compositions comprising any one of the ACCs described herein and a PD-1 or PD-L1 antibody. Provided herein are are compositions comprising any one of the ACCs described herein and an activatable PD-1 or PD-L1 antibody. Also provided herein are kits comprising at least one dose of any one of the ACCs described herein and at least one dose of a PD-1 or PD-L1 antibody or a PD-1 or PD-L1 activatable antibody.

Provided herein are methods of treating a subject in need thereof comprising administering to the subject a therapeutically effective amount of any one of the ACCs described herein with or without a PD1/PD-L1 inhibitor selected from a PD-1 antibody, an activatable PD-1 antibody, a PD-L1 antibody, or an activatable PD-L1 antibody, or any one of the compositions described herein. In some embodiments, the subject has been identified or diagnosed as having a cancer. In some non-limiting embodiments, the cancer is Kaposi sarcoma, hairy cell leukemia, chronic myeloid leukemia (CML), follicular lymphoma, renal cell cancer (RCC), melanoma, neuroblastoma, basal cell carcinoma, bladder cancer, breast cancer, colorectal cancer, cutaneous T-cell lymphoma, nasopharyngeal adenocarcimoa, non-small cell lung cancer (NSCLC), colon cancer, renal cancer, ovarian cancer, pancreatic cancer. In some non-limiting embodiments, the cancer is a carcinoma. In some non-limiting embodiments, the cancer is a sarcoma. In some non-limiting embodiments, the cancer is a lymphoma. In some non-limiting embodiments, the lymphoma is Burkitt's lymphoma.

Provided herein are nucleic acids encoding a polypeptide that comprises the CP1 and the CM1 of any one of the ACCs described herein. In some embodiments, the polypeptide further comprises any one of the DD1 described herein. In some embodiments, the polypeptide further comprises any one of the PM1 and the CM3 described herein. Also provided herein are nucleic acids encoding a polypeptide that comprises the CP2 and the CM2 of any one of the ACCs described herein. When the monomers are identical, then the present disclosure provides a single nucleic acid encoding the monomer that dimerizes to form ACC. In some embodiments, the polypeptide further comprises any one of the DD2 described herein. In some embodiments, the polypeptide further comprises any one of the PM2 and the CM4 described herein. In certain embodiments, the first monomer construct and the second

monomer construct comprise identical CP, CM, and DD components. In some of these embodiments, the first and second monomer constructs are encoded by the same polypeptide (i.e., the same amino acid sequence). Often, when the first and second monomer constructs comprise the same amino acid sequence, they are encoded by the same nucleic acid (i.e., the same nucleic acid sequence). In some of these embodiments, the first and second monomer constructs are encoded by the same nucleic acid. Also provided herein are vectors comprising any one of the nucleic acids described herein. In some embodiments, the vector is an expression vector. Also provided herein are cells comprising any one of the nucleic acids described herein or any one of the vectors described herein.

Provided herein are pairs of nucleic acids that together encode a polypeptide that comprises the CP1 and the CM1 of the first monomer construct and a polypeptide that comprises the CP2 and the CM2 of the second monomer construct of any one of the ACCs described herein. Also provided herein are pairs of nucleic acids that together encode a polypeptide that comprises the PM1, the CM3, CP1 and the CM1 of the first monomer construct and a polypeptide that comprises the PM2, the CM4, the CP2 and the CM2 of the second monomer construct of any one of the ACCs described herein. Also provided herein are pairs of vectors that together comprise any of one of the pair of nucleic acids described herein. In some embodiments, the pair of vectors is a pair of expression vectors. Also provided herein are cells comprising any one of the pairs of nucleic acids described herein or any one of the pairs of vectors described herein. In other embodiments, the present invention provides a vector comprising the pair of vectors.

Provided herein are methods of producing an ACC comprising: culturing any one of the cells described herein in a liquid culture medium under conditions sufficient to produce the ACC; and recovering the ACC from the cell or the liquid culture medium. In some embodiments, the method further comprises: isolating the ACC recovered from the cell or the liquid culture medium. In some embodiments, the method further comprises: formulating isolated ACC into a pharmaceutical composition. In other embodiments, the method further comprises: formulating isolated ACC and a PD1/PD-L1 inhibitor selected

from a PD-1 antibody, an activatable PD-1 antibody, a PD-L1 antibody, or an activatable PD-L1 antibody into a pharmaceutical composition.

Provided herein are ACCs produced by any one of the methods described herein. Also provided herein are compositions comprising any one the ACCs described herein with or without a PD1/PD-L1 inhibitor selected from a PD-1 antibody, an activatable PD-1 antibody, a PD-L1 antibody, or an activatable PD-L1 antibody. Also provided herein are compositions of any one of the compositions described herein, wherein the composition is a pharmaceutical composition. Also provided herein are kits comprising at least one dose of any one of the compositions described herein.

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.

The term “a” and “an” refers to one or more (i.e., at least one) of the grammatical object of the article. By way of example, “a cell” encompasses one or more cells.

As used herein, the terms “about” and “approximately,” when used to modify an amount specified in a numeric value or range, indicate that the numeric value as well as reasonable deviations from the value known to the skilled person in the art. For example, ± 20%, ± 10%, or ± 5%, are within the intended meaning of the recited value where appropriate.

Concentrations, amounts, and other numerical data may be expressed or presented herein in a range format. It is to be understood that such a range format is used merely for convenience and brevity and thus should be interpreted flexibly to include not only the numerical values explicitly recited as the limits of the range, but also to include all the individual numerical values or sub-ranges encompassed within that range as if each

numerical value and sub-range is explicitly recited. As an illustration, a numerical range of "about 0.01 to 2.0" should be interpreted to include not only the explicitly recited values of about 0.01 to about 2.0, but also include individual values and sub-ranges within the indicated range. Thus, included in this numerical range are individual values such as 0.5, 0.7, and 1.5, and sub-ranges such as from 0.5 to 1.7, 0.7 to 1.5, and from 1.0 to 1.5, etc. Furthermore, such an interpretation should apply regardless of the breadth of the range or the characteristics being described. Additionally, it is noted that all percentages are in weight, unless specified otherwise.

In understanding the scope of the present disclosure, the terms "including" or "comprising" and their derivatives, as used herein, are intended to be open ended terms that specify the presence of the stated features, elements, components, groups, integers, and/or steps, but do not exclude the presence of other unstated features, elements, components, groups, integers and/or steps. The foregoing also applies to words having similar meanings such as the terms "including", "having" and their derivatives. The term "consisting" and its derivatives, as used herein, are intended to be closed terms that specify the presence of the stated features, elements, components, groups, integers, and/or steps, but exclude the presence of other unstated features, elements, components, groups, integers and/or steps. The term "consisting essentially of," as used herein, is intended to specify the presence of the stated features, elements, components, groups, integers, and/or steps as well as those that do not materially affect the basic and novel characteristic(s) of features, elements, components, groups, integers, and/or steps. It is understood that reference to any one of these transition terms (i.e. "comprising," "consisting," or "consisting essentially") provides direct support for replacement to any of the other transition term not specifically used. For example, amending a term from "comprising" to "consisting essentially of" or "consisting of" would find direct support due to this definition for any elements disclosed throughout this disclosure. Based on this definition, any element disclosed herein or incorporated by reference may be included in or excluded from the claimed invention.

As used herein, a plurality of compounds, elements, or steps may be presented in a common list for convenience. However, these lists should be construed as though each member of the list is individually identified as a separate and unique member. Thus, no

individual member of such list should be construed as a *de facto* equivalent of any other member of the same list solely based on their presentation in a common group without indications to the contrary.

Furthermore, certain molecules, constructs, compositions, elements, moieties, excipients, disorders, conditions, properties, steps, or the like may be discussed in the context of one specific embodiment or aspect or in a separate paragraph or section of this disclosure. It is understood that this is merely for convenience and brevity, and any such disclosure is equally applicable to and intended to be combined with any other embodiments or aspects found anywhere in the present disclosure and claims, which all form the application and claimed invention at the filing date. For example, a list of constructs, molecules, method steps, kits, or compositions described with respect to a construct, composition, or method is intended to and does find direct support for embodiments related to constructs, compositions, formulations, and methods described in any other part of this disclosure, even if those method steps, active agents, kits, or compositions are not re-listed in the context or section of that embodiment or aspect.

Unless otherwise specified, a "nucleic acid sequence encoding a protein" includes all nucleotide sequences that are degenerate versions of each other and thus encode the same amino acid sequence.

The term "N-terminally positioned" when referring to a position of a first domain or sequence relative to a second domain or sequence in a polypeptide primary amino acid sequence means that the first domain or sequence is located closer to the N-terminus of the polypeptide primary amino acid sequence than the second domain or sequence. In some embodiments, there may be additional sequences and/or domains between the first domain or sequence and the second domain or sequence.

The term "C-terminally positioned" when referring to a position of a first domain or sequence relative to a second domain or sequence in a polypeptide primary amino acid sequence means that the first domain or sequence is located closer to the C-terminus of the polypeptide primary amino acid sequence than the second domain or sequence. In some embodiments, there may be additional sequences and/or domains between the first domain or sequence and the second domain or sequence.

The term "exogenous" refers to any material introduced from or originating from outside a cell, a tissue, or an organism that is not produced by or does not originate from the same cell, tissue, or organism in which it is being introduced.

The term "transduced," "transfected," or "transformed" refers to a process by which an exogenous nucleic acid is introduced or transferred into a cell. A "transduced," "transfected," or "transformed" cell (e.g., mammalian cell) is one that has been transduced, transfected, or transformed with exogenous nucleic acid (e.g., a vector) that includes an exogenous nucleic acid encoding any of the activatable cytokine constructs described herein.

The term "nucleic acid" refers to a deoxyribonucleic acid (DNA) or ribonucleic acid (RNA), or a combination thereof, in either a single- or double-stranded form. Unless specifically limited, the term encompasses nucleic acids containing known analogues of natural nucleotides that have similar binding properties as the reference nucleotides. Unless otherwise indicated, a particular nucleic acid sequence also implicitly encompasses complementary sequences as well as the sequence explicitly indicated. In some embodiments of any of the nucleic acids described herein, the nucleic acid is DNA. In some embodiments of any of the nucleic acids described herein, the nucleic acid is RNA.

Modifications can be introduced into a nucleotide sequence by standard techniques known in the art, such as site-directed mutagenesis and polymerase chain reaction (PCR)-mediated mutagenesis. Conservative amino acid substitutions are ones in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include: amino acids with acidic side chains (e.g., aspartate and glutamate), amino acids with basic side chains (e.g., lysine, arginine, and histidine), non-polar amino acids (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, and tryptophan), uncharged polar amino acids (e.g., glycine, asparagine, glutamine, cysteine, serine, threonine and tyrosine), hydrophilic amino acids (e.g., arginine, asparagine, aspartate, glutamine, glutamate, histidine, lysine, serine, and threonine), hydrophobic amino acids (e.g., alanine, cysteine, isoleucine, leucine, methionine, phenylalanine, proline, tryptophan, tyrosine, and valine). Other families of

amino acids include: aliphatic-hydroxy amino acids (e.g., serine and threonine), amide family (e.g., asparagine and glutamine), alphatic family (e.g., alanine, valine, leucine and isoleucine), and aromatic family (e.g., phenylalanine, tryptophan, and tyrosine).

As used herein the phrase "specifically binds," or "immunoreacts with" means that the activatable antigen-binding protein complex reacts with one or more antigenic determinants of the desired target antigen and does not react with other polypeptides, or binds at much lower affinity, e.g., about or greater than 10^{-6} M.

The term "treatment" refers to ameliorating at least one symptom of a disorder. In some embodiments, the disorder being treated is a cancer and to ameliorate at least one symptom of a cancer.

BRIEF DESCRIPTION OF DRAWINGS

Figs. 1-4 are schematics of illustrative activatable cytokine constructs.

Figs. 5A-5B depict the cleavage reaction of a cytokine construct without a peptide mask, IFNα-2b-hIgG4 Fc (with either cleavable moiety 1204dL or cleavable moiety 1490), and a protease (either uPA or MT-SP1), which generates monomeric mature IFNα-2b.

Figs. 6A-6C show activation of a cytokine construct (ProC440) by proteases uPa and MMP14. The ProC440 in Fig. 6B has a sequence of SEQ ID NO: 286.

Figs. 7A-7B show the activity of a cytokine construct (ProC440) tested in vitro using IFN-responsive HEK293 cells (**Fig. 7A**) and Daudi cells (**Fig. 7B**).

Fig. 8 shows the sequence of a masked cytokine construct, ProC732 with an optional signal sequence in italics, the masking peptide sequence in double-underline, the sequences of cleavable moieties in bold, and the sequence of the mature IFNalpha-2b underlined.

Fig. 9 shows shows the sequence of a masked cytokine construct with no cleavable moiety sequence between the cytokine and the dimerization domain, ProC733, with an optional signal sequence in italics, the masking peptide sequence in double-underline, the cleavable moiety sequence in bold, and the sequence of the mature IFNalpha-2b underlined.

Fig. 10A shows schematics of ProC440, ProC732 and ProC733. **Fig. 10B** shows the activity of cytokine constructs (ProC440, ProC732 and ProC733) tested using IFN-responsive HEK293 cells.

Fig. 11A shows a schematic of the structure of cytokine construct ProC286, and the activity of ProC286 compared to the activity of Sylatron® (PEGylated interferon alpha-2b) in the Daudi apoptosis assay. ProC286 and Sylatron® showed similar levels of activity indicating that ProC286 could be used as surrogate Sylatron® control to evaluate the tolerability of IFNα-2b in the hamster study. **Fig. 11B** depicts a schematic of the structure of ProC291 and the activity of ProC291 compared to the activity of Sylatron® in the Daudi apotosis assay. ProC291 showed significantly reduced activity compared to Sylatron® and ProC286

Fig. 12 shows the specific activity of IFNa-con (recombinant interferon alpha, a non-naturally occurring type-I interferon); the active cytokine cleavage product of ProC440 (ProC440+uPA); Sylatron® ("PEG-IFNa2b"); and ProC440, and and anticipated toxic dosages in a dose-escalation study in vivo, e.g., at escalating doses of 0.08, 0.4, 2, 10, and 15 mg/kg ("mpk").

Fig. 13A-13D show body weight loss profiles of animals in response to different doses of cytokine constructs ProC286, ProC440, and ProC732 or control (human IgG4) in tolerability tests at different dosages in Syrian Gold Hamsters. Fig. 13A shows data for 2 mg/kg ("2 mpk") dosages; Fig. 13B shows data for 10 mg/kg dosages; and Fig. 13C shows data for 15 mg/kg dosages of each construct tested; **Fig. 13D** shows INFa2b mediated toxicity in animals dosed with unmasked IFNa2b/Fc corresponding to increased ALP and increased therapeutic index of IFNa2b single and dual mask.

Fig. 14 shows clinical chemistry analysis outcomes (Alkaline phosphatase, Alanine transaminase, and Aspartate transaminase) of Syrian Gold Hamsters in response to different doses (2 mpk, 10 mpk, and 15 mpk) of cytokine constructs ProC286, ProC440, and ProC732 or control (human IgG4) in tolerability tests.

Fig. 15 shows hematology analysis outcomes (Reticulocyte, Neutrophil, and White Blood Cells (WBC) counts) in Syrian Gold Hamsters in response to different doses (2 mpk, 10 mpk, and 15 mpk) of cytokine constructs ProC286, ProC440, and ProC732 or control (human IgG4) in tolerability tests.

Fig. 16 depicts the effect of length of a Linking Region (LR) on the activities of IFNalpha-2b-Fc fusion proteins without a peptide mask, as determined from a Daudi apoptosis assay.

Fig. 17 schematically illustrates a cytokine construct without a peptide mask, including a depiction of the linking region (LR).

Fig. 18A shows anti-tumor activity of masked activatable IFNa A/D (ProC1023) at 10, 50, and 200 µg. **Fig. 18B** shows *in vivo* activation of masked IFNa A/D relative (ProC1023) to an uncleavable masked IFNa A/D (ProC1549). **Fig. 18C** shows the anti-tumour activity of the combination of masked IFNa A/D (ProC1023) with PD-L1 monoclonal antibody (CX-171) compared to masked IFNa A/D (ProC1023) alone and compared to PD-L1 monoclonal antibody (CX-171) alone.

Figs. 19A-19B show immune memory in response to MC38 tumor cell rechallenge in mice previously treated with activatable IFNa A/D (200 micrograms ProC1023) (bottom, Fig. 19B) compared to MC38 tumor cell challenge in naïve control mice (top, Fig. 19A).

Fig. 20 shows the combinatorial effect of Pro-IFN-a2b and PD-L1 monoclonal antibody on IFN-gamma release in patients' tissues compared to masked IFN-a2b, unmasked IFN-a2b, Peg-IFN-a2b alone, PD-L1 monoclonal antibody alone, and control in Patient's PBMC (left) and Patient's dissociated tumor cells (right).

Fig. 21 shows activation-dependent induction of type I interferon signature by unmasked IFN-a2b.

Fig. 22 shows pharmacokinetics of the dual masked INF-a2b (ProC732) and control molecules in hamsters.

Fig. 23 shows anti-tumor activity of masked activatable IFNa A/D at 20 µg and 200 µg compared to control.

Fig. 24A shows the activity of ProC1023 compared to ProC859 in an IFNa reporter assay in B16 mouse melanoma cells. **Figs. 24B and 24C** show the activity of ProC1023 compared to ProC1549 in an IFNa reporter assay in B16 mouse melanoma cells.

Fig. 25 shows the activity of ProC1239 and ProC732 tested in vitro using IFN-responsive HEK293 cells.

Fig. 26 shows the activity of ProC732, ProC1550 and ProC1552 tested *in vitro* using IFN-responsive HEK293 cells in an uncleaved state and after protease activation with either uPa or MTSP1.

Fig. 27 shows activity of recombinant IFNa2b, monomeric IFNa2b/Fc, activated homodimeric IFNa2b/Fc, and homodimeric IFNa2b/Fc using IFN-responsive HEK293 cells in an uncleaved state and after protease activation.

Fig. 28 shows anti-tumor activity of single masked IFNa2b/Fc (top) and peginterferon (bottom) at increasing doses.

Fig. 29 depicts the structure of ACC ProC859 universal interferon (top), the anti-proliferative effects of ACC ProC859 in a B16 mouse melanoma cell assay and the activity of ACC ProC859 in the IFN-responsive HEK293 assay.

Fig. 30 shows CD14, CD3, PD-L1, and IFNAR1 positive cells in the PBMC population and myeloid cells from healthy donors compared to patient PBMC and disassociated tumor.

Fig. 31 shows the combinatorial effect of activated IFN-a2b and PD-L1 monoclonal antibody on IFN-gamma release in patients' tissues compared to untreated, dual masked IFN-a2b, sylatron alone, and PD-L1 monoclonal antibody or dual masked IFN-a2b alone.

Fig. 32 shows the activity of activated and non-activated single masked IFNa2b and activated and non-activated dual mask IFNa2b tested *in vitro* using IFN-responsive HEK293 cells in an uncleaved state and after protease activation.

Fig. 33A shows anti-tumor activity of dual masked activatable IFNa A/D compared to dual masked non-activatable IFNa A/D at 10 μg, 50 μg, and 200 μg.

Fig. 33B shows shows anti-tumor activity of dual masked IFNa A/D in combination with PD-L1 monoclonal antibody compared to dual masked IFNa A/D or PD-L1 monoclonal antibody alone.

Fig. 34A shows anti-tumor activity of Pro IFNa A/D (ProC1023) at 10, 50, and 200 μg compared to PBS control. **Fig. 34B** shows anti-tumor activity of Pro IFNa A/D (ProC1023) compared to IFNa A/D NSUB (ProC1549) at 200 μg.

Fig. 35A shows anti-tumor activity of Pro IFNa A/D (ProC1023) at 10 μg, 50 μg, and 200 μg compared to 200 μg PD-L1 monoclonal antibody (CX-171). **Fig. 35B** shows

anti-tumor activity of IFNa A/D NSUB (ProC1549) at 50 and 200 μg compared to PBS control.

Fig. 36 schematically illustrates a cytokine construct including a depiction of the linking region (LR) and mask linking region (MLR).

Fig. 37 shows changes in tumor volume over time and survival for mice implanted with CT26 and B16 synegeneic tumor models.

Figs. 38A-38D show binding of single masked Pb-IFN-a2b molecules to human IFNAR2. The ligands were captured on a chip coated with immobilized anti-human Fc (Figs. 38A-38B) or anti-histidine antibodies (Figs. 38C-38D). Concentrations of IFN-a2b (ProC1640) ranging from 25 nM to 1.5625 μM were flowed over the ligand-captured chip to generate multi-cycle kinetic sensorgrams (Figs. 38A and 38C). Masked Pb-IFN-a2b molecules (ProC440 – Fig. 38D, ProC1976 – Fig. 38B) at concentrations ranging from 250 nM to 15.625 μM were flowed over the ligand-captured chip to generate multi-cycle kinetic sensorgrams.

Fig. 39A shows MMP restores NSUB (ProC649) activity. **Fig. 39B** shows conditional activation of ProC732 and ProC1299 by uPA. **Fig. 39C** shows IFNa2b (SEQ ID NO: 1) compared to IFNaAD and that ProC1301 is resistant to activation compared to ProC732.

Figs. 40A-40D show binding of activated Pb-IFN-a2b to interferon alpha receptors in vitro. Human IFNAR1, human IFNAR2, cyno IFNAR1 or cyno IFNAR2 proteins were captured on a chip coated with immobilized anti-human Fc. Concentrations of activated IFN-a2b (ProC1640) ranging from 25 nM to 1.5625 μM were flowed over the ligand-captured chip to generate multi-cycle kinetic sensorgrams.

Figs. 41A-41C show an assay of activation of ProC732 by tumor tissues (Fig. 41A) and results. Fluorescently labeled ProC732 was incubated on tumor tissue sections at 37°C. Recovered solution was then analyzed through capillary electrophoresis enabling quantification of active molecules (Fig. 41C) and using HEK-blue IFNA reporter model (Fig. 41B). Enzymatically inactive samples were used as control tissues.

Figs. 42A-42C show changes in bioactivity of ProC732 (Fig. 42A) and recombinant IFN-a2b (Fig. 42B) molecules after incubation with tumor tissues analyzed by HEK-blue IFNA reporter model. Fold change of bioactivity of 10 ng/mL ProC732or 1

ng/mL of recombinant IFN-a2b was calculated relative to 0h values. Bioactivity of ProC732 and IFN-a2b proteins incubated in the absence of tumor tissues for 24h (Fig. 42C). Each line connects an individual sample (concentration range 100-0.01 ng/mL) analyzed before and after 24h incubation.

Figs. 43, 44A, and 44B show pharmacokinetics of the masked INF-a2b and control molecules in non-human primates. Cynomolgus monkey (N=2 per group) were treated with a single dose subcutaneous administration of ProC732 at 0.03, 0.3, 3 or 15 mg/kg. Fig. 43 shows results where plasma samples were collected at indicated time points and analyzed for total ProC732 concentration. Fig. 44A shows concentrations of IP-10 in serum were measured by MSD V-plex assay. Fig. 44B shows concentrations of circulating Pb-IFN-a2b and IP-10 plotted against each other at day 1 and day 7 after administration.

Figs. 45 and 46 show gene expression profile changes induced by ProC732 non-human primates based on concentration (Fig. 45). Cynomolgus monkey (N=2 per group) were treated with a single dose subcutaneous administration of ProC732 at 0.03, 0.3, 3 or 15 mg/kg. PBMC from treated animals were harvested and analyzed by bulk RNAseq. Genes were called differentially expressed if number of reads changes were >3 (Fig. 46).

Fig. 47 shows that ProC1023 preferentially activates immune cells in tumor tissues. Six days after the treatment tumors and tissues were harvested and analyzed by flow cytometry. Gated on viable CD45+CD3+ cells.

Fig. 48 shows that ProC732 is well tolerated after multidose administration. Male Syrian golden hamsters (N=5) were treated i.p. with three weekly administrations of 15, 30 or 60 mg/kg Pb-IFN-a2b (ProC732), or 3.75, 7.5 or 15 mg/kg of unmasked Fc-IFN-a2b (ProC286) fusion proteins. Survival results include animals found dead or experienced body weight loss >15%.

Fig. 49 shows that masking of ProC732 attenuates cytokine/chemokine release in non-human primates.

Fig. 50 shows that dual masked Pb-IFN-a2b (ProC732) suppresses tumor growth in immune competent rodents in vivo. Male Syrian golden hamsters (N=16) were implanted with 10 mln RPMI-1846 hamster melanoma cells subcutaneously and treated intraperitoneally with twice weekly administrations of 5, 10 or 20 mg/kg Pb-IFN-a2b.

Fig. 51 shows anti-tumor activity of dual masked IFNa2b/Fc and peginterferon at increasing doses. Beige/SCID mice (n=8 per group) were implanted subcutaneously with 10 mln human lymphoma (Daudi) cells and treated when the average tumor volume reached ~200 mm3. Indicated doses of Pb-IFN-a2b (ProC732), unmasked Fc-IFN-a2b (ProC286) and Peg-IFN-a2b were administered i.v. once weekly for 3 weeks.

Fig. 52 shows pharmacokinetics of the dual masked Pb-INF-a2b (ProC732) in Biege/SCID mice. Beige/SCID mice (n=15 per group) were treated with single administration of indicated doses of Pb-IFN-a2b (ProC732). Plasma for PK studies was collected at 1, 2, 3, 6, 24, 48, 72, 120 hours, 7 and 14 days after the administration. Samples were analyzed by MSD assay.

Fig. 53 shows that Pb-IFN-a2b is stable in non-human primates. Cynomolgus monkey (N=4 per group, 2 males + 2 females) were treated intravenously with three weekly administrations of 7.5, 15, 30 or 60 mg/kg of Pb-IFN-a2b (ProC732). In a satellite experiment, a single group of monkeys (N=2, 1 per sex) was treated with 30 mg/kg Pb-IFN-a2b weekly for three weeks. Plasma concentration of Pb-IFN-a2b (ProC732) and its activation products was measured by LC-MS.

DETAILED DESCRIPTION

Provided herein are activatable cytokine constructs (ACCs) that exhibit a reduced level of at least one activity of the corresponding cytokine, but which, after exposure to an activation condition, yield a cytokine product having substantially restored activity. Activatable cytokine constructs of the present invention may be designed to selectively activate upon exposure to diseased tissue, and not in normal tissue. Further provided herein is a combination therapy or use of an ACC described herein in combination with a PD1/PD-L1 inhibitor selected from a PD-1 antibody, an activatable PD-1 antibody, a PD-L1 antibody, or an activatable PD-L1 antibody. As such, these compounds have the potential for conferring the benefit of a cytokine-based therapy, with potentially less of the toxicity associated with certain cytokine-based therapies. Further, this combination therapy may confer the benefits of a cytokine-based therapy and an anti-PD1 and/or anti-PD-L1 therapy, with potentially less of the toxicity associated with respective monotherapies and respective combination therapies that do not include use of the ACCs disclosed herein.

Also provided herein are related intermediates, compositions, kits, nucleic acids, and recombinant cells, as well as related methods, including methods of using and methods of producing any of the activatable cytokine constructs described herein.

The inventors have surprisingly found that ACCs having the specific elements and structural orientations described herein appear potentially effective in improving the safety and therapeutic index of cytokines in therapy, particulary for treating cancers. While cytokines are regulators of innate and adaptive immune system and have broad anti-tumor activity in pre-clinical models, their clinical success has been limited by systemic toxicity and poor systemic exposure to target tissues. The inventors have surprisingly found that ACCs having the specific elements and structural orientations described herein appear to reduce the systemic toxicity associated with cytokine therapeutics and improve targeting and exposure to target issues. As such, the present disclosure provides a method of reducing target-mediated drug disposition (TMDD) of cytokine therapeutics by administering ACCs having the specific elements and structural orientations described herein to a subject. As such, the invention solves the problem of sequestration of a significant fraction of the administered cytokine dose by normal tissues, which is a problem that limits the fraction of the dose available in the systemic circulation to reach the target tissues, e.g., cancerous tissue, in conventional cytokine therapeutics. The present cytokine constructs localizes target binding to tumor tissues, thereby maintaining potency, reducing side effects, enabling new target opportunities, improving the therapeutic window for validated targets, creating a therapeutic window for undruggable targets, and providing multiple binding modalities.

The present disclosure further provides methods of administering ACCs in combination with a PD1/PD-L1 inhibitor selected from a PD-1 antibody, an activatable PD-1 antibody, a PD-L1 antibody, or an activatable PD-L1 antibody. In some embodiments, the combination of an ACC and PD1/PDL1 inhibitor may augment or potentiate therapeutic efficacy and/or therapeutic index relative to a conventional cytokine therapy. In some embodiments, the combination of an ACC and PD1/PDL1 inhibitor may augment or potentiate therapeutic efficacy and/or therapeutic index relative to a conventional PD1/PDL1 inhibitor therapy. In some embodiments, the combination of an ACC and PD1/PDL1 inhibitor may augment or potentiate therapeutic efficacy

and/or therapeutic index relative to a conventional cytokine and PD1/PDL1 inhibitor combination therapy. In still other embodiments, the combination of an ACC and a PD1/PDL1 inhibitor may augment or potentiate therapeutic efficacy and/or therapeutic index relative to administering an ACC of the present disclsosure alone.

The present disclosure enables safe and effective systemic delivery, thereby avoiding the dose-dependent toxicities of conventional systemic cytokine therapies, and also avoids a requirement for intra-tumoral injection. The present disclosure provides a means for imparting localized anti-viral activity, immunomodulatory activity, antiproliferative activity and pro-apoptotic activity. The inventors surprisingly found that dimerization of the first and second monomer constructs achieves high reduction of cytokine activity, and surprisingly discovered that the cytokine activity can be substantially reduced with very high masking efficiency by the addition of a peptide mask at the other terminus of the activatable construct. See, e.g., Figs. 10A-10B.

Applicant's U.S. Provisional App. No. 63/008,542, filed April 10, 2020, and U.S. Provisional App. No. 63/161,889 filed March 16, 2021, which describe certain activatable cytokine constructs without an affinity peptide mask, are incorporated herein by reference in their entireties.

Activatable Cytokine Constructs and Activatable Antibodies

Activatable cytokine constructs (ACCs) of the present invention are dimer complexes comprising a first monomer construct and a second monomer construct. Dimerization of the monomeric components is facilitated by a pair of dimerization domains. In one aspect, each monomer construct includes a cytokine protein (CP), one or more cleavable moieties (CM), a dimerization domain (DD), and a peptide mask (PM). The present inventors unexpectedly found that ACC structures comprising both a dimerization domain and a peptide mask have improved masking efficiency to minimize or eliminate off-target effects and undesired activity and/or toxic side effects of cytokines.

In a specific embodiment, the present invention provides an activatable cytokine construct (ACC) that includes a first monomer construct and a second monomer construct, wherein:

(a) the first monomer construct comprises a first peptide mask (PM1), a first mature cytokine protein (CP1), a first and third cleavable moieties (CM1 and CM2), and a first dimerization domain (DD1),

wherein the CM1 is positioned between the CP1 and the DD1 and the CM2 is positioned between the PM1 and the CP1; and

(b) the second monomer construct comprises a second mature cytokine protein (CP2), a second cleavable moiety (CM3), and a second dimerization domain (DD2),

wherein the CM3 is positioned between the CP2 and the DD2;

wherein the DD1 and the DD2 bind each other thereby forming a dimer of the first monomer construct and the second monomer construct; and

wherein the ACC is characterized by having a reduced level of at least one CP1 and/or CP2 activity as compared to a control level of the at least one CP1 and/or CP2 activity. In some embodiments, the second monomer construct further comprises a second peptide mask (PM2) and a fourth cleavable moiety (CM4) positioned between the PM2 and the CP2. In some embodiments, the first monomer construct and the second monomer construct are identical and bind one another to form a homodimer. In other embodiments, at least one of the CP, CM, PM, or DD components in each of the first and second monomer constructs is not identical, and the first and second monomer constructs bind one another to form a heterodimer.

In another specific embodiment, the ACC is used in a combination therapy with an isolated antibody or antigen binding fragment thereof (AB) that specifically binds to mammalian PD-1 or PD-L1.

In further specific embodiment, the ACC is used in a combination therapy with an activatable anti-PD-1 or an anti-PD-L1 antibody that, in an activated state, specifically binds to mammalian PD-1 or PD-L1, wherein said activatable antibody comprises: an antibody or an antigen binding fragment thereof (AB) that specifically binds to mammalian PD-1 or anti-PD-L1; a masking moiety (MM) that inhibits the binding of the AB to mammalian PD-1 or PD-L1 when the activatable antibody is in an uncleaved state; a cleavable moiety (CM) coupled to the AB, wherein the CM is a polypeptide that functions as a substrate for a protease; and optionally a first linking peptide (LP1) and/or a second linking peptide (LP2).

The term "activatable" when used in reference to a cytokine construct and an activatable anti-PD-1 or anti-PD-L1 antibody, refers to a cytokine construct or anti-PD-1 or anti-PD-L1 antibody that exhibits a first level of one or more activities, whereupon exposure to a condition that causes cleavage of one or more cleavable moieties results in the generation of a cytokine construct or an anti-PD-1 or anti-PD-L1 antibody that exhibits a second level of the one or more activities, where the second level of activity is greater than the first level of activity. Non-limiting examples of an activities include any of the exemplary activities of a cytokine, anti-PD-1, or anti-PD-L1 described herein or known in the art, respectively.

The term "mature cytokine protein" refers herein to a cytokine protein that lacks a signal sequence. A signal sequence is also referred to herein as a "signal peptide." A cytokine protein (CP) may be a mature cytokine protein or a cytokine protein with a signal peptide. Thus, the ACCs of the present disclosure may include a mature cytokine protein sequence in some aspects. In some aspects, the ACCs of the present disclosure may include a mature cytokine protein sequence and, additionally, a signal sequence. In some aspects, the ACCs of the present disclosure may include sequences disclosed herein, including or lacking the signal sequences recited herein. In some embodiments, a signal sequence is selected from the group consisting of SEQ ID NO: 468, SEQ ID NO: 469, and SEQ ID NO: 470.

The terms "cleavable moiety" and "CM" are used interchangeably herein to refer to a peptide, the amino acid sequence of which comprises a substrate for a sequence-specific protease. Cleavable moieties that are suitable for use as a CM include any of the protease substrates that are known the art. Exemplary cleavable moieties are described in more detail below.

The terms "peptide mask" and "PM" are used interchangeably herein to refer to an amino acid sequence of less than 50 amino acids that reduces or inhibits one or more activities of a cytokine protein. The PM may bind to the cytokine and limit the interaction of the cytokine with its receptor. In some embodiments, the PM is no more than 40 amino acids in length. In preferred embodiments, the PM is no more than 20 amino acids in length. In some embodiments, the PM is no more than 19, 18, 17, 16, or 15 amino acids in length. In some aspects, the PM has at least 13 amino acids (including

any number from 13 to 49). In some aspects, the PM has at least 14 amino acids (including any number from 14 to 49). In some aspects, the PM has at least 15 amino acids (including any number from 15 to 49). In certain aspects, the number of amino acids in the PM may be counted as those amino acids that bind to the cytokine protein. For example, the PM excludes large polypeptides. For example, the PM is not a latency associated peptide. For example, the PM is not a cytokine. For example, the PM is not a receptor for a cytokine. For example, the PM is not a fragment of a receptor for a cytokine. In some aspects, the PM does not have an amino acid sequence that is at least 85% identical to a receptor for a cytokine. For example, the PM is not an albumin. For example, the PM excludes proteins or polypeptides having more than 50 amino acids. In some aspects, the PM excludes proteins or polypeptides having more than 25 amino acids. In some aspects, the PM excludes proteins or polypeptides having more than 20 amino acids. In some aspects, the PM excludes proteins or polypeptides having more than 15 amino acids. In some aspects, the PM does not include amino acids forming flexible N-terminal or C-terminal tail regions.

A "masking moiety" or "MM" in an activatable macromolecule (that is not yet activated) "masks" or reduces or otherwise inhibits the binding of the activatable macromolecule to its target and/or epitope. In some embodiments, the coupling or modifying of anti-PD-1 or anti-PD-L1 antibody with a MM can inhibit the ability of the anti-PD-1 or anti-PD-L1 antibody to specifically bind its target and or epitope by means of inhibition known in the art (e.g., without limitation, structural change and competition for antigen-binding domain). In some embodiments, the coupling or modifying of anti-PD-1 or anti-PD-L1 antibody with a MM can effect a structural change that reduces or inhibits the ability of the protein to specifically bind its target and or epitope. In some embodiments, the coupling or modifying of anti-PD-1 or anti-PD-L1 antibody with a MM sterically blocks, reduces or inhibits the ability of the anti-PD-1 or anti-PD-L1 antibody to specifically bind its target and or epitope. In some embodiments, the MM may be a polypeptide of about 2 to 50 amino acids in length. For example, the MM may be a polypeptide of from 2 to 40, from 2 to 30, from 2 to 20, from 2 to 10, from 5 to 15, from 10 to 20, from 15 to 25, from 20 to 30, from 25 to 35, from 30 to 40, from 35 to 45, from 40 to 50 amino acids in length. For example, the MM may be a polypeptide with 2,

3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 amino acids in length. In some examples, the MM may be a polypeptide of more than 50 amino acids in length, e.g., 100, 200, 300, 400, 500, 600, 700, 800, or more amino acids.

The terms "dimerization domain" and "DD" are used interchangeably herein to refer to one member of a pair of dimerization domains, wherein each member of the pair is capable of binding to the other via one or more covalent or non-covalent interactions. The first DD and the second DD may be the same or different. Exemplary DDs suitable for use as DD1 and or DD2 are described in more detail herein below.

As used herein, the terms "linker," "linking peptide," "LP" refers to a peptide, the amino acid sequence of which is not a substrate for a protease. Exemplary linkers and LPs are described in more detail below.

As used herein, the term "linking region" or "LR" refers to the stretch of amino acid residues between the C-terminus of the cytokine and the amino acid residue that is N-terminally adjacent to the proximal point of interaction between the dimerization domains (i.e., the linking region does not include the C-terminal amino acid of the cytokine or the N-terminal amino acid of the DD that forms the proximal point of interaction to the DD of the corresponding second monomer). For example, when the DDs are a pair of Fc domains, the linking region is the stretch of amino acid residues between the C-terminus of the cytokine and the first N-terminal cysteine residue of the Fc that participates in the disulfide linkage with the second Fc domain (e.g., Cysteine 226 of an IgG1 or IgG4 Fc domain, according to EU numbering). When the dimerization domain is not a polypeptide, then the linking region is the stretch of amino acid residues following the C-terminus of the cytokine until the last amino acid. For example, when the DDs are a biotin-streptavidin pair, the linking region of the biotin-containing monomer is the stretch of amino acid residues between the C-terminus of the cytokine and the biotin molecule, and the linking region of the streptavidin-containing monomer is the stretch of amino acid residues between the C-terminus of the cytokine and the streptavidin molecule.

As used herein, the term "mask linking region" or "MLR" refers to the stretch of amino acid residues between a PM and a CP. As shown in Fig. 36, the MLR spans from

the N-terminus of a CP to the C-terminus of a PM. Thus, the MLR may include a PM, a PM and a linker, or a PM and two linkers. In some aspects, the MLR spans 15 to 22 amino acids. In some aspects, the MLR spans 16 to 21 amino acids. In some aspects, the MLR spans 17 to 20 amino acids. In some aspects, the MLR spans 18 to 20 amino acids. In some aspects, the MLR spans 15, 16, 17, 18, 18, 20, 21, or 22 amino acids.

As used herein, the term "masking efficiency" refers to the activity (e.g., EC50) of the uncleaved ACC, activatable anti-PD-1, or activatable anti-PD-L1 antibody divided by the activity of a control cytokine, anti-PD-1, or anti-PD-L1 antibody wherein the control cytokine, anti-PD-1, or anti-PD-L1 antibody may be either cleavage product of the ACC, activatable anti-PD-1, or activatable anti-PD-L1 or the cytokine, anti-PD-1, or anti-PD-L1 used as the CP of the ACC, activatable anti-PD-1, or activatable anti-PD-L1 antibody. An ACC having a reduced level of at least one CP1 and/or CP2 activity has a masking efficiency that is greater than 10. In some embodiments, the ACCs, activatable anti-PD-1, or activatable anti-PD-L1 antibodies described herein have a masking efficiency that is greater than 10, greater than 100, greater than 1000, or greater than 5000.

As used herein, the term "spacer" refers herein to an amino acid residue or a peptide incorporated at a free terminus of the mature ACC, for example between the signal peptide and the N-terminus of the mature ACC. In some aspects, a spacer (or "header") may contain glutamine (Q) residues. In some aspects, residues in the spacer minimize aminopeptidase and/or exopeptidase action to prevent cleavage of N-terminal amino acids. Illustrative and non-limiting spacer amino acid sequences may comprise or consist of any of the following exemplary amino acid sequences: QGQSGS (SEQ ID NO: 471); GQSGS (SEQ ID NO: 472); QSGS (SEQ ID NO: 473); SGS; GS; S; QGQSGQG (SEQ ID NO: 474); GQSGQG (SEQ ID NO: 475); QSGQG (SEQ ID NO: 476); SGQG (SEQ ID NO: 477); GQG; QG; G; QGQSGQ (SEQ ID NO: 478); GQSGQ (SEQ ID NO: 479); QSGQ (SEQ ID NO: 480); QGQSG (SEQ ID NO: 481); QGQS (SEQ ID NO: 482); SGQ; GQ; and Q. In some embodiments, spacer sequences may be omitted.

As used herein, a polypeptide, such as a cytokine or an Fc domain, may be a wild-type polypeptide (e.g., a naturally-existing polypeptide) or a variant of the wild-type

polypeptide. A variant may be a polypeptide modified by substitution, insertion, deletion and/or addition of one or more amino acids of the wild-type polypeptide, provided that the variant retains the basic function or activity of the wild-type polypeptide. In some examples, a variant may have altered (e.g., increased or decreased) function or activity comparing with the wild-type polypeptide. In some aspects, the variant may be a functional fragment of the wild-type polypeptide. The term "functional fragment" means that the sequence of the polypeptide (e.g., cytokine) may include fewer amino acids than the full-length polypeptide sequence, but sufficient polypeptide chain length to confer activity (e.g., cytokine activity).

The first and second monomer constructs may further comprise additional elements, such as, for example, one or more linkers, and the like. The additional elements are described below in more detail. The organization of the CP, CM, PM, and DD components in each of the first and second monomer constructs may be arranged in the same order in each monomer construct. The CP1, CM1, PM1, and DD1 components may be the same or different as compared to the corresponding CP2, CM2, PM2, and DD2, in terms of, for example, molecular weight, size, amino acid sequence of the CP, CM, and PM components (and the DD components in embodiments where the DD components are polypeptides), and the like. Thus, the resulting dimer may have symmetrical or asymmetrical monomer construct components.

In some embodiments, the first monomer construct comprises, from N- to C-terminus of the CP and CM components, the PM1, the CM3, the CP1, the CM1, and, linked directly or indirectly (via a linker) to the C-terminus of the CM1, the DD1. In other embodiments, the first monomer construct comprises from C- to N- terminus of the CP and CM components, the PM1, the CM3, the CP1, the CM1, and, linked directly or indirectly (via a linker) to the N-terminus of the CM1, the DD1. In some embodiments, the second monomer construct comprises, from N- to C- terminal terminus of the CP and CM components, the PM2, the CM4, the CP2, the PM2, the CM2, and, linked directly or indirectly (via a linker) to the C-terminus of the CM2, the DD2. In other embodiments, the second monomer construct comprises, from C- to N- terminus of the CP and CM components, the PM2, the CM4, the CP2, the PM2, the CM2, and, linked directly or indirectly (via a linker) to the N-terminus of the CM2, the DD2. In one example, the first

monomer construct comprises a first polypeptide that comprises the PM1, the CM3, the CP1, the CM1, and the DD1. In one example, the second monomer construct comprises a second polypeptide that comprises the CP2, the CM2, and the DD2. In another example, second monomer construct comprises a second polypeptide that comprises the PM2, the CM4, the CP2, the CM2, and the DD2.

In some embodiments, the CP and DD components are linked by a linker that is not cleavable by a protease. For example, the CP and DD components may be linked by a non-cleavable substrate sequence (NSUB). In some embodiments, one of the first and second monomer constructs comprises a NSUB between the CP and DD, and the other comprises a CM between the CP and DD. In some aspects, the linker may be an amino acid substrate sequence that includes glycine and serine residues, but is not susceptible to protease cleavage. Examples of non-cleavable linker sequences include those described in U.S. Patent No. 10,611,845B2, which is incorporated by reference herein by its entirety. In such cases, the CP and/or the DD may have a cleavage site for a protease.

Examples of the ACCs in the present disclosure can be presented by the following formulae (in the form of monomer 1/monomer 2, from the N-terminus to the C-terminus in each monomer)

PM1-CM3-CP1-CM1-DD1 / PM2-CM4-CP2-CM2-DD2

PM1-CM3-CP1-CM1-DD1 / CP2-CM2-DD2

DD1-CM1-CP1-CM3-PM1 / DD2-CM2-CP2-CM4-PM2

DD1-CM1-CP1-CM3-PM1 / DD2-CM2-CP2

The ACCs may comprise one or more linkers between the components. For example, the ACCs may comprise one or more linkers between PM and CP, and/or between CP and DD. Thus, as used herein and unless otherwise stated, each dash (-) between the ACC components represents either a direct linkage or linkage via one or more linkers.

In some aspects, when the ACC has an orientation of N-PM-CM1-CP-CM2-DD-C, then the entire span of amino acids from the N-terminus of the ACC to the N-terminal amino acid of the cytokine is 17 to 71 amino acids in length. In some aspects, when the ACC has an orientation of N-DD-CM1-CP-CM2-PM-C, then the entire span of amino

acids from the C-terminus of the ACC to the C-terminal amino acid of the cytokine is 17 to 71 amino acids in length.

In certain embodiments, the first and second monomeric constructs are oriented such that the components in each member of the dimer are organized in the same order from N-terminus to C-terminus of the CP and CM components. A schematic of an illustrative ACC is provided in Fig. 1. With reference to Fig. 1, the ACC comprises, from N-terminus to C-terminus: (1) a first monomer construct **110** having a PM1 **119**, a CM3 **117**, a CP1 **115**, a CM1 **113**, and a DD1 **111**, and; (2) a second monomer construct **120** having optionally a PM2 **129** and a CM4 **127**, a CP2 **125**, a CM2 **123**, and a DD2 **121**; and (3) one or more covalent or non-covalent bonds (←→) bonding the first monomer construct **110** to the second monomer construct **120**. The ACC may further comprise one or more of the optional linkers **112**, **114**, **116**, **118**, **122**, **124**, **126**, and **128** between the components. In one example, DD1 **111** and DD2 **121** are the same. In another example, DD1 **111** and DD2 **121** are different.

A schematic of a further illustrative ACC, with its components organized in the reverse orientation of the ACC is provided in Fig. 2. With reference to Fig. 2, the ACC comprises, from N-terminus to C-terminus of the CP and CM components: (1) a first monomer construct **210** having a DD1 **211**, a CM1 **213**, a CP1 **215**, a CM3 **217**, and a PM1 **219**; (2) a second monomer construct **220** having a DD2 **221**, a CM2 **223**, a CP2 **225**, and optionally a CM4 **227** and a PM2 **229**; and (3) one or more covalent or non-covalent bonds (←→) bonding the first monomer construct **210** to the second monomer construct **220**. The ACC may further comprise one or more of the optional linkers **212**, **214**, **216**, **218**, **222**, **224**, **226**, and **228** between the components. In one example, DD1 **211** and DD2 **221** are the same. In another example, DD1 **211** and DD2 **221** are different.

A schematic of another illustrative ACC is provided in Fig. 3. With reference to Fig. 3, the ACC comprises, from N-terminus to C-terminus: (1) a first monomer construct **310** having a PM1 **319**, a CM3 **317**, a CP1 **315**, a CM1 **313**, and a DD1 **311**; and (2) a second monomer construct **320** having a CP2 **325**, a CM2 **323**, and a DD2 **321, and** optionally a PM2 **329** and a CM4 **327**. DD1 **311** and DD2 **321** are binding partners, e.g., a ligand/receptor pair or an antigen/antigen-binding peptide pair, so that DD1 and DD2

are covalently or non-covalently bound together. The ACC may further comprise one or more of the optional linkers **312**, **314**, **316**, **318**, **322**, **324**, **326**, and **328** between the components. In one example, DD1 **311** and DD2 **321** are the same. In another example, DD1 **311** and DD2 **321** are different.

In alternative aspects, one of the two moieties depicted as CP1 **315** and CP2 **325** is a truncated cytokine protein that lacks cytokine activity. For example, either CP1 or CP2 may be a truncated interferon alpha 2b having the first 151 amino acids of wild-type interferon alpha 2b. In alternative aspects, one of the two moieties depicted as CP1 **315** and CP2 **325** is a mutated cytokine protein that lacks cytokine activity. For example, either CP1 or CP2 may be a truncated interferon alpha 2b having a L130P mutation (e.g., SEQ ID NO: 298). In alternative aspects, one of the two moieties depicted as CP1 **315** and CP2 **325** is a polypeptide sequence that lacks cytokine activity, e.g., a signal moiety and/or a stub sequence. In alternative aspects, a first one of the two moieties depicted as CP1 **315** and CP2 **325** is a polypeptide sequence that binds with high affinity to a second one of the two moieties depicted as CP1 **315** and CP2 **325** and reduces the cytokine activity of the second moiety as compared to the control level of the second moiety.

A schematic of another illustrative ACC, with its components organized in the reverse orientation, is provided in Fig. 4. With reference to Fig. 4, the ACC comprises, from N-terminus to C-terminus of the CP and CM components: (1) a first monomer construct **410** having a DD1 **411**, a CM1 **413**, a CP1 **415**, a CM3 **417**, and a PM1 **419**; and (2) a second monomer construct **420** having a DD2 **421**, a CM2 **423**, a CP2 **425**, and optionally a CM4 **427** and a PM2 **429**. DD1 **411** and DD2 **421** are binding partners, e.g., a ligand/receptor pair or an antigen/antigen-binding peptide pair, so that DD1 and DD2 are covalently or non-covalently bound together. The ACC may further comprise one or more of the optional linkers **412**, **414**, **416**, **418**, **422**, **424**, **426**, and **428** between the components. In one example, DD1 **411** and DD2 **421** are the same. In another example, DD1 **411** and DD2 **421** are different.

In certain aspects of the present disclosure, the PM1 and PM2 depicted in the figures may be absent in ACCs used in combination with an anti-PD1 or anti-PD-L1 antibody.

The ACC structure was discovered to be highly effective at reducing activity of the mature cytokine protein components in a way that does not lead to substantially impaired cytokine activity after activation. The CP's activity in the ACC may be reduced by both the structure of the ACC (e.g., the dimer structure) and the peptide mask(s) in the ACC. In some embodiments, the activation condition for the ACCs described herein is exposure to one or more proteases that can dissociate the CP from both the DD and the PM. For example, the one or more proteases may cleave the CM between the CP and the PM and the CM between the CP and the DD. As demonstrated in the Examples, activation of the ACC resulted in substantial recovery of cytokine activity. The results suggest that conformation of the cytokine components was not irreversibly altered within the context of the ACC. Significantly, the inventors have discovered that the present structure, utilizing both a dimerization domain and one or more peptide masks that have specific binding affinity for the cytokine protein appears to result in a substantial masking effect achieved over use of either a peptide mask alone or a dimerization domain alone.

The ACC may employ any of a variety of mature cytokine proteins, cleavable moieties, peptide masks, and dimerization domains as the CP1, CP2, CM1, CM2, CM3, CM4, PM1, PM2, DD1, and DD2, respectively. For example, any of a variety of mature cytokine proteins that are known in the art or sequence and/or truncation variants thereof, may be suitable for use as either or both CP1 and CP2 components of the ACC. The mature cytokine proteins, CP1 and CP2 may be the same or different. In certain specific embodiments, CP1 and CP2 are the same. In other embodiments, CP1 and CP2 are different. The ACC may comprise additional amino acid residues at either or both N- and/or C-terminal ends of the CP1 and/or CP2.

In some embodiments, the CP1 and/or the CP2 may each independently comprise a mature cytokine protein selected from the group of: an interferon (such as, for example, an interferon alpha, an interferon beta, an interferon gamma, an interferon tau, and an interferon omega), an interleukin (such as, for example, IL-1α, IL-1β, IL-1RA, IL-18, IL-2, IL-4, IL-7, IL-9, IL-13, IL-15, IL-3, IL-5, GM-CSF, IL-6, IL-11, IL-21), G-CSF, IL-12, LIF, OSM, IL-10, IL-20, IL-14, IL-16, IL-17, CD154, LT-β, TNF-α, TNF-β, 4-1BBL, APRIL, CD27, CD70, CD153, CD178, GITRL, LIGHT, OX40L, OX40, TALL-1, TRAIL, TWEAK, TRANCE, TGF-β1, TGF-β2, TGF-β3, EPOo, TPO, Flt-3L, SCF, M-

CSF, and MSP, and the like, as well as sequence and truncation variants thereof. In particular, an ACC for use in combination may contain IL-2, IL-7, IL-8, IL-10, IL-12, IL-15, IL-21, an IFN-alpha, an IFN beta, an IFN gamma, GM-CSF, TGF-beta, LIGHT, GITR-L, CD40L, CD27L, 4-1BB-L, OX40, OX40L. For example, sequences of such proteins include those in Table 23 and additional examples of the sequences can be obtained from ncbi.nlm.nih.gov/protein. Truncation variants that are suitable for use in the ACCs of the present invention include any N- or C- terminally truncated cytokine that retains a cytokine activity. Exemplary truncation variants employed in the present invention include any of the truncated cytokine polypeptides that are known in the art (see, e.g., Slutzki et al., *J. Mol. Biol.* 360:1019-1030, 2006, and US 2009/0025106), as well as cytokine polypeptides that are N- and/or C-terminally truncated by 1 to about 40 amino acids, 1 to about 35 amino acids, 1 to about 30 amino acids, 1 to about 25 amino acids, 1 to about 20 amino acids, 1 to about 15 amino acids, 1 to about 10 amino acids, 1 to about 8 amino acids, 1 to about 6 amino acids, 1 to about 4 amino acids, that retain a cytokine activity. In some of the foregoing embodiments, the truncated CP is an N-terminally truncated CP. In other embodiments, the truncated CP is a C-terminally truncated CP. In certain embodiments, the truncated CP is a C- and an N-terminally truncated CP.

In some embodiments, the CP1 and/or the CP2 each independently comprise an amino acid sequence that is at least 80% identical (e.g., at least 82%, at least 84%, at least 86%, at least 88%, at least 90%, at least 92%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical) to a cytokine reference sequence selected from the group consisting of: SEQ ID NO: 101, SEQ ID NO: 102, SEQ ID NO: 103, SEQ ID NO: 104, SEQ ID NO: 105, SEQ ID NO: 106, SEQ ID NO: 107, SEQ ID NO: 108, SEQ ID NO: 109, SEQ ID NO: 110, SEQ ID NO: 111, SEQ ID NO: 112, SEQ ID NO: 113, SEQ ID NO: 114, SEQ ID NO: 115, SEQ ID NO: 116, SEQ ID NO: 117, SEQ ID NO: 118, SEQ ID NO: 119, SEQ ID NO: 12 , SEQ ID NO: 121, SEQ ID NO: 122, SEQ ID NO: 123, SEQ ID NO: 124, SEQ ID NO: 125, SEQ ID NO: 126, SEQ ID NO: 127, SEQ ID NO: 128, SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID NO: 134, SEQ ID NO: 135, SEQ ID NO: 136, SEQ ID NO: 137, SEQ ID NO: 138, SEQ ID NO: 139, SEQ ID NO: 140, SEQ ID NO:

141, SEQ ID NO: 142, SEQ ID NO: 143, SEQ ID NO: 144, SEQ ID NO: 145, SEQ ID NO: 146, SEQ ID NO: 147, SEQ ID NO: 148, SEQ ID NO: 149, SEQ ID NO: 150, SEQ ID NO: 151, SEQ ID NO: 152, SEQ ID NO: 153, SEQ ID NO: 154, SEQ ID NO: 155, SEQ ID NO: 156, SEQ ID NO: 157, SEQ ID NO: 158, SEQ ID NO: 159, SEQ ID NO: 160, SEQ ID NO: 161, SEQ ID NO: 162, SEQ ID NO: 163, SEQ ID NO: 164, SEQ ID NO: 165, SEQ ID NO: 166, SEQ ID NO: 167, SEQ ID NO: 168, SEQ ID NO: 169, SEQ ID NO: 170, SEQ ID NO: 171, SEQ ID NO: 172, SEQ ID NO: 173, SEQ ID NO: 174, SEQ ID NO: 175, SEQ ID NO: 176, SEQ ID NO: 177, SEQ ID NO: 178, SEQ ID NO: 179, SEQ ID NO: 180, SEQ ID NO: 181, SEQ ID NO: 182, SEQ ID NO: 183, SEQ ID NO: 184, SEQ ID NO: 185, SEQ ID NO: 186, SEQ ID NO: 187, SEQ ID NO: 188, SEQ ID NO: 189, SEQ ID NO: 190, SEQ ID NO: 191, SEQ ID NO: 192, SEQ ID NO: 193, SEQ ID NO: 194, SEQ ID NO: 195, SEQ ID NO: 196, SEQ ID NO: 197, SEQ ID NO: 198, SEQ ID NO: 199, SEQ ID NO: 200, SEQ ID NO: 201, SEQ ID NO: 202, SEQ ID NO: 203, SEQ ID NO: 204, SEQ ID NO: 205, SEQ ID NO: 206, SEQ ID NO: 207, SEQ ID NO: 208, and SEQ ID NO: 209. The percentage of sequence identity refers to the level of amino acid sequence identity between two or more peptide sequences when aligned using a sequence alignment program, e.g., the suite of BLAST programs, publicly available on the Internet at the NCBI website. See also Altschul et al., J. Mol. Biol. 215:403-10, 1990. In some aspects, the ACC includes an interferon alpha 2b mutant, for example, an interferon alpha 2b molecule having a mutation at position L130, e.g., L130P mutation relative to SEQ ID NO: 1 (e.g., SEQ ID NO: 298), as either CP1 or CP2. In some aspects, the ACC includes an interferon alpha 2b mutant having a mutation at position I24, F64, I60, I63, F64, W76, I116, L117, F123, or L128, or a combination thereof. For example, the interferon alpha 2b mutant may include mutations I116 to T, N. or R; L128 to N, H, or R; I24 to P or Q; L117H; or L128T, or a combination thereof. In some aspects, the interferon alpha 2b mutant may include mutations I24Q, I60T, F64A, W76H, I116R, and L128N, or a subset thereof. In some aspects, the ACC includes as one of CP1 and CP2 a truncated interferon alpha 2b molecule that lacks cytokine activity. For example, the truncated interferon alpha 2b may consist of 151 or fewer amino acids of interferon alpha 2b, e.g., any one of amino acids in the wild-type interferon alpha 2b sequence from N to C-terminus: 1 to 151, 1 to 150, 1 to 149, 1 to 148, . . . 1 to 10, 1 to 9,

1 to 8, 1 to 7, 1 to 6, or 2 to 151, 3 to 151, 4 to 151, 5 to 150, 6 to 149, 7 to 148, 8 to 147, or any intervening sequence of amino acids or mutants thereof.

In certain specific embodiments, the CP1 and/or the CP2 comprise an interferon. Interferons that are suitable for use in the constructs of the present invention as CP1 and/or CP2 include, for example, an interferon-alpha, an interferon-beta, an interferon-gamma, an interferon-omega, and an interferon-tau. In some embodiments, when the interferon is an interferon alpha, it may be an interferon alpha-2a, an interferon alpha-2b, or an interferon alpha-n3. Further examples of interferon alpha include interferon alpha-1, interferon alpha-4, interferon alpha-5, interferon alpha-6, interferon alpha-7, interferon alpha-8, interferon alpha-10, interferon alpha-13, interferon alpha-14, interferon alpha-16, interferon alpha-17, and interferon alpha-21. In some embodiments, the interferon is a recombinant or purified interferon alpha. In certain embodiments, when the interferon is an interferon-beta, it is selected from the group consisting of an interferon beta-1a and an interferon beta-1b. In some embodiments, the CP1 and/or the CP2 comprises an IFab domain, which is a conserved protein domain found in interferon alpha or interferon beta. The IFab domain is responsible for the cytokine release and antivirus functions of interferons. Exemplary IFab sequences are provided in SEQ ID Nos: 449-458. In one example, the CP1 and the CP2 are different interferons. In another example, the CP1 and the CP2 are the same interferon.

In some embodiments, the CP1 and/or the CP2 exhibit(s) an interferon activity and include(s) an amino acid sequence that is 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, or at least 99% identical, or 100% identical to an interferon alpha reference sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 101, SEQ ID NO: 102, SEQ ID NO: 103, SEQ ID NO: 104, and SEQ ID NO: 105. In certain specific embodiments, the interferon alpha reference sequence is SEQ ID NO: 1 (human interferon alpha-2b). In some embodiments, the CP1 and/or the CP2 comprise a mature alpha interferon having an amino acid sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 101, SEQ ID NO: 102, SEQ ID NO: 103, SEQ ID NO: 104, and SEQ ID NO: 105. In certain embodiments, the CP1 and/or the CP2

comprise a mature human alpha interferon having the amino acid sequence of SEQ ID NO: 1. In some of the above-described embodiments, the CP1 and the CP2 comprise the same amino acid sequence.

In other embodiments, the CP1 and/or the CP2 exhibit(s) an interferon activity and include(s) an amino acid sequence that is 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, or at least 99% identical, or 100% identical to an interferon beta reference sequence selected from the group consisting of SEQ ID NO: 106, SEQ ID NO: 107, SEQ ID NO: 108, and SEQ ID NO: 109. In certain embodiments, the interferon beta reference sequence is a human interferon beta reference sequence selected from the group consisting of SEQ ID NO: 106 and SEQ ID NO: 107. In some embodiments, the CP1 and/or the CP2 comprise a mature beta interferon having an amino acid sequence selected from the group consisting of SEQ ID NO: 106, SEQ ID NO: 107, SEQ ID NO: 108, and SEQ ID NO: 109. In some of the above-described embodiments, the CP1 and the CP2 comprise the same amino acid sequence.

In some embodiments, the CP1 and/or CP2 exhibit(s) an interferon activity and include(s) an amino acid sequence that is 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, or at least 99% identical, or 100% identical to an interferon omega reference sequence corresponding to SEQ ID NO: 110 (human interferon omega). In certain specific embodiments, the CP1 and/or CP2 comprise a mature human omega interferon having the amino acid sequence of SEQ ID NO: 110. In some of the above-described embodiments, the CP1 and the CP2 comprise the same amino acid sequence.

In some embodiments, the CP1 and/or the CP2 exhibit(s) an interleukin activity and include(s) an amino acid sequence that is at least 80% identical, at least 82%, at least 84%, at least 86%, at least 88%, at least 90%, at least 92%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical or 100% identical to an interleukin reference sequence selected from the group consisting of: SEQ ID NO: 111, SEQ ID NO: 112, SEQ ID NO: 113, SEQ ID NO: 114, SEQ ID NO: 115, SEQ ID NO:

116, SEQ ID NO: 117, SEQ ID NO: 118, SEQ ID NO: 119, SEQ ID NO: 12 , SEQ ID NO: 121, SEQ ID NO: 122, SEQ ID NO: 123, SEQ ID NO: 124, SEQ ID NO: 125, SEQ ID NO: 126, SEQ ID NO: 127, SEQ ID NO: 128, SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID NO: 134, SEQ ID NO: 135, SEQ ID NO: 136, SEQ ID NO: 137, SEQ ID NO: 138, SEQ ID NO: 139, SEQ ID NO: 140, SEQ ID NO: 143, SEQ ID NO: 144, SEQ ID NO: 145, SEQ ID NO: 146, SEQ ID NO: 151, SEQ ID NO: 152, SEQ ID NO: 153, SEQ ID NO: 154, SEQ ID NO: 155, SEQ ID NO: 156, SEQ ID NO: 157, SEQ ID NO: 158, SEQ ID NO: 159, and SEQ ID NO: 160. In some embodiments, CP1 and/or CP2 comprises a mature interleukin having an amino acid sequence selected from the group consisting of: SEQ ID NO: 111, SEQ ID NO: 112, SEQ ID NO: 113, SEQ ID NO: 114, SEQ ID NO: 115, SEQ ID NO: 116, SEQ ID NO: 117, SEQ ID NO: 118, SEQ ID NO: 119, SEQ ID NO: 12 , SEQ ID NO: 121, SEQ ID NO: 122, SEQ ID NO: 123, SEQ ID NO: 124, SEQ ID NO: 125, SEQ ID NO: 126, SEQ ID NO: 127, SEQ ID NO: 128, SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID NO: 134, SEQ ID NO: 135, SEQ ID NO: 136, SEQ ID NO: 137, SEQ ID NO: 138, SEQ ID NO: 139, SEQ ID NO: 140, SEQ ID NO: 143, SEQ ID NO: 144, SEQ ID NO: 145, SEQ ID NO: 146, SEQ ID NO: 151, SEQ ID NO: 152, SEQ ID NO: 153, SEQ ID NO: 154, SEQ ID NO: 155, SEQ ID NO: 156, SEQ ID NO: 157, SEQ ID NO: 158, SEQ ID NO: 159, and SEQ ID NO: 160. In some of the above-described embodiments, the CP1 and the CP2 comprise the same amino acid sequence.

In some embodiments, CP1 and/or CP2 exhibit(s) an interleukin activity and include(s) an amino acid sequence that is at least 80% identical, at least 82%, at least 84%, at least 86%, at least 88%, at least 90%, at least 92%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to an interleukin reference sequence selected from the group consisting of SEQ ID NO: 111 (human IL-1 alpha), SEQ ID NO: 113 (human IL-1 beta), SEQ ID NO: 115 (human IL-1RA), SEQ ID NO: 117 (human IL-18), SEQ ID NO: 119 (human IL-2), SEQ ID NO: 121 (human IL-4), SEQ ID NO: 123 (human IL-7), SEQ ID NO: 125 (human IL-9), SEQ ID NO: 127 (human IL-13), SEQ ID NO: 129 (human IL-15), SEQ ID NO: 131 (human IL-3), SEQ ID NO: 133 (human IL-5), SEQ ID NO: 137 (human IL-6), SEQ ID NO: 139 (human IL-

11), SEQ ID NO: 143 (human IL-12 alpha), SEQ ID NO: 144 (human IL-12 beta), SEQ ID NO: 151 (human IL-10), SEQ ID NO: 153 (human IL-20); SEQ ID NO: 155 (human IL-14), SEQ ID NO: 157 (human IL-16), and SEQ ID NO: 159 (human IL-17). In certain of these embodiments, CP1 and/or CP2 comprise an amino acid sequence from the group consisting of SEQ ID NO: 111 (human IL-1 alpha), SEQ ID NO: 113 (human IL-1 beta), SEQ ID NO: 115 (human IL-1RA), SEQ ID NO: 117 (human IL-18), SEQ ID NO: 119 (human IL-2), SEQ ID NO: 121, SEQ ID NO: 123 (human IL-7), SEQ ID NO: 125 (human IL-9), SEQ ID NO: 127 (human IL-13), SEQ ID NO: 129 (human IL-15), SEQ ID NO: 131 (human IL-3), SEQ ID NO: 133 (human IL-5), SEQ ID NO: 137 (human IL-6), SEQ ID NO: 139 (human IL-11), SEQ ID NO: 143 (human IL-12 alpha), SEQ ID NO: 144 (human IL-12 beta), SEQ ID NO: 151 (human IL-10), SEQ ID NO: 153 (human IL-20); SEQ ID NO: 155 (human IL-14), SEQ ID NO: 157 (human IL-16), and SEQ ID NO: 159 (human IL-17). In some of the above-described embodiments, the CP1 and the CP2 comprise the same amino acid sequence.

The number of amino acids in the sequence of the cytokine proteins employed may vary, depending on the specific cytokine protein employed. In some embodiments, the CP1 and/or the CP2 includes a total of about 10 amino acids to about 700 amino acids, about 10 amino acids to about 650 amino acids, about 10 amino acids to about 600 amino acids, about 10 amino acids to about 550 amino acids, about 10 amino acids to about 500 amino acids, about 10 amino acids to about 450 amino acids, about 10 amino acids to about 400 amino acids, about 10 amino acids to about 350 amino acids, about 10 amino acids to about 300 amino acids, about 10 amino acids to about 250 amino acids, about 10 amino acids to about 200 amino acids, about 10 amino acids to about 150 amino acids, about 10 amino acids to about 100 amino acids, about 10 amino acids to about 80 amino acids, about 10 amino acids to about 60 amino acids, about 10 amino acids to about 40 amino acids, about 10 amino acids to about 20 amino acids, about 20 amino acids to about 700 amino acids, about 20 amino acids to about 650 amino acids, about 20 amino acids to about 600 amino acids, about 20 amino acids to about 550 amino acids, about 20 amino acids to about 500 amino acids, about 20 amino acids to about 450 amino acids, about 20 amino acids to about 400 amino acids, about 20 amino acids to about 350 amino acids, about 20 amino acids to about 300 amino acids, about 20 amino acids to

about 250 amino acids, about 20 amino acids to about 200 amino acids, about 20 amino acids to about 150 amino acids, about 20 amino acids to about 100 amino acids, about 20 amino acids to about 80 amino acids, about 20 amino acids to about 60 amino acids, about 20 amino acids to about 40 amino acids, about 40 amino acids to about 700 amino acids, about 40 amino acids to about 650 amino acids, about 40 amino acids to about 600 amino acids, about 40 amino acids to about 550 amino acids, about 40 amino acids to about 500 amino acids, about 40 amino acids to about 450 amino acids, about 40 amino acids to about 400 amino acids, about 40 amino acids to about 350 amino acids, about 40 amino acids to about 300 amino acids, about 40 amino acids to about 250 amino acids, about 40 amino acids to about 200 amino acids, about 40 amino acids to about 150 amino acids, about 40 amino acids to about 100 amino acids, about 40 amino acids to about 80 amino acids, about 40 amino acids to about 60 amino acids, about 60 amino acids to about 700 amino acids, about 60 amino acids to about 650 amino acids, about 60 amino acids to about 600 amino acids, about 60 amino acids to about 550 amino acids, about 60 amino acids to about 500 amino acids, about 60 amino acids to about 450 amino acids, about 60 amino acids to about 400 amino acids, about 60 amino acids to about 350 amino acids, about 60 amino acids to about 300 amino acids, about 60 amino acids to about 250 amino acids, about 60 amino acids to about 200 amino acids, about 60 amino acids to about 150 amino acids, about 60 amino acids to about 100 amino acids, about 60 amino acids to about 80 amino acids, about 80 amino acids to about 700 amino acids, about 80 amino acids to about 650 amino acids, about 80 amino acids to about 600 amino acids, about 80 amino acids to about 550 amino acids, about 80 amino acids to about 500 amino acids, about 80 amino acids to about 450 amino acids, about 80 amino acids to about 400 amino acids, about 80 amino acids to about 350 amino acids, about 80 amino acids to about 300 amino acids, about 80 amino acids to about 250 amino acids, about 80 amino acids to about 200 amino acids, about 80 amino acids to about 150 amino acids, about 80 amino acids to about 100 amino acids, about 100 amino acids to about 700 amino acids, about 100 amino acids to about 650 amino acids, about 100 amino acids to about 600 amino acids, about 100 amino acids to about 550 amino acids, about 100 amino acids to about 500 amino acids, about 100 amino acids to about 450 amino acids, about 100 amino acids to about 400 amino acids, about 100 amino acids to about 350 amino acids,

about 100 amino acids to about 300 amino acids, about 100 amino acids to about 250 amino acids, about 100 amino acids to about 200 amino acids, about 100 amino acids to about 150 amino acids, about 150 amino acids to about 700 amino acids, about 150 amino acids to about 650 amino acids, about 150 amino acids to about 600 amino acids, about 150 amino acids to about 550 amino acids, about 150 amino acids to about 500 amino acids, about 150 amino acids to about 450 amino acids, about 150 amino acids to about 400 amino acids, about 150 amino acids to about 350 amino acids, about 150 amino acids to about 300 amino acids, about 150 amino acids to about 250 amino acids, about 150 amino acids to about 200 amino acids, about 200 amino acids to about 700 amino acids, about 200 amino acids to about 650 amino acids, about 200 amino acids to about 600 amino acids, about 200 amino acids to about 550 amino acids, about 200 amino acids to about 500 amino acids, about 200 amino acids to about 450 amino acids, about 200 amino acids to about 400 amino acids, about 200 amino acids to about 350 amino acids, about 200 amino acids to about 300 amino acids, about 200 amino acids to about 250 amino acids, about 250 amino acids to about 700 amino acids, about 250 amino acids to about 650 amino acids, about 250 amino acids to about 600 amino acids, about 250 amino acids to about 550 amino acids, about 250 amino acids to about 500 amino acids, about 250 amino acids to about 450 amino acids, about 250 amino acids to about 400 amino acids, about 250 amino acids to about 350 amino acids, about 250 amino acids to about 300 amino acids, about 300 amino acids to about 700 amino acids, about 300 amino acids to about 650 amino acids, about 300 amino acids to about 600 amino acids, about 300 amino acids to about 550 amino acids, about 300 amino acids to about 500 amino acids, about 300 amino acids to about 450 amino acids, about 300 amino acids to about 400 amino acids, about 300 amino acids to about 350 amino acids, about 350 amino acids to about 700 amino acids, about 350 amino acids to about 650 amino acids, about 350 amino acids to about 600 amino acids, about 350 amino acids to about 550 amino acids, about 350 amino acids to about 500 amino acids, about 350 amino acids to about 450 amino acids, about 350 amino acids to about 400 amino acids, about 400 amino acids to about 700 amino acids, about 400 amino acids to about 650 amino acids, about 400 amino acids to about 600 amino acids, about 400 amino acids to about 550 amino acids, about 400 amino acids to about 500 amino acids, about 400

amino acids to about 450 amino acids, about 450 amino acids to about 700 amino acids, about 450 amino acids to about 650 amino acids, about 450 amino acids to about 600 amino acids, about 450 amino acids to about 550 amino acids, about 450 amino acids to about 500 amino acids, about 500 amino acids to about 700 amino acids, about 500 amino acids to about 650 amino acids, about 500 amino acids to about 600 amino acids, about 500 amino acids to about 550 amino acids, about 550 amino acids to about 700 amino acids, about 550 amino acids to about 650 amino acids, about 550 amino acids to about 600 amino acids, about 600 amino acids to about 700 amino acids, about 600 amino acids to about 650 amino acids, or about 650 amino acids to about 700 amino acids. In some embodiments, CP1 and/or the CP2 is a mature wildtype human cytokine protein.

Each monomer construct of the ACC may employ any of a variety of dimerization domains. Suitable DDs include both polymeric (e.g., a synthetic polymer, a polypeptide, a polynucleotide, and the like) and small molecule (non-polymeric moieties having a molecular weight of less than about 1 kilodalton, and sometimes less than about 800 daltons) types of moieties. The pair of DDs may be any pair of moieties that are known in the art to bind to each other.

For example, in some embodiments, the DD1 and the DD2 are members of a pair selected from the group of: a sushi domain from an alpha chain of human IL-15 receptor (IL15Rα) and a soluble IL-15; barnase and barnstar; a protein kinase A (PKA) and an A-kinase anchoring protein (AKAP); adapter/docking tag molecules based on mutated RNase I fragments; a pair of antigen-binding domains (e.g., a pair of single domain antibodies); soluble N-ethyl-maleimide sensitive factor attachment protein receptors (SNARE); modules based on interactions of the proteins syntaxin, synaptotagmin, synaptobrevin, and SNAP25; a single domain antibody (sdAb) and corresponding epitope; an antigen-binding domain (e.g., a single chain antibody such as a single chain variable fragment (scFv), a single domain antibody, and the like) and a corresponding epitope; coiled coil polypeptide structions (e.g., Fos-Jun coiled coil structures, acid/base coiled-coil helices, Glu-Lys coiled coil helices, leucine zipper structures), small molecule binding pairs such as biotin and avidin or streptavidin, amine/aldehyde, lectin/carbohydrate; a pair of polymers that can bind each other, such as, for example, a

pair of sulfur- or thiol-containing polymers (e.g., a pair of Fc domains, a pair of thiolized-human serum albumin polypeptides, and the like); and the like.

In some embodiments, the DD1 and DD2 are non-polypeptide polymers. The non-polypeptide polymers may covalently bound to each other. In some examples, the non-polypeptide polymers may be a sulfur-containing polymer, e.g., sulfur-containing polyethylene glycol. In such cases, the DD1 and DD2 may be covalently bound to each other via one or more disulfide bonds.

When the pair of DD1 and DD2 are members of a pair of epitope and antigen-binding domain, the epitope may be a naturally or non-naturally occurring epitope. Exemplary non-naturally occurring epitopes include, for example, a non-naturally occurring peptide, such as, for example, a poly-His peptide (e.g., a His tag, and the like).

In certain specific embodiments, the DD1 and the DD2 are a pair of Fc domains. As used herein, an "Fc domain" refers to a contiguous amino acid sequence of a single heavy chain of an immunoglobulin. A pair of Fc domains associate together to form an Fc region of an immunoglobulin.

In some embodiments, the pair of Fc domains is a pair of human Fc domains (e.g., a pair of wildtype human Fc domains). In some embodiments, the human Fc domains are human IgG1 Fc domains (e.g., wildtype human IgG1 Fc domains), human IgG2 Fc domains (e.g., wildtype human IgG2 Fc domains), human IgG3 Fc domains (e.g., wildtype human IgG3 Fc domains), or human IgG4 Fc domains (e.g., wildtype human IgG4 Fc domains). In some embodiments, the human Fc domains comprise a sequence that is at least 80% identical (e.g., at least 82%, at least 84%, at least 85%, at least 86%, at least 88%, at least 90%, at least 92%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical) to SEQ ID NO: 3.

In some embodiments, the pair of Fc domains comprise a knob mutant and a hole mutant of a Fc domain. The knob and hole mutants may interact with each other to facilitate the dimerization. In some embodiments, the knob and hole mutants may comprise one or more amino acid modifications within the interface between two Fc domains (e.g., in the CH3 domain). In one example, the modifications comprise amino acid substitution T366W and optionally the amino acid substitution S354C in one of the antibody heavy chains, and the amino acid substitutions T366S, L368A, Y407V and

optionally Y349C in the other one of the antibody heavy chains (numbering according to EU index of Kabat numbering system). Examples of the knob and hole mutants include Fc mutants of SEQ ID NOs: 287 and 288, as well as those described in U.S. Pat. Nos. 5,731,168; 7,695,936; and 10,683,368, which are incorporated herein by reference in their entireties. In some embodiments, the dimerization domains comprise a sequence that is at least 80% identical (e.g., at least 82%, at least 84%, at least 85%, at least 86%, at least 88%, at least 90%, at least 92%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical) to SEQ ID NOs: 287 and 288, respectively.

In some embodiments, DD1 and/or DD2 can further include a serum half-life extending moiety (e.g., polypeptides that bind serum proteins, such as immunoglobulin (e.g., IgG) or serum albumin (e.g., human serum albumin (HSA)). Examples of half-life extending moieties include hexa-hat GST (glutathione S-transferase) glutathione affinity, Calmodulin-binding peptide (CBP), Strep-tag, Cellulose Binding Domain, Maltose Binding Protein, S-Peptide Tag, Chitin Binding Tag, Immuno-reactive Epitopes, Epitope Tags, E2Tag, HA Epitope Tag, Myc Epitope, FLAG Epitope, AU1 and AU5 Epitopes, Glu-Glu Epitope, KT3 Epitope, IRS Epitope, Btag Epitope, Protein Kinase-C Epitope, and VSV Epitope.

In some embodiments, DD1 and/or DD2 each include a total of about 5 amino acids to about 250 amino acids, about 5 amino acids to about 200 amino acids, about 5 amino acids to about 180 amino acids, about 5 amino acids to about 160 amino acids, about 5 amino acids to about 140 amino acids, about 5 amino acids to about 120 amino acids, about 5 amino acids to about 100 amino acids, about 5 amino acids to about 80 amino acids, about 5 amino acids to about 60 amino acids, about 5 amino acids to about 40 amino acids, about 5 amino acids to about 20 amino acids, about 5 amino acids to about 10 amino acids, about 10 amino acids to about 250 amino acids, about 10 amino acids to about 200 amino acids, about 10 amino acids to about 180 amino acids, about 10 amino acids to about 160 amino acids, about 10 amino acids to about 140 amino acids, about 10 amino acids to about 120 amino acids, about 10 amino acids to about 100 amino acids, about 10 amino acids to about 80 amino acids, about 10 amino acids to about 60 amino acids, about 10 amino acids to about 40 amino acids, about 10 amino acids to

about 20 amino acids, about 20 amino acids to about 250 amino acids, about 20 amino acids to about 200 amino acids, about 20 amino acids to about 180 amino acids, about 20 amino acids to about 160 amino acids, about 20 amino acids to about 140 amino acids, about 20 amino acids to about 120 amino acids, about 20 amino acids to about 100 amino acids, about 20 amino acids to about 80 amino acids, about 20 amino acids to about 60 amino acids, about 20 amino acids to about 40 amino acids, about 40 amino acids to about 250 amino acids, about 40 amino acids to about 200 amino acids, about 40 amino acids to about 180 amino acids, about 40 amino acids to about 160 amino acids, about 40 amino acids to about 140 amino acids, about 40 amino acids to about 120 amino acids, about 40 amino acids to about 100 amino acids, about 40 amino acids to about 80 amino acids, about 40 amino acids to about 60 amino acids, about 60 amino acids to about 250 amino acids, about 60 amino acids to about 200 amino acids, about 60 amino acids to about 180 amino acids, about 60 amino acids to about 160 amino acids, about 60 amino acids to about 140 amino acids, about 60 amino acids to about 120 amino acids, about 60 amino acids to about 100 amino acids, about 60 amino acids to about 80 amino acids, about 80 amino acids to about 250 amino acids, about 80 amino acids to about 200 amino acids, about 80 amino acids to about 180 amino acids, about 80 amino acids to about 160 amino acids, about 80 amino acids to about 140 amino acids, about 80 amino acids to about 120 amino acids, about 80 amino acids to about 100 amino acids, about 100 amino acids to about 250 amino acids, about 100 amino acids to about 200 amino acids, about 100 amino acids to about 180 amino acids, about 100 amino acids to about 160 amino acids, about 100 amino acids to about 140 amino acids, about 100 amino acids to about 120 amino acids, about 120 amino acids to about 250 amino acids, about 120 amino acids to about 200 amino acids, about 120 amino acids to about 180 amino acids, about 120 amino acids to about 160 amino acids, about 120 amino acids to about 140 amino acids, about 140 amino acids to about 250 amino acids, about 140 amino acids to about 200 amino acids, about 140 amino acids to about 180 amino acids, about 140 amino acids to about 160 amino acids, about 160 amino acids to about 250 amino acids, about 160 amino acids to about 200 amino acids, about 160 amino acids to about 180 amino acids, about 180 amino acids to about 250 amino acids, about 180 amino acids to about 200 amino acids, or about 200 amino acids to about 250 amino acids. In some embodiments,

DD1 and DD2 are each an Fc domain that comprises a portion of the hinge region that includes two cysteine residues, a CH2 domain, and a CH3 domain. In some embodiments, DD1 and DD2 are each an Fc domain whose N-terminus is the first cysteine residue (reading in the N- to C- direction) in the hinge region that participates in a disulfide linkage with a second Fc domain (e.g., Cysteine 226 of human IgG1 or IgG4, using EU numbering).

In some aspects, positioned between the CP and the DD, and/or between the CP and the PM components, either directly or indirectly (e.g., via a linker), is a cleavable moiety (CM) that comprises a substrate for a protease. In some embodiments, the CMs may each independently comprise a substrate for a protease selected from the group consisting of ADAM8, ADAM9, ADAM10, ADAM12, ADAM15, ADAM17/TACE, ADEMDEC1, ADAMTS1, ADAMTS4, ADAMTS5, BACE, Renin, Cathepsin D, Cathepsin E, Caspase 1, Caspase 2, Caspase 3, Caspase 4, Caspase 5, Caspase 6, Caspase 7, Caspase 8, Caspase 9, Caspase 10, Caspase 14, Cathepsin A, Cathepsin B, Cathepsin C, Cathepsin G, Cathepsin K, Cathepsin L, Cathepsin S, Cathepsin V/L2, Cathepsin X/Z/P, Chymase, Cruzipain, DESC1, DPP-4, FAP, Legumain, Otubain-2, Elastase, FVIIa, FiXA, FXa, FXIa, FXIIa, Granzyme B, Guanidinobenzoatase, Hepsin, HtrA1, Human Neutrophil Elastase, KLK4, KLK5, KLK6, KLK7, KLK8, KLK10, KLK11, KLK13, KLK14, Lactoferrin, Marapsin, Matriptase-2, Meprin, MT-SP1/Matriptase, Neprilysin, NS3/4A, PACE4, Plasmin, PSMA, PSA, BMP-1, MMP1, MMP2, MMP3, MMP7, MMP8, MMP9, MMP10, MMP11, MMP12, MMP13, MMP14, MMP15, MMP16, MMP17, MMP19, MMP20, MMP23, MMP24, MMP26, MMP27, TMPRSS2, TMPRSS3, TMPRSS4, tPA, Thrombin, Tryptase, and uPA, and any combination of two or more thereof.

In some embodiments of any of the ACCs described herein, the protease that cleaves any of the CMs described herein can be ADAM8, ADAM9, ADAM10, ADAM12, ADAM15, ADAM17/TACE, ADAMDEC1, ADAMTS1, ADAMTS4, ADAMTS5, BACE, Renin, Cathepsin D, Cathepsin E, Caspase 1, Caspase 2, Caspase 3, Caspase 4, Caspase 5, Caspase 6, Caspase 7, Caspase 8, Caspase 9, Caspase 10, Caspase 14, Cathepsin B, Cathepsin C, Cathepsin K, Cathespin L, Cathepsin S, Cathepsin V/L2, Cathepsin X/Z/P, Cruzipain, Legumain, Otubain-2, KLK4, KLK5, KLK6, KLK7, KLK8,

KLK10, KLK11, KLK13, KLK14, Meprin, Neprilysin, PSMA, BMP-1, MMP-1, MMP-2, MMP-3, MMP-7, MMP-9, MMP-10, MMP-11, MMP-12, MMP-13, MMP-14, MMP-15, MMP-16, MMP-17, MMP-19, MMP-20, MMP-23, MMP-24, MMP-26, MMP-27, activated protein C, cathepsin A, cathepsin G, Chymase, FVIIa, FIXa, FXa, FXIa, FXIIa, Elastase, Granzyme B, Guanidinobenzoatase, HtrA1, human neutrophil lyase, lactoferrin, marapsin, NS3/4A, PACE4, Plasmin, PSA, tPA, thrombin, tryptase, uPA, DESC1, DPP-4, FAP, Hepsin, Matriptase-2, MT-SP1/Matripase, TMPRSS2, TMPRSS3, and TMPRSS4, and any combination of two or more thereof.

In some embodiments of any of the ACCs described herein, the protease is selected from the group of: uPA, legumain, MT-SP1, ADAM17, BMP-1, TMPRSS3, TMPRSS4, MMP-2, MMP-9, MMP-12, MMP-13, and MMP-14.

Increased levels of proteases having known substrates have been reported in a number of cancers. See, e.g., La Roca et al., *British J. Cancer* 90(7):1414-1421, 2004. Substrates suitable for use in the CMs components employed herein include those which are more prevalently found in cancerous cells and tissue. Thus, in certain embodiments, CMs each independently comprise a substrate for a protease that is more prevalently found in diseased tissue associated with a cancer. In some embodiments, the cancer is selected from the group of: gastric cancer, breast cancer, osteosarcoma, and esophageal cancer. In some embodiments, the cancer is breast cancer. In some embodiments, the cancer is a HER2-positive cancer. In some embodiments, the cancer is Kaposi sarcoma, hairy cell leukemia, chronic myeloid leukemia (CML), follicular lymphoma, renal cell cancer (RCC), melanoma, neuroblastoma, basal cell carcinoma, cutaneous T-cell lymphoma, nasopharyngeal adenocarcimoa, breast cancer, ovarian cancer, bladder cancer, BCG-resistant non-muscle invasive bladder cancer (NMIBC), endometrial cancer, pancreatic cancer, non-small cell lung cancer (NSCLC), colorectal cancer, esophageal cancer, gallbladder cancer, glioma, head and neck carcinoma, uterine cancer, cervical cancer, or testicular cancer, and the like. In some of the above-described embodiments, the CM components comprise substrates for protease(s) that is/are more prevalent in tumor tissue

In some embodiments, CMs each independently include(s) a sequence selected from the group consisting of SEQ ID NO: 5 through SEQ ID NO: 100, as well as C-terminal and N-terminal truncation variants thereof.

In some embodiments, the CM includes a sequence selected from the group of: ISSGLLSGRSDNH (SEQ ID NO: 28), LSGRSDDH (SEQ ID NO: 33), ISSGLLSGRSDQH (SEQ ID NO: 54), and ISSGLLSGRSDNI (SEQ ID NO: 68).

In certain embodiments, CM1 and/or CM1 include(s) a sequence selected from the group of: AQNLLGMY (SEQ ID NO: 237), LSGRSDNHGGAVGLLAPP (SEQ ID NO: 238), VHMPLGFLGPGGLSGRSDNH (SEQ ID NO: 239), LSGRSDNHGGVHMPLGFLGP (SEQ ID NO: 240), LSGRSDNHGGSGGSISSGLLSS (SEQ ID NO: 241), ISSGLLSSGGSGGSLSGRSGNH (SEQ ID NO: 242), LSGRSDNHGGSGGSQNQALRMA (SEQ ID NO: 243), QNQALRMAGGSGGSLSGRSDNH (SEQ ID NO:244), LSGRSGNHGGSGGSQNQALRMA (SEQ ID NO: 245), QNQALRMAGGSGGSLSGRSGNH (SEQ ID NO: 246), ISSGLLSGRSGNH (SEQ ID NO: 247), as well as C-terminal and N-terminal truncation variants thereof. Examples of CMs also include those described in U.S. Patent Application Publication Nos. US20160289324, US20190284283, and in publication numbers WO 2010/081173, WO 2015/048329, WO 2015/116933, WO 2016/118629, and WO 2020/118109, which are incorporated herein by reference in their entireties.

Truncation variants of the aforementioned amino acid sequences that are suitable for use in the CMs are any that retain the recognition site for the corresponding protease. These include C-terminal and/or N-terminal truncation variants comprising at least 3 contiguous amino acids of the above-described amino acid sequences, or at least 4, or at least 5, or at least 6, or at least 7 amino acids of the foregoing amino acid sequences that retain a recognition site for a protease. In certain embodiments, the truncation variant of the above-described amino acid sequences is an amino acid sequence corresponding to any of the above, but that is C- and/or N-terminally truncated by 1 to about 10 amino acids, 1 to about 9 amino acids, 1 to about 8 amino acids, 1 to about 7 amino acids, 1 to about 6 amino acids, 1 to about 5 amino acids, 1 to about 4 amino acids, or 1 to about 3 amino acids, and which: (1) has at least three amino acid residues; and (2) retains a

recognition site for a protease. In some of the foregoing embodiments, the truncated CM is an N-terminally truncated CM. In some embodiments, the truncated CM is a C-terminally truncated CM. In some embodiments, the truncated C is a C- and an N-terminally truncated CM.

In some embodiments of any of the ACCs or activatable antibodies described herein, the CM may comprise a total of about 3 amino acids to about 25 amino acids. In some embodiments, the CM may comprise a total of about 3 amino acids to about 25 amino acids, about 3 amino acids to about 20 amino acids, about 3 amino acids to about 15 amino acids, about 3 amino acids to about 10 amino acids, about 3 amino acids to about 5 amino acids, about 5 amino acids to about 25 amino acids, about 5 amino acids to about 20 amino acids, about 5 amino acids to about 15 amino acids, about 5 amino acids to about 10 amino acids, about 10 amino acids to about 25 amino acids, about 10 amino acids to about 20 amino acids, about 10 amino acids to about 15 amino acids, about 15 amino acids to about 25 amino acids, about 15 amino acids to about 20 amino acids, or about 20 amino acids to about 25 amino acids.

In some embodiments, the ACC, activatable anti-PD1, or activatable anti-PD-L1 may comprise multiple CMs that comprise substrates for different proteases. In some embodiments, the ACC, activatable anti-PD1, or activatable anti-PD-L1 may comprise multiple CMs that are substrates for the same protease. In one example, the CM(s) between each CP and PM may be substrates for the same protease as each other, and the CM(s) between each CP and DD may be substates for the same protease as each other, but may be substrates for a different protease than the CM(s) between the CP and the PM. In another example, the CM(s) between the CP and the PM and the CM(s) between the CP and the DD may comprise substrates for the same protease. In another example, the CM(s) between the CP and the PM may comprise substrates for different proteases. In another example, the CM(s) between the CP and the PM may comprise substrates for the same protease. In another example, the CM(s) between the CP and the DD may comprise substrates for different proteases. In another example, the CM(s) between the CP and the DD may comprise substrates for the same protease. In one example, the CM(s) between each activatable anti-PD1 or activatable anti-PD-L1 and MM may be substrates for the same protease as each other. In another example, the CM(s) between the activatable anti-

PD1 or activatable anti-PD-L1 and the MM may comprise substrates for different proteases. In another example, the CM(s) between the activatable anti-PD1 or activatable anti-PD-L1 and the MM may comprise substrates for the same protease.

The first and second monomer constructs may comprise one or more additional components including one or more linkers, and the like. In some embodiments, the first monomer can include a linker disposed between the CP1 and the CM1. In some embodiments, the CP1 and the CM1 directly abut each other in the first monomer. In some embodiments, the first monomer comprises a linker disposed between the CM1 and the DD1. In some embodiments, the CM1 and the DD1 directly abut each other in the first monomer. In some embodiments, the first monomer can include a linker disposed between the CP1 and the CM3. In some embodiments, the CP1 and the CM3 directly abut each other in the first monomer. In some embodiments, the first monomer can include a linker disposed between the CP1 and the PM1. In some embodiments, the CP1 and the PM1 directly abut each other in the first monomer. In some embodiments, the linker has a total length of 1 amino acid to about 15 amino acids. In some embodiments, the CM and any linkers disposed between the CP1 and DD1 have a combined total length of 3 to 15 amino acids, or 3 to 10 amino acids, or 3 to 7 amino acids.

In some embodiments, the second monomer comprises a linker disposed between the CP2 and the CM2. In some embodiments, the CP2 and the CM2 directly abut each other in the second monomer. In some embodiments, the second monomer comprises a linker disposed between the CM2 and the DD2. In some embodiments, the CM2 (e.g., any of the cleavable moieties described herein) and the DD2 (e.g., any of the DDs described herein) directly abut each other in the second monomer. In some embodiments, the second monomer can include a linker disposed between the CP2 and the CM4. In some embodiments, the CP2 and the CM4 directly abut each other in the second monomer. In some embodiments, the second monomer can include a linker disposed between the CP2 and the PM2. In some embodiments, the CP2 and the PM2 directly abut each other in the second monomer. In some embodiments, the linker has a total length of 1 amino acid to about 15 amino acids. In some embodiments, the linker comprises a sequence of GGGS (SEQ ID NO: 2). In some embodiments, the CM and any

linkers disposed between the CP2 and DD2 have a combined total length of 3 to 15 amino acids, or 3 to 10 amino acids, or 3 to 7 amino acids.

In some embodiments, the first monomer and/or the second monomer can include a total of 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 450 amino acids, about 50 amino acids to about 400 amino acids, about 50 amino acids to about 350 amino acids, about 50 amino acids to about 300 amino acids, about 50 amino acids to about 250 amino acids, about 50 amino acids to about 200 amino acids, about 50 amino acids to about 150 amino acids, about 50 amino acids to about 100 amino acids, about 100 amino acids to about 800 amino acids, about 100 amino acids to about 750 amino acids, about 100 amino acids to about 700 amino acids, about 100 amino acids to about 650 amino acids, about 100 amino acids to about 600 amino acids, about 100 amino acids to about 550 amino acids, about 100 amino acids to about 500 amino acids, about 100 amino acids to about 450 amino acids, about 100 amino acids to about 400 amino acids, about 100 amino acids to about 350 amino acids, about 100 amino acids to about 300 amino acids, about 100 amino acids to about 250 amino acids, about 100 amino acids to about 200 amino acids, about 100 amino acids to about 150 amino acids, about 150 amino acids to about 800 amino acids, about 150 amino acids to about 750 amino acids, about 150 amino acids to about 700 amino acids, about 150 amino acids to about 650 amino acids, about 150 amino acids to about 600 amino acids, about 150 amino acids to about 550 amino acids, about 150 amino acids to about 500 amino acids, about 150 amino acids to about 450 amino acids, about 150 amino acids to about 400 amino acids, about 150 amino acids to about 350 amino acids, about 150 amino acids to about 300 amino acids, about 150 amino acids to about 250 amino acids, about 150 amino acids to about 200 amino acids, about 200 amino acids to about 800 amino acids, about 200 amino acids to about 750 amino acids, about 200 amino acids to about 700 amino acids, about 200 amino acids to about 650 amino acids, about 200 amino acids to about 600 amino acids, about 200 amino acids to about 550 amino acids, about 200 amino acids to about 500 amino acids, about 200 amino acids to

about 450 amino acids, about 200 amino acids to about 400 amino acids, about 200 amino acids to about 350 amino acids, about 200 amino acids to about 300 amino acids, about 200 amino acids to about 250 amino acids, about 250 amino acids to about 800 amino acids, about 250 amino acids to about 750 amino acids, about 250 amino acids to about 700 amino acids, about 250 amino acids to about 650 amino acids, about 250 amino acids to about 600 amino acids, about 250 amino acids to about 550 amino acids, about 250 amino acids to about 500 amino acids, about 250 amino acids to about 450 amino acids, about 250 amino acids to about 400 amino acids, about 250 amino acids to about 350 amino acids, about 250 amino acids to about 300 amino acids, about 300 amino acids to about 800 amino acids, about 300 amino acids to about 750 amino acids, about 300 amino acids to about 700 amino acids, about 300 amino acids to about 650 amino acids, about 300 amino acids to about 600 amino acids, about 300 amino acids to about 550 amino acids, about 300 amino acids to about 500 amino acids, about 300 amino acids to about 450 amino acids, about 300 amino acids to about 400 amino acids, about 300 amino acids to about 350 amino acids, about 350 amino acids to about 800 amino acids, about 350 amino acids to about 750 amino acids, about 350 amino acids to about 700 amino acids, about 350 amino acids to about 650 amino acids, about 350 amino acids to about 600 amino acids, about 350 amino acids to about 550 amino acids, about 350 amino acids to about 500 amino acids, about 350 amino acids to about 450 amino acids, about 350 amino acids to about 400 amino acids, about 400 amino acids to about 800 amino acids, about 400 amino acids to about 750 amino acids, about 400 amino acids to about 700 amino acids, about 400 amino acids to about 650 amino acids, about 400 amino acids to about 600 amino acids, about 400 amino acids to about 550 amino acids, about 400 amino acids to about 500 amino acids, about 400 amino acids to about 450 amino acids, about 450 amino acids to about 800 amino acids, about 450 amino acids to about 750 amino acids, about 450 amino acids to about 700 amino acids, about 450 amino acids to about 650 amino acids, about 450 amino acids to about 600 amino acids, about 450 amino acids to about 550 amino acids, about 450 amino acids to about 500 amino acids, about 500 amino acids to about 800 amino acids, about 500 amino acids to about 750 amino acids, about 500 amino acids to about 700 amino acids, about 500 amino acids to about 650 amino acids, about 500 amino acids to about 600

amino acids, about 500 amino acids to about 550 amino acids, about 550 amino acids to about 800 amino acids, about 550 amino acids to about 750 amino acids, about 550 amino acids to about 700 amino acids, about 550 amino acids to about 650 amino acids, about 550 amino acids to about 600 amino acids, about 600 amino acids to about 800 amino acids, about 600 amino acids to about 750 amino acids, about 600 amino acids to about 700 amino acids, about 600 amino acids to about 650 amino acids, about 650 amino acids to about 800 amino acids, about 650 amino acids to about 750 amino acids, about 650 amino acids to about 700 amino acids, about 700 amino acids to about 800 amino acids, about 700 amino acids to about 750 amino acids, or about 750 amino acids to about 800 amino acids.

In some embodiments of any of the ACCs described herein, one or more linkers (e.g., flexible linkers) can be introduced into the activatable cytokine construct to provide flexibility at one or more of the junctions between domains, between moieties, between moieties and domains, or at any other junctions where a linker would be beneficial. In some embodiments, where the ACC is provided as a conformationally constrained construct, a flexible linker can be inserted to facilitate formation and maintenance of a structure in the uncleaved activatable cytokine construct. Any of the linkers described herein can provide the desired flexibility to facilitate the inhibition of the binding of a target (e.g., a receptor of a cytokine), or to facilitate cleavage of a CM by a protease. In some embodiments, linkers are included in the ACC that are all or partially flexible, such that the linker can include a flexible linker as well as one or more portions that confer less flexible structure to provide for a desired ACC. Some linkers may include cysteine residues, which may form disulfide bonds and reduce flexibility of the construct. It has been found that reducing the length of the linkers or linking region reduces the activity of the mature cytokine protein in ACCs (see, e.g., Fig. 16 showing data for ACCs without a peptide affinity mask). In most instances, linker length is determined by counting, in a N- to C- direction, the number of amino acids from the N-terminus of the linker adjacent to the C-terminal amino acid of the preceding component, to the C-terminus of the linker adjacent to the N-terminal amino acid of the following component (i.e., where the linker length does not include either the C-terminal amino acid of the preceding component or the N-terminal amino acid of the following component). In embodiments in which a

linker is employed at the N-terminus of a DD that comprises an Fc domain, linker length is determined by counting the number of amino acids from the N-terminus of the linker adjacent to the C-terminal amino acid of the preceding component to C-terminus of the linker adjacent to the first cysteine of an Fc hinge region that participates in the disulfide linkage with a second Fc domain (i.e., where the linker length does not include the C-terminal amino acid of the preceding component or the first cysteine of the Fc hinge region).

As apparent from the present disclosure and Fig. 17, ACCs of the present disclosure include a stretch of amino acids between the CP and the proximal point of interaction between the dimerization domains. That stretch of amino acids may be referred to as a Linking Region (LR). As used herein, the term "linking region" or "LR" refers to the stretch of amino acid residues between the C-terminus of the cytokine and the amino acid residue that is N-terminally adjacent to the proximal point of interaction between the dimerization domains (i.e., the linking region does not include the C-terminal amino acid of the cytokine or the N-terminal amino acid of the DD that forms the proximal point of interaction to the DD of the corresponding second monomer). For example, when the DDs are a pair of Fc domains, the linking region is the stretch of amino acid residues between the C-terminus of the cytokine and the first N-terminal cysteine residue of the Fc that participates in the disulfide linkage with the second Fc domain (e.g., Cysteine 226 of an IgG1 or IgG4 Fc domain, according to EU numbering). When the dimerization domain is not a peptide, then the linking region is the stretch of amino acid residues following the C-terminus of the cytokine until the last amino acid. For example, when the DDs are a biotin-streptavidin pair, the linking region of the biotin-containing monomer is the stretch of amino acid residues between the C-terminus of the cytokine and the biotin molecule, and the linking region of the streptavidin-containing monomer is the stretch of amino acid residues between the C-terminus of the cytokine and the streptavidin molecule.

In some embodiments, additional amino acid sequences may be positioned N-terminally or C-terminally to any of the domains of any of the ACCs. Examples include, but are not limited to, targeting moieties (e.g., a ligand for a receptor of a cell present in a target tissue) and serum half-life extending moieties (e.g., polypeptides that bind serum

proteins, such as immunoglobulin (e.g., IgG) or serum albumin (e.g., human serum albumin (HSA)).

In some embodiments of any of the activatable cytokine constructs described herein, the linker can include a total of about 1 amino acid to about 25 amino acids (e.g., about 1 amino acid to about 24 amino acids, about 1 amino acid to about 22 amino acids, about 1 amino acid to about 20 amino acids, about 1 amino acid to about 18 amino acids, about 1 amino acid to about 16 amino acids, about 1 amino acid to about 15 amino acids, about 1 amino acid to about 14 amino acids, about 1 amino acid to about 12 amino acids, about 1 amino acid to about 10 amino acids, about 1 amino acid to about 8 amino acids, about 1 amino acid to about 6 amino acids, about 1 amino acid to about 5 amino acids, about 1 amino acid to about 4 amino acids, about 1 amino acid to about 3 amino acids, about 1 amino acid to about 2 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 15 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 5 amino acids, about 2 amino acids to about 4 amino acids, about 2 amino acids to about 3 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 15 amino acids, about 4 amino acids to about 14 amino acids, about 4 amino acids to about 12 amino acids, about 4 amino acids to about 10 amino acids, about 4 amino acids to about 8 amino acids, about 4 amino acids to about 6 amino acids, about 4 amino acids to about 5 amino acids, about 5 amino acids to about 25 amino acids, about 5 amino acids to about 24 amino acids, about 5 amino acids to about 22 amino acids, about 5 amino acids to about 20 amino acids, about 5 amino acids to about 18 amino acids, about 5 amino acids to about 16 amino acids, about 5 amino acids to about 15 amino acids, about 5 amino acids to about 14 amino acids, about 5 amino acids to about 12 amino acids, about 5 amino acids

to about 10 amino acids, about 5 amino acids to about 8 amino acids, about 5 amino acids to about 6 amino acids, about 6 amino acids to about 25 amino acids, about 6 amino acids to about 24 amino acids, about 6 amino acids to about 22 amino acids, about 6 amino acids to about 20 amino acids, about 6 amino acids to about 18 amino acids, about 6 amino acids to about 16 amino acids, about 6 amino acids to about 15 amino acids, about 6 amino acids to about 14 amino acids, about 6 amino acids to about 12 amino acids, about 6 amino acids to about 10 amino acids, about 6 amino acids to about 8 amino acids, about 8 amino acids to about 25 amino acids, about 8 amino acids to about 24 amino acids, about 8 amino acids to about 22 amino acids, about 8 amino acids to about 20 amino acids, about 8 amino acids to about 18 amino acids, about 8 amino acids to about 16 amino acids, about 8 amino acids to about 15 amino acids, about 8 amino acids to about 14 amino acids, about 8 amino acids to about 12 amino acids, about 8 amino acids to about 10 amino acids, about 10 amino acids to about 25 amino acids, about 10 amino acids to about 24 amino acids, about 10 amino acids to about 22 amino acids, about 10 amino acids to about 20 amino acids, about 10 amino acids to about 18 amino acids, about 10 amino acids to about 16 amino acids, about 10 amino acids to about 15 amino acids, about 10 amino acids to about 14 amino acids, about 10 amino acids to about 12 amino acids, about 12 amino acids to about 25 amino acids, about 12 amino acids to about 24 amino acids, about 12 amino acids to about 22 amino acids, about 12 amino acids to about 20 amino acids, about 12 amino acids to about 18 amino acids, about 12 amino acids to about 16 amino acids, about 12 amino acids to about 15 amino acids, about 12 amino acids to about 14 amino acids, about 14 amino acids to about 25 amino acids, about 14 amino acids to about 24 amino acids, about 14 amino acids to about 22 amino acids, about 14 amino acids to about 20 amino acids, about 14 amino acids to about 18 amino acids, about 14 amino acids to about 16 amino acids, about 14 amino acids to about 15 amino acids, about 15 amino acids to about 25 amino acids, about 15 amino acids to about 24 amino acids, about 15 amino acids to about 22 amino acids, about 15 amino acids to about 20 amino acids, about 15 amino acids to about 18 amino acids, about 15 amino acids to about 16 amino acids, about 16 amino acids to about 25 amino acids, about 16 amino acids to about 24 amino acids, about 16 amino acids to about 22 amino acids, about 16 amino acids to about 20 amino acids, about 16 amino

acids to about 18 amino acids, about 18 amino acids to about 25 amino acids, about 18 amino acids to about 24 amino acids, about 18 amino acids to about 22 amino acids, about 18 amino acids to about 20 amino acids, about 20 amino acids to about 25 amino acids, about 20 amino acids to about 24 amino acids, about 20 amino acids to about 22 amino acids, about 22 amino acid to about 25 amino acids, about 22 amino acid to about 24 amino acids, or about 24 amino acid to about 25 amino acids).

In some embodiments of any of the ACCs described herein, the linker includes a total of about 1 amino acid, about 2 amino acids, about 3 amino acids, about 4 amino acids, about 5 amino acids, about 6 amino acids, about 7 amino acids, about 8 amino acids, about 9 amino acids, about 10 amino acids, about 11 amino acids, about 12 amino acids, about 13 amino acids, about 14 amino acids, about 15 amino acids, about 16 amino acids, about 17 amino acids, about 18 amino acids, about 19 amino acids, about 20 amino acids, about 21 amino acids, about 22 amino acids, about 23 amino acids, about 24 amino acids, or about 25 amino acids.

Surprisingly, the applicant has discovered that ACCs that do not comprise any linkers between the CP and the DD exhibit the most significant reduction in cytokine activity relative to the wildtype mature cytokine, compared to ACCs that include linkers or additional sequences in the linking region. See, e.g., Fig. 16 (showing data for ACCs without a peptide affinity mask). Further, a configuration in which there are no linkers between the CP and the DD still allows effective cleavage of a CM positioned between the CP and the DD. See e.g., Figs. 7A, 7B, 10A and 10B. Thus, in some embodiments, the ACC does not comprise any linkers between the CP and the DD, and the CM between the CP and the DD comprises not more than 10, 9, 8, 7, 6, 5, 4, or 3 amino acids. In some embodiments the total number of amino acids in the LR comprises not more than 25 amino acids, e.g., not more than 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, or 3 amino acids, or 3 to 10 amino acids or 5 to 15 amino acids, or 7 to 12 amino acids, or any range or specific number of amino acids selected from the range encompassed by 3 to 25 amino acids.

In some embodiments of any of the ACCs described herein, a linker can be rich in glycine (Gly or G) residues. In some embodiments, the linker can be rich in serine (Ser or S) residues. In some embodiments, the linker can be 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 of any of the ACCs described herein, a linker includes any one of or a combination of one or more of: GSSGGSGGSGG (SEQ ID NO: 210), GGGS (SEQ ID NO: 2), GGGSGGGS (SEQ ID NO: 211), GGGSGGGSGGGS (SEQ ID NO: 212), GGGGSGGGGSGGGGS (SEQ ID NO: 213), GGGGSGGGGSGGGGSGGGGSGGGGS (SEQ ID NO: 214), GGGGSGGGGS (SEQ ID NO: 215), GGGGS (SEQ ID NO: 216), GS, GGGGSGS (SEQ ID NO: 217), GGGGSGGGGSGGGGSGS (SEQ ID NO: 218), GGSLDPKGGGGS (SEQ ID NO: 219), PKSCDKTHTCPPCPAPELLG (SEQ ID NO: 220), SKYGPPCPPCPAPEFLG (SEQ ID NO: 221), GKSSGSGSESKS (SEQ ID NO: 222), GSTSGSGKSSEGKG (SEQ ID NO: 223), GSTSGSGKSSEGSGSTKG (SEQ ID NO: 224), and GSTSGSGKPGSGEGSTKG (SEQ ID NO: 225).

Non-limiting examples of linkers can include a sequence that is at least 70% identical (e.g., at least 72%, at least 74%, at least 75%, at least 76%, at least 78%, at least 80%, at least 82%, at least 84%, at least 85%, at least 86%, at least 88%, at least 90%, at least 92%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical) to GGGS (SEQ ID NO: 2), GSSGGSGGSGG (SEQ ID NO: 210), GGGGSGGGGSGGGGS (SEQ ID NO: 213), GGGGSGS (SEQ ID NO: 217), GGGGSGGGGSGGGGSGS (SEQ ID NO: 218), GGGGSGGGGSGGGGSGGGGS (SEQ ID NO: 214), GGSLDPKGGGGS (SEQ ID NO: 215), and GSTSGSGKPGSSEGST (SEQ ID NO: 226).

In some embodiments, the linker includes a sequence selected from the group of: GGSLDPKGGGGS (SEQ ID NO: 219), GGGGSGGGGSGGGGSGS (SEQ ID NO: 218), GGGGSGS (SEQ ID NO: 217), GS, (GS)n, (GGS)n, (GSGGS)n (SEQ ID NO: 227) and (GGGS)n (SEQ ID NO: 228), GGSG (SEQ ID NO: 229), GGSGG (SEQ ID

NO: 230), GSGSG (SEQ ID NO: 231), GSGGG (SEQ ID NO: 232), GGGSG (SEQ ID NO: 233), GSSSG (SEQ ID NO: 234), GGGGSGGGGSGGGGS (SEQ ID NO: 213), GGGGSGGGGSGGGGSGGGGS (SEQ ID NO: 214), GSTSGSGKPGSSEGST (SEQ ID NO: 226), (GGGGS)n (SEQ ID NO: 216), wherein n is an integer of at least one. In some embodiments, the linker includes a sequence selected from the group consisting of: GGSLDPKGGGGS (SEQ ID NO: 219), GGGGSGGGGSGGGGSGS (SEQ ID NO: 218), GGGGSGS (SEQ ID NO: 217), and GS. In some embodiments of any of the ACCs described herein, the linker includes a sequence selected from the group of: GGGGSGGGGSGGGGS (SEQ ID NO: 213), GGGGSGGGGSGGGGSGGGGS (SEQ ID NO: 214), and GSTSGSGKPGSSEGST (SEQ ID NO: 226). In some embodiments of any of the activatable cytokine constructs described herein, the linker includes a sequence selected from the group of: GGGGSGGGGSGGGGS (SEQ ID NO: 213) or GGGGS (SEQ ID NO: 216). In some embodiments, the linker comprises a sequence of GGGS (SEQ ID NO: 2). Additional examples of linkers include those listed in Table 23.

In some embodiments, an ACC can include one, two, three, four, five, six, seven, eight, nine, or ten linker sequence(s) (e.g., the same or different linker sequences of any of the exemplary linker sequences described herein or known in the art). In some embodiments, a linker comprises sulfo-SIAB, SMPB, and sulfo-SMPB, wherein the linkers react with primary amines sulfhydryls.

In some embodiments of any of the ACCs described herein, the ACC is characterized by a reduction in at least one activity of the CP1 and/or CP2 as compared to a control level of the at least one activity of the CP1 and/or CP2. In some embodiments, a control level can be the level of the activity for a recombinant CP1 and/or CP2 (e.g., a commercially available recombinant CP1 and/or CP2, a recombinant wildtype CP1 and/or CP2, and the like). In some embodiments, a control level can be the level of the activity of a cleaved (activated) form of the ACC. In certain embodiments, a control level can be the level of the activity of a pegylated CP1 and/or CP2.

In some embodiments, the at least one activity is the binding affinity of the CP1 and/or the CP2 for its cognate receptor as determined using surface plasmon resonance (e.g., performed in phosphate buffered saline at 25 degrees Celsius). In certain embodiments, the at least one activity is the level of proliferation of lymphoma cells. In

other embodiments, the at least one activity is the level of JAK/STAT/ISGF3 pathway activation in a lymphoma cell. In some embodiments, the at least one activity is a level of SEAP production in a lymphoma cell. In a further embodiment, the at least one activity of the CP1 and/or CP2 is level of cytokine-stimulated gene induction using, for example RNAseq methods (see, e.g., Zimmerer et al., *Clin. Cancer Res.* 14(18):5900-5906, 2008; Hilkens et al., *J. Immunol.* 171:5255-5263, 2003).

In some embodiments, the ACC is characterized by at least a 2-fold reduction in at least one CP1 and/or CP2 activity as compared to the control level of the at least one CP1 and/or CP2 activity. In some embodiments, the ACC is characterized by at least a 5-fold reduction in at least one activity of the CP1 and/or CP2 as compared to the control level of the at least one activity of the CP1 and/or CP2. In some embodiments, the ACC is characterized by at least a 10-fold reduction in at least one activity of the CP1 and/or CP2 as compared to the control level of the at least one activity of the CP1 and/or CP2. In some embodiments, the ACC is characterized by at least a 20-fold reduction in at least one activity of the CP1 and/or CP2 as compared to the control level of the at least one activity of the CP1 and/or CP2. In some embodiments, the ACC is characterized by at least a 30-fold, 40-fold, 50-fold, 60-fold, 70-fold, 80-fold, 90-fold, 100-fold, 500-fold, 1000-fold, 2000-fold, 3000-fold, 5000-fold or 5,000-fold reduction in at least one activity of the CP1 and/or CP2 as compared to the control level of the at least one activity of the CP1 and/or CP2. In some embodiments, ACC is characterized by at least a 1- to 20-fold reduction, a 200- to 2000-fold reduction, a 300- to 2000-fold reduction, a 400- to 2000-fold reduction, a 500- to 2000-fold reduction, a 1000- to 2000-fold reduction, a 1500- to 2000-fold reduction, a 100- to 1500-fold reduction, a 200- to 1500-fold reduction, a 300- to 1500-fold reduction, a 400- to 1500-fold reduction, a 500- to 1500-fold reduction, a 1000- to 1500-fold reduction, a 100- to 1000-fold reduction, a 200- to 1000-fold reduction, a 300- to 1000-fold reduction, a 400- to 1000-fold reduction, a 500- to 1000-fold reduction, a 1000- to 5000-fold reduction, a 2000- to 5000-fold reduction, a 3000- to 5000-fold reduction, a 4000- to 5000-fold reduction, a 1000- to 4000-fold reduction, a 2000- to 4000-fold reduction, a 3000- to 4000-fold reduction, a 1000- to 3000-fold reduction, a 2000- to 3000-fold reduction, or a 1000- to 2000-fold reduction in at least

one activity of the CP1 and/or CP2 as compared to the control level of the at least one activity of the CP1 and/or CP2.

In some embodiments, the control level of the at least one activity of the CP1 and/or CP2 is the activity of the CP1 and/or CP2 released from the ACC following cleavage of the CMs by protease(s) (the "cleavage product"). In some embodiments, the control level of the at least one activity of the CP1 and/or CP2 is the activity of a corresponding wildtype mature cytokine (e.g., recombinant wildtype mature cytokine).

In some embodiments, incubation of the ACC with the protease yields an activated cytokine product(s), where one or more activities of CP1 and/or CP2 of the activated cytokine product(s) is greater than the one or more activities of CP1 and/or CP2 of the intact ACC. In some embodiments, one or more activities of CP1 and/or CP2 of the activated cytokine product(s) is at least 1-fold greater than the one or more activities of CP1 and/or CP2 of the ACC. In some embodiments, one or more activities of CP1 and/or CP2 of the activated cytokine product(s) is at least 2-fold greater than the one or more activities of CP1 and/or CP2 of the ACC. In some embodiments, one or more activities of CP1 and/or CP2 of the activated cytokine product(s) is at least 5-fold greater than the one or more activities of CP1 and/or CP2 of the ACC. In some embodiments, one or more activities of CP1 and/or CP2 of the activated cytokine product(s) is at least 10-fold greater than the one or more activities of CP1 and/or CP2 of the ACC. In some embodiments, one or more activities of CP1 and/or CP2 of the activated cytokine product(s) is at least 20-fold greater than the one or more activities of CP1 and/or CP2 of the ACC. In some embodiments, one or more activities of CP1 and/or CP2 of the activated cytokine product(s) is at least 1- to 20-fold greater, a 200- to 2000-fold greater, a 300- to 2000-fold greater, a 400- to 2000-fold greater, a 500- to 2000-fold greater, a 1000- to 2000-fold greater, a 1500- to 2000-fold greater, a 100- to 1500-fold greater, a 200- to 1500-fold greater, a 300- to 1500-fold greater, a 400- to 1500-fold greater, a 500- to 1500-fold greater, a 1000- to 1500-fold greater, a 100- to 1000-fold greater, a 200- to 1000-fold greater, a 300- to 1000-fold greater, a 400- to 1000-fold greater, a 500- to 1000-fold greater, a 1000- to 5000-fold greater, a 2000- to 5000-fold greater, a 3000- to 5000-fold greater, a 4000- to 5000-fold greater, a 1000- to 4000-fold greater, a 2000- to 4000-fold greater, a 3000- to 4000-fold greater, a 1000- to 3000-fold greater, a 2000- to

3000-fold greater, or a 1000- to 2000-fold than the one or more activities of CP1 and/or CP2 of the ACC.

In some embodiments, an ACC can include a sequence that is at least 80% (e.g., at least 82%, at least 84%, at least 86%, at least 88%, at least 90%, at least 92%, at least 94%, at least 96%, at least 98%, at least 99%, or 100%) identical to SEQ ID NO: 290 or 291. In some embodiments, an ACC can be encoded by a nucleic acid including a sequence that is at least 80% (e.g., at least 82%, at least 84%, at least 86%, at least 88%, at least 90%, at least 92%, at least 94%, at least 96%, at least 98%, at least 99%, or 100%) identical to a nucleic acid encoding SEQ ID NOs: 290 or 291. In some aspects, an ACC may include such sequences but either without the signal sequences of those sequences. Signal sequences are not particularly limited. Some non-limiting examples of signal sequences include, e.g., SEQ ID NO: 470 and corresponding residues and nucleotides in the other sequences, or substituted with a signal sequence from another species or cell line. Other examples of signal sequences include MRAWIFFLLCLAGRALA (SEQ ID NO: 468) and MALTFALLVALLVLSCKSSCSVG (SEQ ID NO: 469).

Various exemplary aspects of these ACCs and activatable antibodies are described below and can be used in any combination in the methods provided herein without limitation. Exemplary aspects of the ACCs and activatable antibodies and methods of making ACCs and activatable antibodies are described below.

In some embodiments, the CM is selected for use with a specific protease. The protease may be one produced by a tumor cell (e.g., the tumor cell may express greater amounts of the protease than healthy tissues). In some embodiments, the CM is a substrate for at least one protease selected from the group of an ADAM 17, a BMP-1, a cysteine protease such as a cathepsin, a HtrA1, a legumain, a matriptase (MT-SP1), a matrix metalloprotease (MMP), a neutrophil elastase, a TMPRSS, such as TMPRSS3 or TMPRSS4, a thrombin, and a u-type plasminogen activator (uPA, also referred to as urokinase).

In some embodiments, a CM is a substrate for at least one matrix metalloprotease (MMP). Examples of MMPs include MMP1, MMP2, MMP3, MMP7, MMP8, MMP9, MMP10, MMP11, MMP12, MMP13, MMP14, MMP15, MMP16, MMP17, MMP19,

MMP20, MMP23, MMP24, MMP26, and MMP27. In some embodiments, the CM is a substrate for MMP9, MMP14, MMP1, MMP3, MMP13, MMP17, MMP11, and MMP19. In some embodiments, the CM is a substrate for MMP7. In some embodiments, the CM is a substrate for MMP9. In some embodiments, the CM is a substrate for MMP14. In some embodiments, the CM is a substrate for two or more MMPs. In some embodiments, the CM is a substrate for at least MMP9 and MMP14. In some embodiments, the CM includes two or more substrates for the same MMP. In some embodiments, the CM includes at least two or more MMP9 substrates. In some embodiments, the CM includes at least two or more MMP14 substrates.

In some embodiments, a CM is a substrate for an MMP and includes the sequence ISSGLLSS (SEQ ID NO: 19); QNQALRMA (SEQ ID NO: 16); AQNLLGMV (SEQ ID NO: 15); STFPFGMF (SEQ ID NO: 18); PVGYTSSL (SEQ ID NO: 74); DWLYWPGI (SEQ ID NO: 75); MIAPVAYR (SEQ ID NO: 42); RPSPMWAY (SEQ ID NO: 43); WATPRPMR (SEQ ID NO: 44); FRLLDWQW (SEQ ID NO: 45); LKAAPRWA (SEQ ID NO: 76); GPSHLVLT (SEQ ID NO: 77); LPGGLSPW (SEQ ID NO: 78); MGLFSEAG (SEQ ID NO: 79); SPLPLRVP (SEQ ID NO: 80); RMHLRSLG (SEQ ID NO: 81); LAAPLGLL (SEQ ID NO: 17); AVGLLAPP (SEQ ID NO: 14); LLAPSHRA (SEQ ID NO: 82); PAGLWLDP (SEQ ID NO: 20); and/or ISSGLSS (SEQ ID NO: 73).

In some embodiments, a CM is a substrate for thrombin. In some embodiments, the CM is a substrate for thrombin and includes the sequence GPRSFGL (SEQ ID NO: 83) or GPRSFG (SEQ ID NO: 84).

In some embodiments, a CM includes an amino acid sequence selected from the group of NTLSGRSENHSG (SEQ ID NO: 9); NTLSGRSGNHGS (SEQ ID NO: 10); TSTSGRSANPRG (SEQ ID NO: 11); TSGRSANP (SEQ ID NO: 12); VAGRSMRP (SEQ ID NO: 21); VVPEGRRS (SEQ ID NO: 22); ILPRSPAF (SEQ ID NO: 23); MVLGRSLL (SEQ ID NO: 24); QGRAITFI (SEQ ID NO: 25); SPRSIMLA (SEQ ID NO: 26); and SMLRSMPL (SEQ ID NO: 27).

In some embodiments, a CM is a substrate for a neutrophil elastase. In some embodiments, a CM is a substrate for a serine protease. In some embodiments, a CM is a substrate for uPA. In some embodiments, a CM is a substrate for legumain. In some embodiments, the CM is a substrate for matriptase. In some embodiments, the CM is a

substrate for a cysteine protease. In some embodiments, the CM is a substrate for a cysteine protease, such as a cathepsin.

In some embodiments, a CM includes a sequence of ISSGLLSGRSDNH (SEQ ID NO: 28); ISSGLLSSGGSGGSLSGRSDNH (SEQ ID NO: 30); AVGLLAPPGGTSTSGRSANPRG (SEQ ID NO: 275); TSTSGRSANPRGGGAVGLLAPP (SEQ ID NO: 276); VHMPLGFLGPGGTSTSGRSANPRG (SEQ ID NO: 277); TSTSGRSANPRGGGVHMPLGFLGP (SEQ ID NO: 278); AVGLLAPPGGLSGRSDNH (SEQ ID NO: 29); LSGRSDNHGGAVGLLAPP (SEQ ID NO: 70); VHMPLGFLGPGGLSGRSDNH (SEQ ID NO: 266); LSGRSDNHGGVHMPLGFLGP (SEQ ID NO: 267); LSGRSDNHGGSGGSISSGLLSS (SEQ ID NO: 268); LSGRSGNHGGSGGSISSGLLSS (SEQ ID NO: 279); ISSGLLSSGGSGGSLSGRSGNH (SEQ ID NO: 269); LSGRSDNHGGSGGSQNQALRMA (SEQ ID NO: 270); QNQALRMAGGSGGSLSGRSDNH (SEQ ID NO: 271); LSGRSGNHGGSGGSQNQALRMA (SEQ ID NO: 272); QNQALRMAGGSGGSLSGRSGNH (SEQ ID NO: 273), and/or ISSGLLSGRSGNH (SEQ ID NO: 274).

In some embodiments, a CM comprises a sequence selected from the group consisting of SEQ ID NO: 5 through SEQ ID NO: 100. In some embodiments, the CM comprises a sequence selected from the group of: ISSGLLSGRSDNH (SEQ ID NO: 28), LSGRSDDH (SEQ ID NO: 33), ISSGLLSGRSDQH (SEQ ID NO: 54), SGRSDNI (SEQ ID NO: 100), and ISSGLLSGRSDNI (SEQ ID NO: 68). Any one or combination of the CMs disclosed herein may be used in the context of any of the ACCs and activatable antibodies of the present disclosure.

In some aspects, the ACC includes a first monomer comprising a CP1 selected from SEQ ID Nos: 1 and 101-209, a CM1 selected from SEQ ID Nos: 5-100 and 237-281, a PM1 selected from SEQ ID Nos: 297, 298, 292, and 299-446, a CM3 selected from SEQ ID Nos: 5-100 and 237-281, and a DD1 dimerized with a second monomer comprising a CP2 selected from SEQ ID Nos: 1 and 101-209, a CM2 selected from SEQ ID Nos: 5-100 and 237-281, a PM2 selected from SEQ ID Nos: 297, 298, 292, and 299-446, a CM3 selected from SEQ ID Nos: 5-100 and 237-281and a DD2. In some aspects,

the ACC may include, between CP1 and CM1, between CP1 and PM1, between CP1 and CM3, between PM1 and CM3, and/or between CM1 and DD1, a linker selected from SEQ ID Nos: 2 and 210-263, and between CP2 and CM2, between CP2 and PM2, between CP2 and CM4, between PM2 and CM4, and/or between CM2 and DD2, a linker selected from SEQ ID Nos: 2 and 210-2236. In some aspects, the PM1 is selected for use with the CP1 in accordance with Table 24, and the PM2 is selected for use with the CP2, in accordance with Table 24.

In some embodiments, the ACC includes a DD1 and/or a DD2 that has an amino acid sequence that is at least 80% identical (e.g., at least 82%, at least 84%, at least 85%, at least 86%, at least 88%, at least 90%, at least 92%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical) to SEQ ID NO: 3 or SEQ ID NO: 4. In some embodiments, the ACC includes a DD1 that has an amino acid sequence that is at least 80% identical (e.g., at least 82%, at least 84%, at least 85%, at least 86%, at least 88%, at least 90%, at least 92%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical) to SEQ ID NO: 287 or SEQ ID NO: 288. In some embodiments, the ACC includes a DD2 that has an amino acid sequence that is at least 80% identical (e.g., at least 82%, at least 84%, at least 85%, at least 86%, at least 88%, at least 90%, at least 92%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical) to SEQ ID NO: 287 or SEQ ID NO: 288.

One or both monomers of the ACC herein may comprise one or more peptide masks (PMs), which can interfere with the binding of the CP to its binding partner (e.g., receptors). In some embodiments, when an ACC is not activated, the PM in the ACC prevents the CP from target binding; but when the ACC is activated, the PM does not substantially or significantly interfere with the CP's binding to its binding partner. In some embodiments, a PM is coupled to a CP by a CM and optionally one or more linkers described herein.

In some embodiments, a PM may interact with the CP, thus reducing or inhibiting the interaction between the CP and its binding partner. In some embodiments, the PM may not specifically bind to the CP, but rather interfere with CP's binding to its binding partner through non-specific interactions such as steric hindrance. For example, the PM

may be positioned in the uncleaved ACC such that the tertiary or quaternary structure of the ACC allows the PM to mask the CP through charge-based interaction, thereby holding the PM in place to interfere with binding partner access to the CP.

The structural properties of the PM may be selected according to factors such as the minimum amino acid sequence required for interference with protein binding to target, the target protein-protein binding pair of interest, the size of the cytokine, the presence or absence of linkers, and the like.

The PMs may be identified and/or further optimized through a screening procedure from a library of candidate ACC having variable PMs. For example, a CP and a CM can be selected to provide for a desired enzyme/target combination, and the amino acid sequence of the PM can be identified by the screening procedure described below to identify a PM that provides for a switchable phenotype. For example, a random peptide library (e.g., of peptides comprising about 2 to about 40 amino acids or more) may be used in the screening methods disclosed herein to identify a suitable PM. In specific embodiments, PMs with specific binding affinity for a CP can be identified through a screening procedure that includes providing a library of peptide scaffolds consisting of candidate PMs wherein each scaffold is made up of a transmembrane protein and the candidate PM. The library may then be contacted with an entire or portion of a protein such as a full length protein, a naturally occurring protein fragment, or a non-naturally occurring fragment containing a protein (also capable of binding the binding partner of interest), and identifying one or more candidate PMs having detectably bound protein. The screening may be performed by one more rounds of magnetic-activated sorting (MACS) or fluorescence-activated sorting (FACS), as well as determination of the binding affinity of PM towards the CP and subsequent determination of the masking efficiency, e.g., as described in US20200308243A1, which is incorporated herein by reference in its entirety.

In some embodiments, the PM is unique for the coupled CP. Examples of PMs include PMs that were specifically screened to bind a binding domain of the cytokine or protein fragment (e.g., affinity peptide masks). Methods for screening PMs to obtain PMs unique for the cytokine and those that specifically and/or selectively bind a binding

domain of a binding partner/target are provided herein and can include protein display methods. Table 7 discloses exemplary PMs suitable for use with various exemplary CPs.

In some embodiments, when a CP is coupled to a PM and in the presence of a natural binding partner of the CP, there is no binding or substantially no binding of the CP to the binding partner, or no more than 0.001%, 0.01%, 0.1%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, or 50% binding of the CP to its binding partner, as compared to the binding of the CP not coupled to a PM, for at least 2, 4, 6, 8, 12, 28, 24, 30, 36, 48, 60, 72, 84, 96 hours, or 5, 10, 15, 30, 45, 60, 90, 120, 150, 180 days, or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 months or greater when measured in a masking efficiency assay, e.g., as described in Example 1.

The PMs contemplated by this disclosure may range from 1-50 amino acids (e.g., at least 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 20, 30, or 40 amino acids, or no greater than 40, 30, 20, 15, 12, 10, 9, 8, 7, 6, 5, 4, or 3 amino acids). In some examples, the PMs may be from 8 to 15 amino acids in length.

The PMs may contain genetically encoded or genetically non-encoded amino acids. Examples of genetically non-encoded amino acids are but not limited to D-amino acids, β-amino acids, and γ-amino acids. In specific embodiments, the PMs contain no more than 50%, 40%, 30%, 20%, 15%, 10%, 5% or 1% of genetically non-encoded amino acids.

The binding affinity of the cytokine towards the target or binding partner when coupled to a PM may be at least 5, 10, 25, 50, 100, 250, 500, 1,000, 2,500, 5,000, 10,000, 50,000, 100,000, 500,000, 1,000,000, 5,000,000, 10,000,000, 50,000,000 or greater times lower than the binding affinity of the cytokine towards its binding partner when not coupled to a PM, or between 5-10, 10-100, 10-1,000, 10-10,000, 10-100,000, 10-1,000,000, 10-10,000,000, 100-1,000, 100-10,000, 100-100,000, 100-1,000,000, 100-10,000,000, 1,000-10,000, 1,000-100,000, 1,000-1,000,000, 1000-10,000,000, 10,000-100,000, 10,000-1,000,000, 10,000-10,000,000, 100,000-1,000,000, or 100,000-10,000,000 times lower than the binding affinity of the cytokine towards its binding partner when not coupled to a PM.

When the cytokine is coupled to a PM and is in the presence of the binding partner, specific binding of the cytokine to its binding partner may be be reduced or

inhibited, as compared to the specific binding of the cytokine not coupled to a PM to its binding partner. When compared to the binding of the cytokine not coupled to a PM to its binding partner, the cytokine's ability to bind the binding partner when coupled to a PM can be reduced by at least 50%, 60%, 70%, 80%, 90%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% and even 100% for at least 2, 4, 6, 8, 12, 28, 24, 30, 36, 48, 60, 72, 84, 96, hours, or 5, 10, 15, 30, 45, 60, 90, 120, 150, 180 days, or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 months or greater when measured in vivo or in a masking efficiency assay, e.g., as shown in Example 1, an in vitro immunoabsorbant assay, e.g., as described in US20200308243A1.

The K_D of the PM towards the cytokine may be generally greater than the K_D of the cytokine towards the cytokine's binding partner. The K_D of the PM towards the cytokine may be at least 5, 10, 25, 50, 100, 250, 500, 1,000, 2,500, 5,000, 10,000, 100,000, 1,000,000 or even 10,000,000 times greater than the K_D of the cytokine towards its binding partner. Alternatively, the binding affinity of the PM towards the cytokine may be generally lower than the binding affinity of the cytokine towards the cytokine's binding partner. The binding affinity of PM towards the cytokine may be at least 5, 10, 25, 50, 100, 250, 500, 1,000, 2,500, 5,000, 10,000, 100,000, 1,000,000 or 10,000,000 times lower than the binding affinity of the cytokine towards its binding partner.

In some embodiments, the PM comprises at least partial or complete amino acid sequence of a naturally occurring binding partner of the CP (e.g., a receptor of the CP). The PM may be a fragment of a naturally occurring binding partner. The fragment may retain no more than 95%, 90%, 80%, 75%, 70%, 60%, 50%, 40%, 30%, 25%, or 20% nucleic acid or amino acid sequence homology to the naturally occurring binding partner.

In some embodiments, the PM comprises an amino acid sequence that is not naturally occurring or does not contain the amino acid sequence of a naturally occurring binding partner or target protein. In certain embodiments the PM is not a natural binding partner of the CP. The PM may be a modified binding partner for the CP which contains amino acid changes that at least slightly decrease affinity and/or avidity of binding to the CP. In some embodiments the PM contains no or substantially no nucleic acid or amino acid homology to the CP's natural binding partner. In other embodiments the PM is no

more than 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, or 80% similar to the natural binding partner of the CP.

In some embodiments, the PM comprises an amino acid sequence that is at least 80% identical (e.g., at least 82%, at least 84%, at least 86%, at least 88%, at least 90%, at least 92%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical) to a sequence selected from SEQ ID Nos: 297, 298, 292, and 299-446. An exemplary PM for use with a CP that is an interferon, preferably an IFN-alpha, can contain the consensus sequence: TDVDYYREWXXXXXXXX (SEQ ID No: 329), where X is any amino acid.

In some embodiments, an ACC may comprise a pair of PM1 and CP1 or a pair of PM2 and CP2 listed in Table 7, which contains example PMs for use with specific exemplary cytokines. In some examples, the PM1 comprises a sequence selected from SEQ ID NOs: 297, 298, 292, and 299-336, and the CP1 is an interferon; the PM1 comprises a sequence selected from SEQ ID NOs: 297, 298, 292, and 299-332, and the CP1 is an interferon alpha; the PM1 comprises a sequence selected from SEQ ID NOs: 299-328, and 330-332, and the CP1 is an interferon beta; the PM1 comprises a sequence selected from SEQ ID NOs: 299-328, and 333-336, and the CP1 is an interferon gamma; the PM1 comprises a sequence selected from SEQ ID NOs: 337-341, and the CP1 is an IL-12; the PM1 comprises a sequence selected from SEQ ID NOs: 342-349, 436-444, 478, and the CP1 is an IL-15; the PM1 comprises a sequence selected from SEQ ID NOs: 350-435, 436-445, and the CP1 is an IL-2; or the PM1 comprises a sequence selected from SEQ ID NOs: 445 and 446, and the CP1 is an IL-21. In some examples, the PM2 comprises a sequence selected from SEQ ID NOs: 297, 298, 292, and 299-336, and the CP2 is an interferon; the PM2 comprises a sequence selected from SEQ ID NOs: 297, 298, 292, and 299-332, and the CP2 is an interferon alpha; the PM2 comprises a sequence selected from SEQ ID NOs: 299-328, and 330-332, and the CP2 is an interferon beta; the PM2 comprises a sequence selected from SEQ ID NOs: 299-328, and 333-336, and the CP2 is an interferon gamma; the PM2 comprises a sequence selected from SEQ ID NOs: 337-341, and the CP2 is an IL-12; the PM2 comprises a sequence selected from SEQ ID NOs: 342-349, 436-444, 478, and the CP2 is an IL-15; the PM2 comprises a sequence

selected from SEQ ID NOs: 350-435, 436-445, and the CP2 is an IL-2; or the PM2 comprises a sequence selected from SEQ ID NOs: 445 and 446, and the CP2 is an IL-21.

In some embodiments, the PM may comprise an inactive cytokine. For example, the inactive cytokine may interact with the CP component in the ACC and interfere the interaction between the CP and its binding partner. In one example, the inactive cytokine may comprise a mutation, e.g., an IFN alpha-2b with L130P mutation (SEQ ID Nos: 297 and 298). In another example, the inactive cytokine may be a truncation of a wild type cytokine, e.g., IFN alpha-2b with amino acids 1-150.

In some embodiments, once uncoupled from the cytokine and in a free state, the PM may have a biological activity or a therapeutic effect, such as binding capability. For example, the free peptide can bind with the same or a different binding partner. In certain embodiments the free PM (uncoupled PM) can exert a therapeutic effect, providing a secondary function to the compositions disclosed herein. In some embodiments, once uncoupled from the cytokine and in a free state, the PM may advantageously not exhibit biological activity. For example, in some embodiments the PM in a free state does not elicit an immune response in the subject.

Conjugation to Agents

This disclosure also provides methods and materials for including additional elements in any of the ACCs and antibodies described herein including, for example, a targeting moiety to facilitate delivery to a cell or tissue of interest, an agent (e.g., a therapeutic agent, an antineoplastic agent), a toxin, or a fragment thereof. Any of the following disclosures for conjugation of agents to ACCs also apply equally to and should be construed to support conjugation of agents to the antibodies of the present disclosure.

In some embodiments of any of the ACCs described herein, the ACC can be conjugated to a cytotoxic agent, including, without limitation, a toxin (e.g., an enzymatically active toxin of bacterial, fungal, plant, or animal origin, or fragments thereof) or a radioactive isotope. In some embodiments of any of the ACCs described herein, the activatable cytokine construct can be conjugated to a cytotoxic agent including, without limitation, a toxin (e.g., an enzymatically active toxin of bacterial, fungal, plant, or animal origin, or fragments thereof), or a radioactive isotope.

Non-limiting exemplary cytotoxic agents that can be conjugated to any of the ACCs described herein include: dolastatins and derivatives thereof (e.g., auristatin E, AFP, monomethyl auristatin D (MMAD), monomethyl auristatin F (MMAF), monomethyl auristatin E (MMAE), desmethyl auristatin E (DMAE), auristatin F, desmethyl auristatin F (DMAF), dolastatin 16 (DmJ), dolastatin 16 (Dpv), auristatin derivatives (e.g., auristatin tyramine, auristatin quinolone), maytansinoids (e.g., DM-1, DM-4), maytansinoid derivatives, duocarmycin, alpha-amanitin, turbostatin, phenstatin, hydroxyphenstatin, spongistatin 5, spongistatin 7, halistatin 1, halistatin 2, halistatin 3, halocomstatin, pyrrolobenzimidazoles (PBI), cibrostatin6, doxaliform, cemadotin analogue (CemCH2-SH), Pseudomonas toxin A (PES8) variant, Pseudomonase toxin A (ZZ-PE38) variant, ZJ-101, anthracycline, doxorubicin, daunorubicin, bryostatin, camptothecin, 7-substituted campothecin, 10, 11-difluoromethylenedioxycamptothecin, combretastatins, debromoaplysiatoxin, KahaMide-F, discodermolide, and Ecteinascidins.

Non-limiting exemplary enzymatically active toxins that can be conjugated to any of the ACCs described herein include: diphtheria toxin, exotoxin A chain from *Pseudomonas aeruginosa*, ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, *Aleuriies fordii* proteins, dianfhin proteins, *Phytoiaca Americana* proteins (e.g., PAPI, PAPII, and PAP-8), momordica charantia inhibitor, curcin, crotirs, sapaonaria officinalis inhibitor, geionin, mitogeliin, restrictocin, phenomycin, neomycin, and tricothecenes.

Non-limiting exemplary anti-neoplastics that can be conjugated to any of the ACCs described herein include: adriamycin, cerubidine, bleomycin, alkeran, velban, oncovin, fluorouracil, methotrexate, thiotepa, bisantrene, novantrone, thioguanine, procarabizine, and cytarabine.

Non-limiting exemplary antivirals that can be conjugated to any of the ACCs described herein include: acyclovir, vira A, and symmetrel.

Non-limiting exemplary antifungals that can be conjugated to any of the ACCs described herein include: nystatin.

Non-limiting exemplary conjugatable detection reagents that can be conjugated to any of the ACCs described herein include: fluorescein and derivatives thereof, fluorescein isothiocyanate (FITC).

Non-limiting exemplary antibacterials that can be conjugated to any of the activatable cytokine constructs described herein include: aminoglycosides, streptomycin, neomycin, kanamycin, amikacin, gentamicin, and tobramycin.

Non-limiting exemplary 3beta,16beta,17alpha-trihydroxycholest-5-en-22-one 16-O-(2-O-4-methoxybenzoyl-beta-D-xylopyranosyl)-(1-->3)-(2-O-acetyl-alpha-L-arabinopyranoside) (OSW-1) that can be conjugated to any of the activatable cytokine constructs described herein include: s-nitrobenzyloxycarbonyl derivatives of O6-benzylguanine, toposisomerase inhibitors, hemiasterlin, cephalotaxine, homoharringionine, pyrrol obenzodiazepine dimers (PBDs), functionalized pyrrolobenzodiazepenes, calcicheamicins, podophyiitoxins, taxanes, and vinca alkoids.

Non-limiting exemplary radiopharmaceuticals that can be conjugated to any of the activatable cytokine constructs described herein include: ^{123}I , ^{89}Zr, ^{125}I, ^{131}I, ^{99}mTc, ^{201}T1, ^{62}Cu, ^{18}F, ^{68}Ga, ^{13} N, ^{15}O, ^{38}K, ^{82}Rb, ^{111}In, ^{133}Xe, ^{11}C, and ^{99}mTc (Technetium).

Non-limiting exemplary heavy metals that can be conjugated to any of the ACCs described herein include: barium, gold, and platinum.

Non-limiting exemplary anti-mycoplasmals that can be conjugated to any of the ACCs described herein include: tylosine, spectinomycin, streptomycin B, ampicillin, sulfanilamide, polymyxin, and chloramphenicol.

Those of ordinary skill in the art will recognize that a large variety of possible moieties can be conjugated to any of the activatable cytokine constructs described herein. Conjugation can include any chemical reaction that will bind the two molecules so long as the ACC and the other moiety retain their respective activities. Conjugation can include many chemical mechanisms, e.g., covalent binding, affinity binding, intercalation, coordinate binding, and complexation. In some embodiments, the preferred binding is covalent binding. Covalent binding can be achieved either by direct condensation of existing side chains or by the incorporation of external bridging molecules. Many bivalent or polyvalent linking agents are useful in conjugating any of the activatable cytokine constructs described herein. For example, conjugation can include organic compounds, such as thioesters, carbodiimides, succinimide esters, glutaraldehyde, diazobenzenes, and hexamethylene diamines. In some embodiments, the

activatable cytokine construct can include, or otherwise introduce, one or more non-natural amino acid residues to provide suitable sites for conjugation.

In some embodiments of any of the ACCs described herein, an agent and/or conjugate is attached by disulfide bonds (e.g., disulfide bonds on a cysteine molecule) to the antigen-binding domain. Since many cancers naturally release high levels of glutathione, a reducing agent, glutathione present in the cancerous tissue microenvironment can reduce the disulfide bonds, and subsequently release the agent and/or the conjugate at the site of delivery.

In some embodiments of any of the ACCs described herein, when the conjugate binds to its target in the presence of complement within the target site (e.g., diseased tissue (e.g., cancerous tissue)), the amide or ester bond attaching the conjugate and/or agent to the linker is cleaved, resulting in the release of the conjugate and/or agent in its active form. These conjugates and/or agents when administered to a subject, will accomplish delivery and release of the conjugate and/or the agent at the target site (e.g., diseased tissue (e.g., cancerous tissue)). These conjugates and/or agents are particularly effective for the *in vivo* delivery of any of the conjugates and/or agents described herein.

In some embodiments, the linker is not cleavable by enzymes of the complement system. For example, the conjugate and/or agent is released without complement activation since complement activation ultimately lyses the target cell. In such embodiments, the conjugate and/or agent is to be delivered to the target cell (e.g., hormones, enzymes, corticosteroids, neurotransmitters, or genes). Furthermore, the linker is mildly susceptible to cleavage by serum proteases, and the conjugate and/or agent is released slowly at the target site.

In some embodiments of any of the ACCs described herein, the conjugate and/or agent is designed such that the conjugate and/or agent is delivered to the target site (e.g., disease tissue (e.g., cancerous tissue)) but the conjugate and/or agent is not released.

In some embodiments of any of the ACCs described herein, the conjugate and/or agent is attached to an antigen-binding domain either directly or via a non-cleavable linker. Exemplary non-cleavable linkers include amino acids (e.g., D-amino acids), peptides, or other organic compounds that may be modified to include functional groups

that can subsequently be utilized in attachment to antigen-binding domains by methods described herein.

In some embodiments of any of the ACCs described herein, an ACC includes at least one point of conjugation for an agent. In some embodiments, all possible points of conjugation are available for conjugation to an agent. In some embodiments, the one or more points of conjugation include, without limitation, sulfur atoms involved in disulfide bonds, sulfur atoms involved in interchain disulfide bonds, sulfur atoms involved in interchain sulfide bonds but not sulfur atoms involved in intrachain disulfide bonds,, and/or sulfur atoms of cysteine or other amino acid residues containing a sulfur atom. In such cases, residues may occur naturally in the protein construct structure or may be incorporated into the protein construct using methods including, without limitation, site-directed mutagenesis, chemical conversion, or mis-incorporation of non-natural amino acids.

This disclosure also provides methods and materials for preparing an ACC for conjugation. In some embodiments of any of the ACCs described herein, an ACC is modified to include one or more interchain disulfide bonds. For example, disulfide bonds in the ACC can undergo reduction following exposure to a reducing agent such as, without limitation, TCEP, DTT, or β-mercaptoethanol. In some cases, the reduction of the disulfide bonds is only partial. As used herein, the term partial reduction refers to situations where an ACC is contacted with a reducing agent and a fraction of all possible sites of conjugation undergo reduction (e.g., not all disulfide bonds are reduced). In some embodiments, an activatable cytokine construct is partially reduced following contact with a reducing agent if less than 99%, (e.g., less than 98%, 97%, 96%, 95%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, 10% or less than 5%) of all possible sites of conjugation are reduced. In some embodiments, the ACC having a reduction in one or more interchain disulfide bonds is conjugated to a drug reactive with free thiols.

This disclosure also provides methods and materials for conjugating a therapeutic agent to a particular location on an ACC. In some embodiments of any of the ACC described herein, an ACC is modified so that the therapeutic agents can be conjugated to the ACC at particular locations on the ACC. For example, an ACC can be partially

reduced in a manner that facilitates conjugation to the ACC. In such cases, partial reduction of the ACC occurs in a manner that conjugation sites in the ACC are not reduced. In some embodiments, the conjugation site(s) on the ACC are selected to facilitate conjugation of an agent at a particular location on the protein construct. Various factors can influence the "level of reduction" of the ACC upon treatment with a reducing agent. For example, without limitation, the ratio of reducing agent to ACC, length of incubation, incubation temperature, and/or pH of the reducing reaction solution can require optimization in order to achieve partial reduction of the ACC with the methods and materials described herein. Any appropriate combination of factors (e.g., ratio of reducing agent to ACC, the length and temperature of incubation with reducing agent, and/or pH of reducing agent) can be used to achieve partial reduction of the ACC (e.g., general reduction of possible conjugation sites or reduction at specific conjugation sites).

An effective ratio of reducing agent to ACC can be any ratio that at least partially reduces the ACC in a manner that allows conjugation to an agent (e.g., general reduction of possible conjugation sites or reduction at specific conjugation sites). In some embodiments, the ratio of reducing agent to ACC will be in a range from about 20:1 to 1:1, from about 10:1 to 1:1, from about 9:1 to 1:1, from about 8:1 to 1:1, from about 7:1 to 1:1, from about 6:1 to 1:1, from about 5:1 to 1:1, from about 4:1 to 1:1, from about 3:1 to 1:1, from about 2:1 to 1:1, from about 20:1 to 1:1.5, from about 10:1 to 1:1.5, from about 9:1 to 1:1.5, from about 8:1 to 1:1.5, from about 7:1 to 1:1.5, from about 6:1 to 1:1.5, from about 5:1 to 1:1.5, from about 4:1 to 1:1.5, from about 3:1 to 1:1.5, from about 2:1 to 1:1.5, from about 1.5:1 to 1:1.5, or from about 1:1 to 1:1.5. In some embodiments, the ratio is in a range of from about 5:1 to 1:1. In some embodiments, the ratio is in a range of from about 5:1 to 1.5:1. In some embodiments, the ratio is in a range of from about 4:1 to 1:1. In some embodiments, the ratio is in a range from about 4:1 to 1.5:1. In some embodiments, the ratio is in a range from about 8:1 to about 1:1. In some embodiments, the ratio is in a range of from about 2.5:1 to 1:1.

An effective incubation time and temperature for treating an ACC with a reducing agent can be any time and temperature that at least partially reduces the ACC in a manner that allows conjugation of an agent to an ACC (e.g., general reduction of possible

conjugation sites or reduction at specific conjugation sites). In some embodiments, the incubation time and temperature for treating an ACC will be in a range from about 1 hour at 37 °C to about 12 hours at 37 °C (or any subranges therein).

An effective pH for a reduction reaction for treating an ACC with a reducing agent can be any pH that at least partially reduces the ACC in a manner that allows conjugation of the ACC to an agent (e.g., general reduction of possible conjugation sites or reduction at specific conjugation sites).

When a partially-reduced ACC is contacted with an agent containing thiols, the agent can conjugate to the interchain thiols in the ACC. An agent can be modified in a manner to include thiols using a thiol-containing reagent (e.g., cysteine or N-acetyl cysteine). For example, the ACC can be partially reduced following incubation with reducing agent (e.g., TEPC) for about 1 hour at about 37 °C at a desired ratio of reducing agent to ACC. An effective ratio of reducing agent to ACC can be any ratio that partially reduces at least two interchain disulfide bonds located in the ACC in a manner that allows conjugation of a thiol-containing agent (e.g., general reduction of possible conjugation sites or reduction at specific conjugation sites).

In some embodiments of any of the ACCs described herein, an ACC is reduced by a reducing agent in a manner that avoids reducing any intrachain disulfide bonds. In some embodiments of any of the ACCs described herein, an ACC is reduced by a reducing agent in a manner that avoids reducing any intrachain disulfide bonds and reduces at least one interchain disulfide bond.

In some embodiments of any of the ACCs described herein, the ACC can also include an agent conjugated to the ACC. In some embodiments, the conjugated agent is a therapeutic agent.

In some embodiments, the agent (e.g., agent conjugated to an activatable cytokine construct) is a detectable moiety such as, for example, a label or other marker. For example, the agent is or includes a radiolabeled amino acid, one or more biotinyl moieties that can be detected by marked avidin (e.g., streptavidin containing a fluorescent marker or enzymatic activity that can be detected by optical or calorimetric methods), one or more radioisotopes or radionuclides, one or more fluorescent labels, one or more

enzymatic labels, and/or one or more chemiluminescent agents. In some embodiments, detectable moieties are attached by spacer molecules.

In some embodiments, the agent (e.g., cytotoxic agent conjugated to an activatable cytokine construct) is linked to the ACC using a carbohydrate moiety, sulfhydryl group, amino group, or carboxylate group.

In some embodiments of any of the ACCs described herein conjugated to an agent, the agent (e.g., cytotoxic agent conjugated to an activatable cytokine construct) is conjugated to the ACC via a linker and/or a CM (also referred to as a cleavable sequence). In some embodiments, the agent (e.g., cytotoxic agent conjugated to an activatable cytokine construct) is conjugated to a cysteine or a lysine in the ACC. In some embodiments, the agent (e.g., cytotoxic agent conjugated to an activatable cytokine construct) is conjugated to another residue of the ACC, such as those residues disclosed herein. In some embodiments, the linker is a thiol-containing linker. Some non-limiting examples of the linker and/or CMs are provided in Table 1.

Table 1.

Types of Cleavable Sequences/CMs	Amino Acid Sequence
Plasmin CMs	
Pro-urokinase	PRFKIIGG (SEQ ID NO: 253)
	PRFRIIGG (SEQ ID NO: 254)
TGFβ	SSRHRRALD (SEQ ID NO: 255)
Plasminogen	RKSSIIIRMRDVVL (SEQ ID NO: 256)
Staphylokinase	SSSFDKGKYKKGDDA (SEQ ID NO: 257)
	SSSFDKGKYKRGDDA (SEQ ID NO: 258)
Factor Xa CMs	IEGR (SEQ ID NO: 259)
	IDGR (SEQ ID NO: 260)
	GGSIDGR (SEQ ID NO: 261)
MMP CMs	
Gelatinase A	PLGLWA (SEQ ID NO: 262)
Collagenase CMs	

Calf skin collagen (α1(I) chain)	GPQGIAGQ (SEQ ID NO: 263)
Calf skin collagen (α2(I) chain)	GPQGLLGA (SEQ ID NO: 264)
Bovine cartilage collagen (α1(II) chain)	GIAGQ (SEQ ID NO: 265)
Human liver collagen (α1(III) chain)	GPLGIAGI (SEQ ID NO: 266)
Human α_2M	GPEGLRVG (SEQ ID NO: 267)
Human PZP	YGAGLGVV (SEQ ID NO: 268)
	AGLGVVER (SEQ ID NO: 269)
	AGLGISST (SEQ ID NO: 270)
Rat α_1M	EPQALAMS (SEQ ID NO: 271)
	QALAMSAI (SEQ ID NO: 272)
Rat α_2M	AAYHLVSQ (SEQ ID NO: 273)
	MDAFLESS (SEQ ID NO: 274)
Rat α_1I_3(2J)	ESLPVVAV (SEQ ID NO: 275)
Rat α_1I_3(27J)	SAPAVESE (SEQ ID NO: 276)
Human fibroblast collagenase (autolytic cleavages)	DVAQFVLT (SEQ ID NO: 277)
	VAQFVLT (SEQ ID NO: 278)
	VAQFVLTE (SEQ ID NO: 279)
	AQFVLTEG (SEQ ID NO: 280)
	PVQPIGPQ (SEQ ID NO: 281)

Those of ordinary skill in the art will recognize that a large variety of possible moieties can be coupled to the ACCs of the disclosure. (*See, for example*, "Conjugate Vaccines", Contributions to Microbiology and Immunology, J. M. Cruse and R. E. Lewis, Jr (eds), Carger Press, New York, (1989), the entire contents of which are incorporated herein by reference). In general, an effective conjugation of an agent (e.g., cytotoxic agent) to an ACC can be accomplished by any chemical reaction that will bind the agent to the ACC while also allowing the agent and the ACC to retain functionality.

In some embodiments of any of the ACCs conjugated to an agent, a variety of bifunctional protein-coupling agents can be used to conjugate the agent to the ACC including, without limitation, N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP),

iminothiolane (IT), bifunctional derivatives of imidoesters (e.g., dimethyl adipimidate HCL), active esters (e.g., disuccinimidyl suberate), aldehydes (e.g., glutareldehyde), bis-azido compounds (e.g., bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (e.g., bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (e.g., tolyene 2,6-diisocyanate), and bis-active fluorine compounds (e.g., 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta et al., Science 238: 1098 (1987). In some embodiments, a carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) chelating agent can be used to conjugate a radionucleotide to the ACC. (See, e.g., WO94/11026).

Suitable linkers and CMs are described in the literature. (*See*, *for example*, Ramakrishnan, S. et al., Cancer Res. 44:201-208 (1984) describing use of MBS (M-maleimidobenzoyl-N-hydroxysuccinimide ester). *See also*, U.S. Patent No. 5,030,719, describing use of halogenated acetyl hydrazide derivative coupled to an ACC by way of an oligopeptide linker. In some embodiments, suitable linkers include: (i) EDC (1-ethyl-3-(3-dimethylamino-propyl) carbodiimide hydrochloride; (ii) SMPT (4-succinimidyloxycarbonyl-alpha-methyl-alpha-(2-pridyl-dithio)-toluene (Pierce Chem. Co., Cat. (21558G); (iii) SPDP (succinimidyl-6 [3-(2-pyridyldithio) propionamido] hexanoate (Pierce Chem. Co., Cat #21651G); (iv) Sulfo-LC-SPDP (sulfosuccinimidyl 6 [3-(2-pyridyldithio)-propianamide] hexanoate (Pierce Chem. Co. Cat. #2165-G); and (v) sulfo-NHS (N-hydroxysulfo-succinimide: Pierce Chem. Co., Cat. #24510) conjugated to EDC. Additional linkers include, but are not limited to, SMCC, sulfo-SMCC, SPDB, or sulfo-SPDB.

The linkers and CMs described above contain components that have different attributes, thus leading to conjugates with differing physio-chemical properties. For example, sulfo-NHS esters of alkyl carboxylates are more stable than sulfo-NHS esters of aromatic carboxylates. NHS-ester containing linkers are less soluble than sulfo-NHS esters. Further, the linker SMPT contains a sterically-hindered disulfide bond, and can form conjugates with increased stability. Disulfide linkages, are in general, less stable than other linkages because the disulfide linkage is cleaved *in vitro*, resulting in less conjugate available. Sulfo-NHS, in particular, can enhance the stability of carbodimide couplings. Carbodimide couplings (such as EDC) when used in conjunction with sulfo-

NHS, forms esters that are more resistant to hydrolysis than the carbodimide coupling reaction alone.

In some embodiments of any of the ACCs, an agent can be conjugated to the ACC using a modified amino acid sequence included in the amino acid sequence of the ACC. By inserting conjugation-enabled amino acids at specific locations within the amino acid sequence of the ACC, the protein construct can be designed for controlled placement and/or dosage of the conjugated agent (e.g., cytotoxic agent). For example, the ACC can be modified to include a cysteine amino acid residue at positions on the first monomer, the second monomer, the third monomer, and/or the fourth monomer that provide reactive thiol groups and does not negatively impact protein folding and/or assembly and does not alter antigen-binding properties. In some embodiments, the ACC can be modified to include one or more non-natural amino acid residues within the amino acid sequence of the ACC to provide suitable sites for conjugation. In some embodiments, the ACC can be modified to include enzymatically activatable peptide sequences within the amino acid sequence of the ACC.

Nucleic Acids

Provided herein are nucleic acids including sequences that encode the first monomer construct (or the protein portion of the first monomer construct) (e.g., any of the first monomers constructs described herein) and the second monomer construct (or the protein portion of the second monomer construct) (e.g., any of the second monomer constructs described herein) of any of the ACCs described herein. In some embodiments, a pair of nucleic acids together encode the first monomer construct (or the protein portion of the first monomer construct) and the second monomer construct (or the protein portion of the second monomer construct). In some embodiments, the nucleic acid sequence encoding the first monomer construct (or the protein portion of the first monomer construct) is at least 70% identical (e.g., 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 the nucleic acid sequence

encoding the second monomer construct (or the protein portion of the second monomer construct).

In some embodiments, the nucleic acid encoding the protein portion of a first monomer construct encodes a polypeptide comprising the PM1, CP1, CM1, and CM3 moieties. In some embodiments, the nucleic acid encoding the protein portion of a second monomer encodes a polypeptide comprising the CP2 and CM2moieties. In some embodiments, the nucleic acid encoding the protein portion of a second monomer encodes a polypeptide comprising the CP2, CM2, PM2, and CM4 moieties. In some embodiments, a pair of nucleic acids together encode the protein portion of a first monomer construct and the protein portion of the second monomer construct, wherein the protein portions are then conjugated to the DD1 and DD2 moieties, respectively (in a subsequent conjugation step).

In some embodiments, the nucleic acid encoding the first monomer construct encodes a polypeptide comprising the DD1 moiety. In some embodiments, the nucleic acid encoding the second monomer construct encodes a polypeptide comprising the DD2 moiety.

Vectors

Provided herein are vectors and sets of vectors including any of the nucleic acids described herein. One skilled in the art will be capable of selecting suitable vectors or sets of vectors (e.g., expression vectors) for making any of the ACCs described herein, and using the vectors or sets of vectors to express any of the ACCs described herein. For example, in selecting a vector or a set of vectors, the cell must be considered because the vector(s) may need to be able to integrate into a chromosome of the cell and/or replicate in it. Exemplary vectors that can be used to produce an ACC are also described below.

As used herein, the term "vector" refers to a polynucleotide capable of inducing the expression of a recombinant protein (e.g., a first or second monomer) in a cell (e.g., any of the cells described herein). A "vector" is able to deliver nucleic acids and fragments thereof into a host cell, and includes regulatory sequences (e.g., promoter, enhancer, poly(A) signal). Exogenous polynucleotides may be inserted into the

expression vector in order to be expressed. The term "vector" also includes artificial chromosomes, plasmids, retroviruses, and baculovirus vectors.

Methods for constructing suitable vectors that include any of the nucleic acids described herein, and suitable for transforming cells (e.g., mammalian cells) are well-known in the art. See, e.g., Sambrook et al., Eds. "Molecular Cloning: A Laboratory Manual," 2nd Ed., Cold Spring Harbor Press, 1989 and Ausubel et al., Eds. "Current Protocols in Molecular Biology," Current Protocols, 1993.

Non-limiting examples of vectors include plasmids, transposons, cosmids, and viral vectors (e.g., any adenoviral vectors (e.g., pSV or pCMV vectors), adeno-associated virus (AAV) vectors, lentivirus vectors, and retroviral vectors), and any Gateway® vectors. A vector can, for example, include sufficient cis-acting elements for expression; other elements for expression can be supplied by the host mammalian cell or in an *in vitro* expression system. Skilled practitioners will be capable of selecting suitable vectors and mammalian cells for making any of the ACCs described herein.

In some embodiments of any of the ACCs described herein, the ACC may be made biosynthetically using recombinant DNA technology and expression in eukaryotic or prokaryotic species.

In some embodiments, the vector includes a nucleic acid encoding the first monomer and the second monomer of any of the ACCs described herein. In some embodiments, the vector is an expression vector.

In some embodiments, a pair of vectors together include a pair of nucleic acids that together encode the first monomer and the second monomer of any of the ACCs described herein. In some embodiments, the pair of vectors is a pair of expression vectors.

Cells

Also provided herein are host cells including any of the vector or sets of vectors described herein including any of the nucleic acids described herein.

Any of the ACCs and antibodies described herein can be produced by any cell (e.g., a mammalian cell). In some embodiments, a host cell is a mammalian cell (e.g., a

human cell), a rodent cell (e.g., a mouse cell, a rat cell, a hamster cell, or a guinea pig cell), or a non-human primate cell.

Methods of introducing nucleic acids and vectors (e.g., any of the vectors or any of the sets of vectors described herein) into a cell are known in the art. Non-limiting examples of methods that can be used to introducing a nucleic acid into a cell include: lipofection, transfection, calcium phosphate transfection, cationic polymer transfection, viral transduction (e.g., adenoviral transduction, lentiviral transduction), nanoparticle transfection, and electroporation.

In some embodiments, the introducing step includes introducing into a cell a vector (e.g., any of the vectors or sets of vectors described herein) including a nucleic acid encoding the monomers that make up any of the ACCs and antibodies described herein.

In some embodiments of any of the methods described herein, the cell can be a eukaryotic cell. As used herein, the term "eukaryotic cell" refers to a cell having a distinct, membrane-bound nucleus. Such cells may include, for example, mammalian (e.g., rodent, non-human primate, or human), insect, fungal, or plant cells. In some embodiments, the eukaryotic cell is a yeast cell, such as *Saccharomyces cerevisiae*. In some embodiments, the eukaryotic cell is a higher eukaryote, such as mammalian, avian, plant, or insect cells. Non-limiting examples of mammalian cells include Chinese hamster ovary (CHO) cells and human embryonic kidney cells (e.g., HEK293 cells).

In some embodiments, the cell contains the nucleic acid encoding the first monomer and the second monomer of any one of the ACCs and antibodies described herein. In some embodiments, the cell contains the pair of nucleic acids that together encode the first monomer and the second monomer of any of the ACCs and antibodies described herein.

Methods of Producing Activatable Cytokine Constructs

Provided herein are methods of producing any of the ACCs described herein that include: (a) culturing any of the recombinant host cells described herein in a liquid culture medium under conditions sufficient to produce the ACC; and (b) recovering the ACC from the host cell and/or the liquid culture medium.

Methods of culturing cells are well known in the art. Cells can be maintained *in vitro* under conditions that favor cell proliferation, cell differentiation and cell growth. For example, cells can be cultured by contacting a cell (e.g., any of the cells described herein) with a cell culture medium that includes the necessary growth factors and supplements sufficient to support cell viability and growth.

In some embodiments of any of the methods described herein, the method further includes isolating the recovered ACC. Non-limiting examples of methods of isolation include: ammonium sulfate precipitation, polyethylene glycol precipitation, size exclusion chromatography, ligand-affinity chromatography, ion-exchange chromatography (e.g., anion or cation), and hydrophobic interaction chromatography.

In some embodiments, the cells can produce a protein portion of a first monomer construct that includes the CP1, the CM1, the PM2, and the CM3, and a protein portion of a second monomer construct that includes the CP2, and the CM2, and optionally the PM2 and the CM4, and then the protein portions are subsequently conjugated to the DD1 and DD2 moieties, respectively.

Compositions and methods described herein may involve use of non-reducing or partially-reducing conditions that allow disulfide bonds to form between the dimerization domains to form and maintain dimerization of the ACCs.

In some embodiments of any of the methods described herein, the method further includes formulating the isolated ACC into a pharmaceutical composition. Various formulations are known in the art and are described herein. Any of the isolated ACCs and/or antibodies described herein can be formulated for any route of administration (e.g., intravenous, intratumoral, subcutaneous, intradermal, oral (e.g., inhalation), transdermal (e.g., topical), transmucosal, or intramuscular).

Also provided herein are ACCs produced by any of the methods described herein. Also provided are compositions (e.g., pharmaceutical compositions) that include any of the ACCs produced by any of the methods described herein. Also provided herein are kits that include at least one dose of any of the compositions (e.g., pharmaceutical compositions) described herein.

Methods of Treatment

Provided herein are methods of treating a disease (e.g., a cancer (e.g., any of the cancers described herein) or an infectious disease) in a subject including administering a therapeutically effective amount of any of the ACCs and antibodies described herein to the subject.

As used herein, the term "subject" refers to any mammal. In some embodiments, the subject is a feline (e.g., a cat), a canine (e.g., a dog), an equine (e.g., a horse), a rabbit, a pig, a rodent (e.g., a mouse, a rat, a hamster or a guinea pig), a non-human primate (e.g., a simian (e.g., a monkey (e.g., a baboon, a marmoset), or an ape (e.g., a chimpanzee, a gorilla, an orangutan, or a gibbon)), or a human. In some embodiments, the subject is a human.

In some embodiments, the subject has been previously identified or diagnosed as having the disease (e.g., cancer (e.g., any of the cancers described herein)).

As used herein, the term "treat" includes reducing the severity, frequency or the number of one or more (e.g., 1, 2, 3, 4, or 5) symptoms or signs of a disease (e.g., a cancer (e.g., any of the cancers described herein)) in the subject (e.g., any of the subjects described herein). In some embodiments where the disease is cancer, treating results in reducing cancer growth, inhibiting cancer progression, inhibiting cancer metastasis, or reducing the risk of cancer recurrence in a subject having cancer.

In some embodiments, the methods and uses of the present disclosure include administering the ACC and the PD-1/PD-L1 pathway inhibitor simultaneously or sequentially, e.g., in series in any order. In some embodiments, the methods and uses of the present disclosure include administering the ACC and the PD-1/PD-L1 pathway inhibitor separately. In some aspects, a therapeutic or a sub-therapeutic dose of each agent is administered. In some aspects, the methods and uses of the present disclosure include administering the ACC and the PD-1/PD-L1 pathway inhibitor sequentially or simultaneously such that an additive or synergistic therapeutic effect is achieved in the subject. As used herein, the term "combination" broadly includes administration simultaneously or sequentially and also includes administering the actives separately or in the same composition or container. In particular, an ACC for use in combination may contain IL-2, IL-7, IL-8, IL-10, IL-12, IL-15, IL-21, an IFN-alpha, an IFN beta, an IFN

gamma, GM-CSF, TGF-beta, LIGHT, GITR-L, CD40L, CD27L, 4-1BB-L, OX40, OX40L.

In some embodiments, the methods and uses of the present disclosure include any route of administration including intravenous, infusion, intratumoral, subcutaneous, intraperitoneal, intradermal, oral (e.g., inhalation), intranasal, transdermal (e.g., topical), transmucosal, and/or intramuscular.

In some embodiments of any of the methods described herein, the disease is a cancer. Also provided herein are methods of treating a subject in need thereof (e.g., any of the exemplary subjects described herein or known in the art) that include administering to the subject a therapeutically effective amount of any of the ACCs described herein or any of the compositions (e.g., pharmaceutical compositions) described herein.

In some embodiments of these methods, the subject has been identified or diagnosed as having a cancer. Non-limiting examples of cancer include: solid tumor, hematological tumor, sarcoma, osteosarcoma, glioblastoma, neuroblastoma, melanoma, rhabdomyosarcoma, Ewing sarcoma, osteosarcoma, B-cell neoplasms, multiple myeloma, a lymphoma (e.g., B-cell lymphoma, B-cell non-Hodgkin's lymphoma, Hodgkin's lymphoma, cutaneous T-cell lymphoma), a leukemia (e.g., hairy cell leukemia, chronic lymphocytic leukemia (CLL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphocytic leukemia (ALL)), myelodysplastic syndromes (MDS), Kaposi sarcoma, retinoblastoma, stomach cancer, urothelial carcinoma, lung cancer, renal cell carcinoma, gastric and esophageal cancer, pancreatic cancer, prostate cancer, brain cancer, colon cancer, bone cancer, lung cancer, breast cancer, colorectal cancer, ovarian cancer, nasopharyngeal adenocarcimoa, non-small cell lung carcinoma (NSCLC), squamous cell head and neck carcinoma, endometrial cancer, bladder cancer, cervical cancer, liver cancer, and hepatocellular carcinoma. In some embodiments, the cancer is a lymphoma. In some embodiments, the lymphoma is Burkitt's lymphoma. In some aspects, the subject has been identified or diagnosed as having familial cancer syndromes such as Li Fraumeni Syndrome, Familial Breast-Ovarian Cancer (BRCA1 or BRAC2 mutations) Syndromes, and others. The disclosed methods are also useful in treating non-solid cancers. Exemplary solid tumors include malignancies (e.g., sarcomas, adenocarcinomas, and carcinomas) of the various organ systems, such as those of lung,

breast, lymphoid, gastrointestinal (e.g., colon), and genitourinary (e.g., renal, urothelial, or testicular tumors) tracts, pharynx, prostate, and ovary. Exemplary adenocarcinomas include colorectal cancers, renal-cell carcinoma, liver cancer, non-small cell carcinoma of the lung, and cancer of the small intestine.

Exemplary cancers described by the National Cancer Institute include: Acute Lymphoblastic Leukemia, Adult; Acute Lymphoblastic Leukemia, Childhood; Acute Myeloid Leukemia, Adult; Adrenocortical Carcinoma; Adrenocortical Carcinoma, Childhood; AIDS-Related Lymphoma; AIDS-Related Malignancies; Anal Cancer; Astrocytoma, Childhood Cerebellar; Astrocytoma, Childhood Cerebral; Bile Duct Cancer, Extrahepatic; Bladder Cancer; Bladder Cancer, Childhood; Bone Cancer, Osteosarcoma/Malignant Fibrous Histiocytoma; Brain Stem Glioma, Childhood; Brain Tumor, Adult; Brain Tumor, Brain Stem Glioma, Childhood; Brain Tumor, Cerebellar Astrocytoma, Childhood; Brain Tumor, Cerebral Astrocytoma/Malignant Glioma, Childhood; Brain Tumor, Ependymoma, Childhood; Brain Tumor, Medulloblastoma, Childhood; Brain Tumor, Supratentorial Primitive Neuroectodermal Tumors, Childhood; Brain Tumor, Visual Pathway and Hypothalamic Glioma, Childhood; Brain Tumor, Childhood (Other); Breast Cancer; Breast Cancer and Pregnancy; Breast Cancer, Childhood; Breast Cancer, Male; Bronchial Adenomas/Carcinoids, Childhood; Carcinoid Tumor, Childhood; Carcinoid Tumor, Gastrointestinal; Carcinoma, Adrenocortical; Carcinoma, Islet Cell; Carcinoma of Unknown Primary; Central Nervous System Lymphoma, Primary; Cerebellar Astrocytoma, Childhood; Cerebral Astrocytoma/Malignant Glioma, Childhood; Cervical Cancer; Childhood Cancers; Chronic Lymphocytic Leukemia; Chronic Myelogenous Leukemia; Chronic Myeloproliferative Disorders; Clear Cell Sarcoma of Tendon Sheaths; Colon Cancer; Colorectal Cancer, Childhood; Cutaneous T-Cell Lymphoma; Endometrial Cancer; Ependymoma, Childhood; Epithelial Cancer, Ovarian; Esophageal Cancer; Esophageal Cancer, Childhood; Ewing's Family of Tumors; Extracranial Germ Cell Tumor, Childhood; Extragonadal Germ Cell Tumor; Extrahepatic Bile Duct Cancer; Eye Cancer, Intraocular Melanoma; Eye Cancer, Retinoblastoma; Gallbladder Cancer; Gastric (Stomach) Cancer; Gastric (Stomach) Cancer, Childhood; Gastrointestinal Carcinoid Tumor; Germ Cell Tumor, Extracranial, Childhood; Germ Cell Tumor,

Extragonadal; Germ Cell Tumor, Ovarian; Gestational Trophoblastic Tumor; Glioma, Childhood Brain Stem; Glioma, Childhood Visual Pathway and Hypothalamic; Hairy Cell Leukemia; Head and Neck Cancer; Hepatocellular (Liver) Cancer, Adult (Primary); Hepatocellular (Liver) Cancer, Childhood (Primary); Hodgkin's Lymphoma, Adult; Hodgkin's Lymphoma, Childhood; Hodgkin's Lymphoma During Pregnancy; Hypopharyngeal Cancer; Hypothalamic and Visual Pathway Glioma, Childhood; Intraocular Melanoma; Islet Cell Carcinoma (Endocrine Pancreas); Kaposi's Sarcoma; Kidney Cancer; Laryngeal Cancer; Laryngeal Cancer, Childhood; Leukemia, Acute Lymphoblastic, Adult; Leukemia, Acute Lymphoblastic, Childhood; Leukemia, Acute Myeloid, Adult; Leukemia, Acute Myeloid, Childhood; Leukemia, Chronic Lymphocytic; Leukemia, Chronic Myelogenous; Leukemia, Hairy Cell; Lip and Oral Cavity Cancer; Liver Cancer, Adult (Primary); Liver Cancer, Childhood (Primary); Lung Cancer, Non-Small Cell; Lung Cancer, Small Cell; Lymphoblastic Leukemia, Adult Acute; Lymphoblastic Leukemia, Childhood Acute; Lymphocytic Leukemia, Chronic; Lymphoma, AIDS-Related; Lymphoma, Central Nervous System (Primary); Lymphoma, Cutaneous T-Cell; Lymphoma, Hodgkin's, Adult; Lymphoma, Hodgkin's, Childhood; Lymphoma, Hodgkin's During Pregnancy; Lymphoma, Non-Hodgkin's, Adult; Lymphoma, Non-Hodgkin's, Childhood; Lymphoma, Non-Hodgkin's During Pregnancy; Lymphoma, Primary Central Nervous System; Macroglobulinemia, Waldenstrom's; Male Breast Cancer; Malignant Mesothelioma, Adult; Malignant Mesothelioma, Childhood; Malignant Thymoma; Medulloblastoma, Childhood; Melanoma; Melanoma, Intraocular; Merkel Cell Carcinoma; Mesothelioma, Malignant; Metastatic Squamous Neck Cancer with Occult Primary; Multiple Endocrine Neoplasia Syndrome, Childhood; Multiple Myeloma/Plasma Cell Neoplasm; Mycosis Fungoides; Myelodysplastic Syndromes; Myelogenous Leukemia, Chronic; Myeloid Leukemia, Childhood Acute; Myeloma, Multiple; Myeloproliferative Disorders, Chronic; Nasal Cavity and Paranasal Sinus Cancer; Nasopharyngeal Cancer; Nasopharyngeal Cancer, Childhood; Neuroblastoma; Non-Hodgkin's Lymphoma, Adult; Non-Hodgkin's Lymphoma, Childhood; Non-Hodgkin's Lymphoma During Pregnancy; Non-Small Cell Lung Cancer; Oral Cancer, Childhood; Oral Cavity and Lip Cancer; Oropharyngeal Cancer; Osteosarcoma/Malignant Fibrous Histiocytoma of Bone;

Ovarian Cancer, Childhood; Ovarian Epithelial Cancer; Ovarian Germ Cell Tumor; Ovarian Low Malignant Potential Tumor; Pancreatic Cancer; Pancreatic Cancer, Childhood; Pancreatic Cancer, Islet Cell; Paranasal Sinus and Nasal Cavity Cancer; Parathyroid Cancer; Penile Cancer; Pheochromocytoma; Pineal and Supratentorial Primitive Neuroectodermal Tumors, Childhood; Pituitary Tumor; Plasma Cell Neoplasm/Multiple Myeloma; Pleuropulmonary Blastoma; Pregnancy and Breast Cancer; Pregnancy and Hodgkin's Lymphoma; Pregnancy and Non-Hodgkin's Lymphoma; Primary Central Nervous System Lymphoma; Primary Liver Cancer, Adult; Primary Liver Cancer, Childhood; Prostate Cancer; Rectal Cancer; Renal Cell (Kidney) Cancer; Renal Cell Cancer, Childhood; Renal Pelvis and Ureter, Transitional Cell Cancer; Retinoblastoma; Rhabdomyosarcoma, Childhood; Salivary Gland Cancer; Salivary Gland Cancer, Childhood; Sarcoma, Ewing's Family of Tumors; Sarcoma, Kaposi's; Sarcoma (Osteosarcoma)/Malignant Fibrous Histiocytoma of Bone; Sarcoma, Rhabdomyosarcoma, Childhood; Sarcoma, Soft Tissue, Adult; Sarcoma, Soft Tissue, Childhood; Sezary Syndrome; Skin Cancer; Skin Cancer, Childhood; Skin Cancer (Melanoma); Skin Carcinoma, Merkel Cell; Small Cell Lung Cancer; Small Intestine Cancer; Soft Tissue Sarcoma, Adult; Soft Tissue Sarcoma, Childhood; Squamous Neck Cancer with Occult Primary, Metastatic; Stomach (Gastric) Cancer; Stomach (Gastric) Cancer, Childhood; Supratentorial Primitive Neuroectodermal Tumors, Childhood; T-Cell Lymphoma, Cutaneous; Testicular Cancer; Thymoma, Childhood; Thymoma, Malignant; Thyroid Cancer; Thyroid Cancer, Childhood; Transitional Cell Cancer of the Renal Pelvis and Ureter; Trophoblastic Tumor, Gestational; Unknown Primary Site, Cancer of, Childhood; Unusual Cancers of Childhood; Ureter and Renal Pelvis, Transitional Cell Cancer; Urethral Cancer; Uterine Sarcoma; Vaginal Cancer; Visual Pathway and Hypothalamic Glioma, Childhood; Vulvar Cancer; Waldenstrom's Macro globulinemia; and Wilms' Tumor.

Further exemplary cancers include diffuse large B-cell lymphoma (DLBCL) and mantle cell lymphoma (MCL).

Metastases of the aforementioned cancers can also be treated or prevented in accordance with the methods described herein.

In some embodiments, these methods can result in a reduction in the number, severity, or frequency of one or more symptoms of the cancer in the subject (e.g., as compared to the number, severity, or frequency of the one or more symptoms of the cancer in the subject prior to treatment).

In some embodiments of any of the methods described herein, the disease is an infectious disease. The ACCs and antibodies of the present disclosure may also be used to prevent or treat infections and infectious diseases. The ACCs and antibodies can be used to stimulate immune responses against pathogens, toxins, and autoantigens. The ACCs and antibodies can be used to stimulate immune responses to pathogenic viruses including, but not limited to HIV, hepatitis (A, B or C) virus, herpes virus (e.g., VZV, HSV-1, HAV-6, HSV-II, CMV, and Epstein-Barr virus), adenovirus, influenza viruses, flavivirus, echovirus, rhinovirus, coxsackie virus, coronaviruses, respiratory syncytial virus, mumps virus, rotavirus, measles virus, rubella virus, parvovirus, vaccinia virus, HTLV virus, dengue virus, papillomavirus, molluscum virus, poliovirus, rabies virus, JC virus, and arboviral encephalitis virus. The ACCs and antibodies can also be used to stimulate immune responses to infections caused by bacteria, fungi, parasites, or other pathogens.

In some embodiments of any of the methods described herein, the methods further include administering to a subject an additional therapeutic agent (e.g., one or more of the therapeutic agents listed in Table 2).

Table 2. Additional Therapeutic Agents

Antibody Trade Name (antibody name)	Target
Raptiva™ (efalizumab)	CD11a
Arzerra™ (ofatumumab)	CD20
Bexxar™ (tositumomab)	CD20
Gazyva™ (obinutuzumab)	CD20
Ocrevus™ (ocrelizumab)	CD20
Rituxan™ (rituximab)	CD20
Zevalin™ (ibritumomab tiuxetan)	CD20
Adcetris™ (brentuximab vedotin)	CD30
Myelotarg™ (gemtuzumab)	CD33
Mylotarg™ (gemtuzumab ozogamicin)	CD33
(vadastuximab)	CD33
(vadastuximab talirine)	CD33
Campath™ (alemtuzumab)	CD52

Lemtrada™ (alemtuzumab)	CD52
Tactress™ (tamtuvetmab)	CD52
Soliris™ (eculizumab)	Complement C5
Ultomiris™ (ravulizumab)	Complement C5
(olendalizumab)	Complement C5
Yervoy™ (ipilimumab)	CTLA-4
(tremelimumab)	CTLA-4
Orencia™ (abatacept)	CTLA-4
Hu5c8	CD40L
(letolizumab)	CD40L
Rexomun™ (ertumaxomab)	CD3/Her2
Erbitux™ (cetuximab)	EGFR
Portrazza™ (necitumumab)	EGFR
Vectibix™ (panitumumab)	EGFR
CH806	EGFR
(depatuxizumab)	EGFR
(depatuxizumab mafodotin)	EGFR
(futuximab:modotuximab)	EGFR
ICR62 (imgatuzumab)	EGFR
(laprituximab)	EGFR
(losatuxizumab)	EGFR
(losatuxizumab vedotin)	EGFR
mAb 528	EGFR
(matuzumab)	EGFR
(nimotuzumab)	EGFR
(tomuzotuximab)	EGFR
(zalutumumab)	EGFR
MDX-447	EGFR/CD64
(adecatumumab)	EpCAM
Panorex™ (edrecolomab)	EpCAM
Vicinium™	EpCAM
Synagis™ (palivizumab)	F protein of RSV
ReoPro™ (abiciximab)	Glycoprotein receptor IIb/IIIa
Herceptin™ (trastuzumab)	Her2
Herceptin™ Hylecta (trastuzumab; Hyaluronidase)	Her2
(trastuzumab deruxtecan)	Her2
(hertuzumab verdotin)	Her2
Kadcyla™ (trastuzumab emtansine)	Her2
(margetuximab)	Her2
(timigutuzumab)	Her2
Xolair™ (omalizumab)	IgE
(ligelizumab)	IgE
(figitumumab)	IGF1R
(teprotumumab)	IGF1R

Simulect™ (basiliximab)	IL2R
Zenapax™ (daclizumab)	IL2R
Zinbryta™ (daclizumab)	IL2R
Actemra™ (tocilizumab)	IL-6 receptor
Kevzara™ (sarilumab)	IL-6 receptor
(vobarilizumab)	IL-6 receptor
Stelara™ (ustekinumab)	IL-12/IL-23
Tysabri™ (natalizumab)	Integrinα4
(abrilumab)	Integrinα4
	Jagged 1 or Jagged 2
(fasinumab)	NGF
(fulranumab)	NGF
(tanezumab)	NGF
	Notch, e.g., Notch 1
Pidilizumab	Delta like-1 (PD-1 pathway inhibitor)
Opdivo® (nivolumab)	PD1
Keytruda® (pembrolizumab)	PD1
Libtayo® (cemiplimab)	PD1
BGB-A317 (tislelizumab)	PD1
PDR001 (spartalizumab)	PD1
JNJ-63723283 (cetrelimab)	PD1
TSR042 (dostarlimab)	PD1
AGEN2034 (balstilimab)	PD1
JS001 (toripalimab)	PD1
IOBI308 (sintilimab)	PD1
BCD100 (prolgolimab)	PD1
CBT-501 (genolimzumab	PD1
ABBV181 (budigalimab)	PD1
AK105	PD1
BI-754091	PD1
INCSHR-1210	PD1
MEDI0680	PD1
MGA012	PD1
SHR-1210	PD1
Imfinzi™ (durvalumab)	PD-L1
Tecentriq® (atezolizumab)	PD-L1
Bavencio® (avelumab)	PD-L1
KN035 (envafolimab)	PD-L1
BMS936559 (MDX1105)	PD-L1
BGBA 333	PD-L1
FAZ053	PD-L1
LY-3300054	PD-L1
SH-1316	PD-L1
AMP-224	PD-L2

(bavituximab)	Phosphatidylserine
huJ591	PSMA
RAV12	RAAG12
Prolia™ (denosumab)	RANKL
GC1008 (fresolimumab)	TGFbeta
Cimzia™ (Certolizumab Pegol)	TNFα
Remicade™ (infliximab)	TNFα
Humira™ (adalimumab)	TNFα
Simponi™ (golimumab)	TNFα
Enbrel™ (etanercept)	TNF-R
(mapatumumab)	TRAIL-R1
Avastin™ (bevacizumab)	VEGF
Lucentis™ (ranibizumab)	VEGF
(brolucizumab)	VEGF
(vanucizumab)	VEGF

Compositions/Kits

Also provided herein are compositions (e.g., pharmaceutical compositions) including any of the ACCs and/or antibodies described herein and one or more (e.g., 1, 2, 3, 4, or 5) pharmaceutically acceptable carriers (e.g., any of the pharmaceutically acceptable carriers described herein), diluents, or excipients.

In some embodiments, the compositions (e.g. pharmaceutical compositions) that include any of the ACCs and/or antibodies described herein can be disposed in a sterile vial or a pre-loaded syringe.

In some embodiments, the compositions (e.g. pharmaceutical compositions) that include any of the ACCs and/or antibodies described herein can be formulated for different routes of administration (e.g., intravenous, subcutaneous, intramuscular, intraperitoneal, or intratumoral).

In some embodiments, any of the pharmaceutical compositions described herein can include one or more buffers (e.g., a neutral-buffered saline, a phosphate-buffered saline (PBS), amino acids (e.g., glycine), one or more carbohydrates (e.g., glucose, mannose, sucrose, dextran, or mannitol), one or more antioxidants, one or more chelating agents (e.g., EDTA or glutathione), one or more preservatives, and/or a pharmaceutically acceptable carrier (e.g., bacteriostatic water, PBS, or saline).

As used herein, the phrase “pharmaceutically acceptable carrier” refers to any and all solvents, dispersion media, coatings, antibacterial agents, antimicrobial agents,

isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. Suitable carriers include, but are not limited to: water, saline, ringer's solutions, dextrose solution, and about 5% human serum albumin.

In some embodiments of any of the pharmaceutical compositions described herein, any of the ACCs and/or antibodies described herein are prepared with carriers that protect against rapid elimination from the body, e.g., sustained and controlled release formulations, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, e.g., ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collage, polyorthoesters, and polylactic acid. Methods for preparation of such pharmaceutical compositions and formulations are apparent to those skilled in the art.

Also provided herein are kits that include any of the ACCs and/or antibodies described herein, any of the compositions that include any of the ACCs and/or antibodies described herein, or any of the pharmaceutical compositions that include any of the ACCs and/or antibodies described herein. Also provided are kits that include one or more second therapeutic agent(s) selected from Table 2 in addition to an ACC and/or antibody described herein. The second therapeutic agent(s) may be provided in a dosage administration form that is separate from the ACC and/or antibody. Alternatively, the second therapeutic agent(s) may be formulated together with the ACC and/or antibody.

Any of the kits described herein can include instructions for using any of the compositions (e.g., pharmaceutical compositions) and/or any of the ACCs and/or antibodies described herein. In some embodiments, the kits can include instructions for performing any of the methods described herein. In some embodiments, the kits can include at least one dose of any of the compositions (e.g., pharmaceutical compositions) described herein. In some embodiments, the kits can provide a syringe for administering any of the pharmaceutical compositions described herein.

Anti-PD1 sequences

In some embodiments the anti-PD-1, which may in certain aspects be configured as an activable antibody and in others aspects not be configured as an activatable antibody, comprises sequences shown below:

m136-M13– MHC723 mIgG1/K MHC723HC.1 Variable heavy chain region amino acid sequence:

EVKLVESGGGLVKPGGSLKLSCAASGFTFSGYAMSWVRQTPAKRLEWV AYISNSGGNAHYPDSVKGRFTISRDNAKNTLYLQMSSLRSEDTAMYYCTREDYG TSPFVYWGQGTLVTVSA (SEQ ID NO: 610).

MHC723LC.3 Variable light chain region amino acid sequence:

DIVLTQSPASLAVSLGQRTTISCRASESVDNYGISFMNWFQQKPGQPPKLL IYAASNQGSGVPARFSGSGSGTDFSLNIHPMEEDDTAVYFCQQSKDVPWTFGGG TKLEIR (SEQ ID NO: 615).

MHC725HC.2 Variable heavy chain region amino acid sequence:

EVQLQQSGPELVKPGDSVKMSCKASGYTFTDYYMDWVKQSHGKSLEWI GYIYPKNGGSSYNQKFKGKATLTVDKSSSTAYMELHSLTSEDSAVYYCARKVV ATDYWGQGTTLTVSS (SEQ ID NO: 611).

MHC725LC.2 Variable light chain region amino acid sequence:

DIVMSQSPSSLAVSVGEKVTMSCKSSQSLLYSSNQKNYLAWYQQKPGQSPKLLIF WASIRESGVPDRFTGSGSGTDFTLTISSVKAEDRAVYYCQQCDSYPWTFGGGTK LEIK (SEQ ID NO: 616).

MHC728HC.4 Variable heavy chain region amino acid sequence:

EVKLVESGGGLVKPGGSLKLSCAASGFTFSNYAMSWVRQTPAKRLEWV AYISNGGGDTHYPDSLKGRFTVSRDNAKNTLYLQMSSLKSEDTAMYYCARENY GTSPFVYWGQGTLVTVSA (SEQ ID NO: 612).

MHC728LC.2Variable light chain region amino acid sequence:

DIVLTQSPASLAVSLGQRATISCRASESVDNYGISFMNWFQQKPGQPPKLL IYAASNQGSGVPARFSGSGSGTDFSLNIHPMEEDDTAMYFCQQSKDVPWTFGGG TKLEIK (SEQ ID NO: 617).

MHC729HC.1 Variable heavy chain region amino acid sequence:

EVQLVESGGGLVKSGGSLKLSCAHSGFSFSSYDMSWVRQTPAKRLEWVA TISGGGRYTYYPDSVKGRFTISRDNAKNTLYLQMSGLRSEDTAMYYCASNYYGF DYWGQGTTLTVSS (SEQ ID NO: 613).

MHC729LC.3 Variable light chain region amino acid sequence:

DIVMTQSHKFMSTSVGDRVSITCKASQDVGTAVAWYQQKPGQSPKLLIY WASTRHTGVPDRFTGSGSGTDFTLTISNVQSEDLADYFCQQYSSYPWTFGGGTK LEIK (SEQ ID NO: 618).

MHC724HC.3 Variable heavy chain region amino acid sequence:

KVMLVESGGDLVKPGGSLKLSCAASGFTFSSYGMSWVRQTPEKRLEWV ATISGGGRDIYYADTVKGRFTISRDNAKNTLYLQMSSLRSEDTALYFCARLYLGF DYWGQGTTLTVSS (SEQ ID NO: 614).

MHC724LC.1 Variable light chain region amino acid sequence:

DIQMTQSPASQSASLGESVTITCLASQTIGTWLAWYQQKPGKSPQLLIYAA TSLADGVPSRFSG SGSGTKFSFKISSLQAEDFVSYYCQQLYSIPWTFGGGTKLEIK (SEQ ID NO: 619).

PD-1 A Hv Variable heavy chain region amino acid sequence:

EVQLVESGGGLVQPGGSLRLSCAASGFTFSGYAMSWVRQAPGKGLEWV AYISNSGGNAHYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCTREDYG TSPFVYWGQGTLVTVSS (SEQ ID NO: 620).

PD-1 Ab Hv Variable heavy chain region amino acid sequence:

EVQLVESGGGLVQPGGSLRLSCAASGFTFSGYAMSWVRQAPGKGLEWV SYISNSGGNAHYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKEDYG TSPFVYWGQGTLVTVSS (SEQ ID NO: 621).

PD-1 Ae Hv Variable heavy chain region amino acid sequence:

EVQLVESGGGLVQPGGSLRLSCAASGFTFSGYAMSWVRQAPGKGLEWV AYISNSGGNTHYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREDYG TSPFVYWGQGTLVTVSS (SEQ ID NO: 622).

PD-1 Af Hv Variable heavy chain region amino acid sequence:

EVQLVESGGGLVQPGGSLRLSCAASGFTFSGYAMSWVRQAPGKGLEWV AYISNSGGNTHYADSLKGRFTVSRDNSKNTLYLQMNSLRAEDTAVYYCAREDY GTSPFVYWGQGTLVTVSS (SEQ ID NO: 623).

PD-1 Ba Hv Variable heavy chain region amino acid sequence:

QVQLVQSGAEVKKPGASVKMSCKASGYTFTDYYMDWVRQAPGQGLEW IGYIYPKNGGSSYAQKFQGRATLTVDTSTSTAYMELSSLRSEDTAVYYCARKVV ATDYWGQGTLLTVSS (SEQ ID NO: 624).

PD-1 Bb Hv Variable heavy chain region amino acid sequence:

QVQLVQSGAEVKKPGASVKMSCKASGYTFTDYYMDWVRQAPGQGLEW IGYIYPKNGGSSYAQKFQGRATLTVDKSTSTAYMELSSLRSEDTAVYYCARKVV ATDYWGQGTLLTVSS (SEQ ID NO: 625).

PD-1 C Hv Variable heavy chain region amino acid sequence:

EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYAMSWVRQAPGKGLEWV AYISNGGGDTHYADSLKGRFTVSRDNSKNTLYLQMNSLRAEDTAVYYCARENY GTSPFVYWGQGTLVTVSS (SEQ ID NO: 626).

PD-1 Ca Hv Variable heavy chain region amino acid sequence:

EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYAMSWVRQAPGKGLEWV AYISNQGGDTHYADSLKGRFTVSRDNSKNTLYLQMNSLRAEDTAVYYCARENY GTSPFVYWGQGTLVTVSS (SEQ ID NO: 627).

PD-1 D Hv Variable heavy chain region amino acid sequence:

EVQLVESGGGLVQPGGSLRLSCAHSGFSFSSYDMSWVRQAPGKGLEWVA TISGGGRYTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCASNYYGF DYWGQGTLLTVSS (SEQ ID NO: 628).

PD-11.0 Lv Variable light chain region amino acid sequence:

DIQLTQSPSSLSASVGDRVTITCRASESVDNYGISFMNWFQQKPGKAPKLL IYAASNQGSGVPSRFSGSGSGTDFTLTISSMQPEDFATYYCQQSKDVPWTFGQGT KLEIK (SEQ ID NO: 629).

PD-11.1 Lv Variable light chain region amino acid sequence:

DIQLTQSPSSLSVSVGDRATITCRASESVDNYGISFMNWFQQKPGKAPKLL IYAASNQGSGVPSRFSGSGSGTDFTLTISSMQPEDFATYYCQQSKDVPWTFGQGT KLEIK (SEQ ID NO: 630).

Lv Variable light chain region amino acid sequence:

DIQLTQSPSSLSASVGDRVTITCRASESVDQYGISFMNWFQQKPGKAPKLL IYAASNQGSGVPSRFSGSGSGTDFTLTISSMQPEDFATYYCQQSKDVPWTFGQGT KLEIK (SEQ ID NO: 631).

PD-11.4 Lv Variable light chain region amino acid sequence:

DIQLTQSPSSLSASVGDRVTITCRASESVDSYGISFMNWFQQKPGKAPKLL IYAASNQGSGVPSRFSGSGSGTDFTLTISSMQPEDFATYYCQQSKDVPWTFGQGT KLEIK (SEQ ID NO: 632).

PD-11.5 Lv Variable light chain region amino acid sequence:

DIQLTQSPSSLSASVGDRVTITCRASESVDAYGISFMNWFQQKPGKAPKLL IYAASNQGSGVPSRFSGSGSGTDFTLTISSMQPEDFATYYCQQSKDVPWTFGQGT KLEIK (SEQ ID NO: 633).

PD-11.6 Lv Variable light chain region amino acid sequence:

DIQLTQSPSSLSASVGDRVTITCRASESVDNYGISFMNWFQQKPGKAPKLL IYAASDQGSGVPSRFSGSGSGTDFTLTISSMQPEDFATYYCQQSKDVPWTFGQGT KLEIK (SEQ ID NO: 634).

PD-11.7 Lv Variable light chain region amino acid sequence:

DIQLTQSPSSLSVSVGDRATITCRASESVDAYGISFMNWFQQKPGKAPKLL IYAASNQGSGVPSRFSGSGSGTDFTLTISSMQPEDFATYYCQQSKDVPWTFGQGT KLEIK (SEQ ID NO: 635).

PD-11.9 Lv Variable light chain region amino acid sequence:

DIQLTQSPSSLSASVGDRVTITCRASESVDAYGISFMNWFQQKPGKAPKLL IYAASNQGSGVPSRFSGSGSGTDFTLTISSMQPEDFATYYCQQSKDVPWTFGQGT KVEIK (SEQ ID NO: 636).

PD-11.10 Lv Variable light chain region amino acid sequence:

DIQLTQSPSSLSASVGDRVTITCRASESVDAYGISFMNWFQQKPGKAPKLL IYAASNQGSGVPSRFSGSGSGTDFTLTISSMQPEDFATYYCQQSKDVPYTFGQGT KLEIK (SEQ ID NO: 637).

PD-12 Lv Variable light chain region amino acid sequence:

DIQMTQSPSSLSASVGDRVTMTCKSSQSLLYSSNQKNYLAWYQQKPGKA PKLLIFWASIRESGVPSRFSGSGSGTDFTLTISSVQPEDFATYYCQQSDSYPWTFG QGTKLEIK (SEQ ID NO: 638).

PD-14 Lv Variable light chain region amino acid sequence:

DIQMTQSPSSLSASVGDRVTITCKASQDVGTAVAWYQQKPGKAPKLLIY WASTRHTGVPSRFSGSGSGTDFTLTISSVQPEDFATYYCQQYSSYPWTFGQGTKL EIK (SEQ ID NO: 639).

Kappa constant region amino acid sequence:

RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSG NSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG EC (SEQ ID NO: 640).

hIgG4 S228P amino acid sequence:

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPP CPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVD GVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEK TISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSL SLGK (SEQ ID NO: 641).

In some embodiments, anti-PD1 CDR sequences comprise the sequences listed in the following tables.

Table 3

VH		
CDRl (SEQ ID NO)	CDR2 (SEQ ID NO)	CDR3 (SEQ ID NO)
GFTFSGYAMS (487)	YISNSGGNAH (488)	EDYGTSPFVY (489)
GYTFTDYYMD (642)	YIYPKNGGSS (646)	KVVATDY (652)
GFTFSNYAMS (643)	YISNGGGDTH (647)	ENYGTSPFVY (653)
GFSFSSYDMS (644)	TISGGGRYTY (648)	NYYGFDY (654)
GFTFSSYGMS (645)	TISGGGRDIY (649)	LYLGFDY (655)
GFTFSGYAMS (487)	YISNSGGNAH (488)	EDYGTSPFVY (489)
GFTFSGYAMS (487)	YISNSGGNAH (488)	EDYGTSPFVY (489)

GFTFSGYAMS (487)	YISNSGGNTH (650)	EDYGTSPFVY (489)
GFTFSGYAMS (487)	YISNSGGNTH (650)	EDYGTSPFVY (489)
GYTFTDYYMD (487)	YIYPKNGGSS (646)	KVVATDY (652)
GYTFTDYYMD (487)	YIYPKNGGSS (646)	KVVATDY (652)
GFTFSNYAMS (643)	YISNGGGDTH (647)	ENYGTSPFVY (653)
GFTFSNYAMS (643)	AYISNQGGDTH (651)	ENYGTSPFVY (653)
GFSFSSYDMS (644)	TISGGGRYTY (648)	NYYGFDY (654)

Table 4

VL		
CDRl (SEQ IDNO)	CDR2 (SEQ IDNO)	CDR3 (SEQ IDNO)
RASESVDNYGISFMN (656)	AASNQGS (691)	QQSKDVPWT (492)
KSSQSLLYSSNQKNY L(657)	WASIRES (664)	QQCDSYPWT (667)
RASESVDNYGISFMN (656)	AASNQGS (691)	QQSKDVPWT (492)
KASQDVGTAVA (658)	WASTRHT (665)	QQYSSYPWT (668)
LASQTIGTWLA (659)	AATSLAD (666)	QQLYSIPWT (669)
RASESVDNYGISFMN (660)	AASNQGS (691)	QQSKDVPWT (492)
RASESVDQYGISFM N (661)	WASIRES (664)	QQCDSYPWT (667)

RASESVDSYGISFM N (662)	WASTRHT (665)	QQYSSYPWT (668)
RASESVDAYGISFM N (490)		QQLYSIPWT (669)
KSSQSLLYSSNQKN YLA (663)		QQSDSYPWT (670)

In some embodiments, the PD-1 pathway inhibitor is an antibody comprising one or more sequences in Tables 7-9 of WO2017011580A2. In some embodiments, the PD1 pathway inhibitor comprises an activatable PD-1 antibody that comprises: (i) an antibody or an antigen binding fragment thereof (AB) that comprises one or more sequences in Tables 7-9 of WO2017011580A2; (ii) a masking moiety (MM) that, when the activatable antibody is in an uncleaved state, inhibits the binding of the AB to PD-1; and (c) a cleavable moiety (CM) coupled to the AB, wherein the CM is a polypeptide that functions as a substrate for a protease; and optionally a first linking peptide and/or a second linking peptide.

Any of the polypeptides described above can be combined with human immunoglobulin constant regions to result in fully human IgGs including IgGl, IgG2, IgG4 or mutated constant regions to result in human IgGs with altered functions such as IgGl N297A, IgGl N297Q, or IgG4 S228P. The polypeptides described above are not limited by the particular combinations and include any mask sequence matched with any substrate sequence matched with any VL sequence matched with any VH sequence. In addition to the substrate sequences any CM disclosed herein can be used.

Anti-PD-L1 sequences

In some embodiments the anti-PD-L1, which may in certain aspects be configured as an activable antibody and in others aspects not be configured as an activatable antibody, comprises sequences shown below:

Variable light chain region amino acid sequence:

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYYA STLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQDNGYPSTFGQGTKVEIK R (SEQ ID NO: 671).

Variable light chain region amino acid sequence:

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAA SSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQDNGYPSTFGGGTKVEIK R (SEQ ID NO: 672).

Variable heavy chain region amino acid sequence:

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS SIYSTGGATAYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSSAGQ SRPGFDYWGQGTLVTVSS (SEQ ID NO: 673).

Variable heavy chain region amino acid sequence:

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS SIYSTGGATAYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSSAGQ SWPGFDYWGQGTLVTVSS (SEQ ID NO: 674).

Variable heavy chain region amino acid sequence:

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS SIYSTGGATAYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSSAGQ SFPGFDYWGQGTLVTVSS (SEQ ID NO: 675).

Variable heavy chain region amino acid sequence:

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS SIYSTGGATAYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKWSAAF DYWGQGTLVTVSS (SEQ ID NO: 676).

Variable heavy chain region amino acid sequence:

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS SIYSTGGATAYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKWSAG YDYWGQGTLVTVSS (SEQ ID NO: 677).

Variable heavy chain region amino acid sequence:

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS SIYSTGGATAYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKWSKGF DYWGQGTLVTVSS (SEQ ID NO: 678).

Variable heavy chain region amino acid sequence:

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS SIWKQGIVTVYDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSSAGFD YWGQGTLVTV (SEQ ID NO: 679).

Variable heavy chain region amino acid sequence:

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS SIWRNGIVTVYDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSSAGFD YWGQGTLVTVSS (SEQ ID NO: 680).

Variable heavy chain region amino acid sequence:

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS DIWKQGMVTVYDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSSAGF DYWGQGTLVTVSS (SEQ ID NO: 681).

Variable heavy chain region amino acid sequence:

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS SIWRQGLATAYDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSSAGFD YWGQGTLVTVSS (SEQ ID NO: 682).

Variable heavy chain region amino acid sequence:

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS EIVATGILTSYDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSSAGFDY WGQGTLVTVSS (SEQ ID NO: 683).

Variable heavy chain region amino acid sequence:

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS SIGRQGLITVYDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSSAGFDY WGQGTLVTVSS (SEQ ID NO: 684).

Variable heavy chain region amino acid sequence:

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS SIWYQGLVTVYDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSSAGFD YWGQGTLVTVSS (SEQ ID NO: 685).

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS DIWKQGFATADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSSAGFD YWGQGTLVTVSS (SEQ ID NO: 686).

Variable heavy chain region amino acid sequence:

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS SIWKQGIVTVYDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSSAGFD YWGQGTLVTVSS (SEQ ID NO: 687).

Variable heavy chain region amino acid sequence:

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS SIWRQGLATAYDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSSAGFD YWGQGTLVTVSS (SEQ ID NO: 688).

Variable heavy chain region amino acid sequence:

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS SIWRNGIVTVYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKWSAAF DYWGQGTLVTVSS (SEQ ID NO: 689).

Variable heavy chain region amino acid sequence:

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS SIWRNGIVTVYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKWSAG YDYWGQGTLVTVSS (SEQ ID NO: 690).

Variable heavy chain region amino acid sequence:

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS SIWRNGIVTVYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKWSKGF DYWGQGTLVTVSS (SEQ ID NO: 691).

Variable heavy chain region amino acid sequence:

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS SIWYQGLVTVYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKWSAA FDYWGQGTLVTVSS (SEQ ID NO: 692).

Variable heavy chain region amino acid sequence:

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS SIWYQGLVTVYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKWSAG YDYWGQGTLVTVSS (SEQ ID NO: 693).

Variable heavy chain region amino acid sequence:

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS SIWYQGLVTVYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKWSKG FDYWGQGTLVTVSS (SEQ ID NO: 694).

In some embodiments, anti-PD-L1 CDR sequences comprise the sequences listed in the following tables.

Table 5

VH		
CDRl (SEQ ID NO)	CDR2 (SEQ ID NO)	CDR3 (SEQ ID NO)
SYAMS (SEQ ID NO: 538)	DITASGQRTTYADS (SEQ IDNO: 695)	SKAIFDY (SEQ ID NO: 696)
	SINKDGHYTSYADS (SEQ IDNO: 697)	NLDEFDY (SEQ ID NO: 698)
	SIMATGAGTLYADS (SEQ IDNO: 699)	DGAGEDY (SEQ ID NO: 700)
	TITSSGAATYYADS (SEQ IDNO: 701)	NYTGFDY (SEQ ID NO: 702)
	SIYSTGGATAYADS (SEQ ID NO: 703)	SSAGFDY (SEQ ID NO: 704)
	SSIYSTGGATAYADS (SEQ IDNO: 705)	SSAGOSRPGFDY (SEQ ID NO: 706)
	SSIWKQGIVTVYDS (SEQ ID NO: 707)	SSAGQSWPGFDY (SEQ ID NO: 708)
	SSIWRNGIVTVYDS (SEQ ID NO: 709)	SSAGQSFPGFDY (SEQ IDNO: 710)

	SDIWKQGMVTVYDS (SEQ ID NO: 711)	WSAAFDY (SEQ ID NO: 540)
	SSIWROGLATAYDS (SEQ IDNO: 712)	WSAGYDY (SEQ ID NO: 713)
	SEIVATGILTSYDS (SEQ IDNO: 714)	WSKGFDY (SEQ ID NO: 715)
	SSIGRQGLITVYDS (SEQ ID NO: 716)	
	SSIWYQGLVTVYD (SEQ ID NO: 717)	
	SDIWKQGFATADS (SEQ ID NO: 718)	
	SSIWRNGIVTVYADS (SEQ ID NO: 539)	
	SSIWYQGLVTVYADS (SEQ ID NO: 719)	

Table 6

VL		
CDRl (SEQ ID NO)	CDR2 (SEQ ID NO)	CDR3 (SEQID NO)
RASQSISSYLN (SEQ ID NO: 535)	KASRLOS (SEQ ID NO: 720)	RALKPVT (SEQ ID NO: 721)
	AASSLQS (SEQ ID NO: 536)	SYSTPNT (SEQ IDNO: 722)

	SASQLQS (SEQ ID NO: 723)	ANSRPST (SEQ ID NO: 724)
	NASSLOS (SEQ ID NO: 725)	YPYGPG (SEQ IDNO: 726)
	YASTLQS (SEQ ID NO: 727)	DNGYPST (SEQ ID NO: 537)

Any of the polypeptides described above can be combined with human immunoglobulin constant regions to result in fully human IgGs including IgGl, IgG2, IgG4 or mutated constant regions to result in human IgGs with altered functions such as IgGl N297A, IgGl N297Q, or IgG4 S228P. The polypeptides described above are not limited by the particular combinations and include any mask sequence matched with any substrate sequence matched with any VL sequence matched with any VH sequence. In addition to the substrate sequences any CM disclosed herein can be used.

As a non-limiting example a spacer sequence and Mask can be combined with substrate and combined with human kappa constant domain to give SEQ ID NO: 496; or Mask can be combined with substrate and combined with human kappa constant domain to give SEQ ID NO: 728. Furthermore, a VH domain can be combined with human immunoglobulin heavy chain constant domains to give human IgG1 (SEQ ID NO: 729), mutated human IgG4 S228P (SEQ ID NO: 485), mutated human IgG1 N297A (SEQ ID NO: 730), or mutated human IgG1 N297Q (SEQ ID NO: 731). Co-expression will yield an activatable antibody.

Light chain sequence with spacer:

[QGQSGS][GIALCPSHFCQLPQTGGGSSGGSGGSGGISSGLLSGRSDNHGG SDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQDNGYPSTFGGGTKVEIKRTVA APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE QDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC] (SEQ ID NO: 496).

Light chain sequence without spacer:

GIALCPSHFCQLPQTGGGSSGGSGGSGGISSGLLSGRSDNHGGSDIQMTQS
PSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFS
GSGSGTDFTLTISSLQPEDFATYYCQQDNGYPSTFGGGTKVEIKRTVAAPSVFIFP
PSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDST
YSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 728).

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS
SIWRNGIVTVYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKWSAAF
DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW
NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK
KVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC
KVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDI
AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE
ALHNHYTQKSLSLSPG (SEQ ID NO: 729).

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS
SIWRNGIVTVYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKWSAAF
DYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW
NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDK
RVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPE
VQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVS
NKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALH
NHYTQKSLSLSLG (SEQ ID NO: 485).

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS
SIWRNGIVTVYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKWSAAF
DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW
NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK
KVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKC
KVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDI

AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE
ALHNHYTQKSLSLSPG (SEQ ID NO: 730).

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVS
SIWRNGIVTVYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKWSAAF
DYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW
NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK
KVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYQSTYRVVSVLTVLHQDWLNGKEYKC
KVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDI
AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE
ALHNHYTQKSLSLSPG (SEQ ID NO: 731).

In some embodiments, the PD-L1 pathway inhibitor is an antibody comprising one or more sequences in Tables 15-17 of WO2016149201A2. In some embodiments, the PD-L1 pathway inhibitor comprises an activatable PD-L1 antibody that comprises: (i) an antibody or an antigen binding fragment thereof (AB) that comprises one or more sequences in Tables 15-17 of WO2016149201A2; (ii) a masking moiety (MM) that, when the activatable antibody is in an uncleaved state, inhibits the binding of the AB to PD-L1; and (c) a cleavable moiety (CM) coupled to the AB, wherein the CM is a polypeptide that functions as a substrate for a protease; and optionally a first linking peptide and/or a second linking peptide.

In some embodiments, the PD1/PD-L1 pathway inhibitor is an antibody comprising one or more sequences in Table 7, below. In some embodiments, the PD1/PD-L1 pathway inhibitor comprises an activatable PD-1 antibody or an activatable PD-L1 antibody that comprises: (i) an antibody or an antigen binding fragment thereof (AB) that comprises one or more sequences in Table 7, below; (ii) a masking moiety (MM) that, when the activatable antibody is in an uncleaved state, inhibits the binding of the AB to PD-1 or PD-L1; and (c) a cleavable moiety (CM) coupled to the AB, wherein the CM is a polypeptide that functions as a substrate for a protease; and optionally a first linking peptide and/or a second linking peptide.

Table 7. PD-1/PD-L1 Pathway Inhibitors

Peptides	Sequences	SEQ ID NOs
Nivolumab VH_CDR1	NSGMH	732
Nivolumab VH_CDR2	VIWYDGSKRYYADSVKG	733
Nivolumab VH_CDR3	NDDY	734
Nivolumab VL_CDR1	RASQSVS SYLA	735
Nivolumab VL_CDR2	DASNRAT	736
Nivolumab VL_CDR3	QQSSNWPRT	529
Nivolumab Heavy Chain VH region is underlined.	QVQLVESGGG VVQPGRSLRL DCKASGITFS NSGMHWVRQA PGKGLEWVAV IWYDGSKRYY ADSVKGRFTI SRDNSKNTLF LQMNSLRAED TAVYYCATND DYWGQGTLVT VSSASTKGPS VFPLAPCSRS TSESTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSSLG TKTYTCNVDH KPSNTKVDKR VESKYGPPCP PCPAPEFLGG PSVFLFPPKP KDTLMISRTP EVTCVVVDVS QEDPEVQFNW YVDGVEVHNA KTKPREEQFN STYRVVSVLT VLHQDWLNGK EYKCKVSNKG LPSSIEKTIS KAKGQPREPQ VYTLPPSQEE MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SRLTVDKSRW QEGNVFSCSV MHEALHNHYT QKSLSLSLGK	737
Nivolumab Light Chain VL region is underlined.	EIVLTQSPAT LSLSPGERAT LSCRASQSVS SYLAWYQQKP GQAPRLLIYD ASNRATGIPA RFSGSGSGTD FTLTISSLEP EDFAVYYCQQ SSNWPRTFGQ GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT	738

	LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC	
Pembrolizumab VH_CDR1	NYYMY	739
Pembrolizumab VH_CDR2	GINPSNGGTNFNEKFKN	740
Pembrolizumab VH_CDR3	RDYRFDMGFDY	741
Pembrolizumab VL_CDR1	RASKGVSTSGYSYLH	742
Pembrolizumab VL_CDR2	LASYLES	743
Pembrolizumab VL_CDR3	QHSRDLPLT	534
Pembrolizumab Heavy Chain VH region is underlined.	QVQLVQSGVE VKKPGASVKV SCKASGYTFT NYYMYWVRQA PGQGLEWMGG INPSNGGTNF NEKFKNRVTL TTDSSTTTAY MELKSLQFDD TAVYYCARRD YRFDMGFDYW GQGTTVTVSS ASTKGPSVFP LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTKT YTCNVDHKPS NTKVDKRVES KYGPPCPPCP APEFLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSQED PEVQFNWYVD GVEVHNAKTK PREEQFNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKGLPS SIEKTISKAK GQPREPQVYT LPPSQEEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS DGSFFLYSRL TVDKSRWQEG NVFSCSVMHE ALHNHYTQKS LSLSLGK	744

Pembrolizumab Light Chain VL region is underlined.	EIVLTQSPAT LSLSPGERAT LSCRASKGVS TSGYSYLHWY QQKPGQAPRL LIYLASYLES GVPARFSGSG SGTDFTLTIS SLEPEDFAVY YCQHSRDLPL TFGGGTKVEI KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFYPREAKV QWKVDNALQS GNSQESVTEQ DSKDSTYSLS STLTLSKADY EKHKVYACEV THQGLSSPVT KSFNRGEC	745
Tislelizumab VH_CDR1	SYGVH	746
Tislelizumab VH_CDR2	VIYADGSTNYNPSLKS	747
Tislelizumab VH_CDR3	AYGNYWYIDV	748
Tislelizumab VL_CDR1	KSSESVSNDVA	749
Tislelizumab VL_CDR2	YAFHRFT	750
Tislelizumab VL_CDR3	HQAYSSPYT	751
Tislelizumab Heavy Chain VH region is underlined.	QVQLQESGPG LVKPSETLSL TCTVSGFSLT SYGVHWIRQP PGKGLEWIGV IYADGSTNYN PSLKSRVTIS KDTSKNQVSL KLSSVTAADT AVYYCARAYG NYWYIDVWGQ GTTVTVSSAS TKGPSVFPLA PCSRSTSEST AALGCLVKDY FPEPVTVSWN SGALTSGVHT FPAVLQSSGL YSLSSVVTVP SSSLGTKTYT CNVDHKPSNT KVDKRVESKY GPPCPPCPAP PVAGGPSVFL FPPKPKDTLM ISRTPEVTCV VVAVSQEDPE VQFNWYVDGV EVHNAKTKPR	752

	EEQFNSTYRV VSVLTVVHQD WLNGKEYKCK VSNKGLPSSI EKTISKAKGQ PREPQVYTLP PSQEEMTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQEGNV FSCSVMHEAL HNHYTQKSLS LSLGK	
Tislelizumab Light Chain VL region is underlined.	DIVMTQSPDS LAVSLGERAT INCKSSESVS NDVAWYQQKP GQPPKLLINY AFHRFTGVPD RFSGSGYGTD FTLTISSLQA EDVAVYYCHQ AYSSPYTFGQ GTKLEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC	753
Spartalizumab VH_CDR1	TYWMH	754
Spartalizumab VH_CDR2	NIYPGTGGSNFDEKFKN	755
Spartalizumab VH_CDR3	WTTGTGAY	756
Spartalizumab VL_CDR1	KSSQSLLDSGNQKNFLT	757
Spartalizumab VL_CDR2	WASTRES	758
Spartalizumab VL_CDR3	QNDYSYPYT	759
Spartalizumab Heavy Chain	EVQLVQSGAE VKKPGESLRI SCKGSGYTFT TYWMHWVRQA TGQGLEWMGN IYPGTGGSNF DEKFKNRVTI TADKSTSTAY MELSSLRSED TAVYYCTRWT TGTGAYWGQG	760

VH region is underlined.	TTVTVSSAST KGPSVFPLAP CSRSTSESTA ALGCLVKDYF PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS SSLGTKTYTC NVDHKPSNTK VDKRVESKYG PPCPPCPAPE FLGGPSVFLF PPKPKDTLMI SRTPEVTCVV VDVSQEDPEV QFNWYVDGVE VHNAKTKPRE EQFNSTYRVV SVLTVLHQDW LNGKEYKCKV SNKGLPSSIE KTISKAKGQP REPQVYTLPP SQEEMTKNQV SLTCLVKGFY PSDIAVEWES NGQPENNYKT TPPVLDSDGS FFLYSRLTVD KSRWQEGNVF SCSVMHEALH NHYTQKSLSL SLG	
Spartalizumab Light Chain VL region is underlined.	EIVLTQSPAT LSLSPGERAT LSCKSSQSLL DSGNQKNFLT WYQQKPGQAP RLLIYWASTR ESGVPSRFSG SGSGTDFTFT ISSLEAEDAA TYYCQNDYSY PYTFGQGTKV EIKRTVAAPS VFIFPPSDEQ LKSGTASVVC LLNNFYPREA KVQWKVDNAL QSGNSQESVT EQDSKDSTYS LSSTLTLSKA DYEKHKVYAC EVTHQGLSSP VTKSFNRGEC	761
Camrelizumab VH_CDR1	SYMMS	762
Camrelizumab VH_CDR2	TISGGGNTYYPDSVKG	763
Camrelizumab VH_CDR3	QLYYFDY	764
Camrelizumab VL_CDR1	LASQTIGTWLT	765
Camrelizumab VL_CDR2	TATSLAD	766

Camrelizumab VL_CDR3	QQVYSIPWT	767
Camrelizumab Heavy Chain VH region is underlined.	EVQLVESGGGLVQPGGSLRLSCAASGFTF SSYMMSWVRQAPGKGLEWVATISGGGANTYYP DSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVY YCARQLYYFDYWGQGTTVTVSSASTKGPSVFPL APCSRSTSESTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKT YTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPE AAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS QEDPEVQFNWYVDGVEVHNAKTKPREEQFNST YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSI EKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS DGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALH NHYTQKSLSLSLGK	768
Camrelizumab Light Chain VL region is underlined.	DIQMTQSPSSLSASVGDRVTITCLASQTIGT WLTWYQQKPGKAPKLLIYT ATSLADGVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQQVYSIPWTFGG GTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCL LNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKA DYEKHKVYACEVTHQG LSSPVTKSFNRGEC	769
Cetrelimab VH_CDR1	SYAIS	770
Cetrelimab VH_CDR2	GIIPIFDTANYAQKFQG	771
Cetrelimab VH_CDR3	PGLAAAYDTGSLDY	772
Cetrelimab VL_CDR1	RASQSVRSYLA	773
Cetrelimab VL_CDR2	DASNRAT	774

Cetrelimab VL_CDR3	QQRNYWPLT	775
Cetrelimab Heavy Chain VH region is underlined.	QVQLVQSGAEVKKPGSSVKVSCKASGGT FSSYAISWVRQAPGQGLEWMGGIIPIFDTANYAQ KFQGRVTITADESTSTAYMELSSLRSEDTAVYYC ARPGLAAAYDTGSLDYWGQGTLVTVSSASTKGP SVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCP PCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSQEDPEVQFNWYVDGVEVHNAKTKPREE QFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK GLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVM HEALHNHYTQKSLSLSLGK	776
Cetrelimab Light Chain VL region is underlined.	EIVLTQSPATLSLSPGERATLSCRASQSVRS YLAWYQQKPGQAPRLLIYDASNRATGIPARFSGS GSGTDFTLTISSLEPEDFAVYYCQQRNYWPLTFG QGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQ GLSSPVTKSFNRGEC	777
Balstilimab VH_CDR1	SYGMH	778
Balstilimab VH_CDR2	VIWYDGSNKYYADSVKG	779
Balstilimab VH_CDR3	NGDH	780
Balstilimab VL_CDR1	RASQSVSSNLA	781
Balstilimab VL_CDR2	GASTRAT	782
Balstilimab VL_CDR3	QQYNNWPRT	783
Balstilimab Heavy Chain	QVQLVESGGGVVQPGRSLRLSCAASGFTF SSYGMHWVRQAPGKGLEWVAVIWYDGSNKYY	784

VH region is underlined.	ADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCASNGDHWGQGTLVTVSSASTKGPSVFPLAP CSRSTSESTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYT CNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLG GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDP EVQFNWYVDGVEVHNAKTKPREEQFNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIS KAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYT QKSLSLSLGK	
Balstilimab Light Chain VL region is underlined.	EIVMTQSPATLSVSPGERATLSCRASQSVS SNLAWYQQKPGQAPRLLIYGASTRATGIPARFSG SGSGTEFTLTISSLQSEDFAVYYCQQYNNWPRTF GQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQ GLSSPVTKSFNRGEC	785
Dostarlimab VH_CDR1	GFTFSSYDMS	786
Dostarlimab VH_CDR2	TISGGGSYTY	787
Dostarlimab VH_CDR3	PYYAMDY	788
Dostarlimab VL_CDR1	KASQDVGTAVA	789
Dostarlimab VL_CDR2	WASTLHT	790

Dostarlimab VL_CDR3	QHYSSYPWT	791
Dostarlimab Heavy Chain VH region is underlined.	EVQLLESGGGLVQPGGSLRLSCAASGFTFS SYDMSWVRQAPGKGLEWVSTISGGGSYTYYQD SVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYY CASPYYAMDYWGQGTTVTVSSASTKGPSVFPLA PCSRSTSESTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTY TCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFL GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQE DPEVQFNWYVDGVEVHNAKTKPREEQFNSTYR VVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEK TISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD GSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHN HYTQKSLSLSLGK	792
Dostarlimab Light Chain VL region is underlined.	DIQLTQSPSFLSAYVGDRVTITCKASQDVG TAVAWYQQKPGKAPKLLIYWASTLHTGVPSRFS GSGSGTEFTLTISSLQPEDFATYYCQHYSSYPWTF GQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVV CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQ GLSSPVTKSFNRGEC	793
Prolgolimab VH_CDR1	SSYWMY	794
Prolgolimab VH_CDR2	AIDTGGGRTYYADSVKG	795
Prolgolimab VH_CDR3	DEGGGTGWGVLKDWPYGLDA	796

Prolgolimab VL_CDR1	GGNNIGSKNVH	797
Prolgolimab VL_CDR2	RDSNRPS	798
Prolgolimab VL_CDR3	QVWDSSTAV	799
Prolgolimab Heavy Chain VH region is underlined.	QVQLVQSGGGLVQPGGSLRLSCAASGFTF SSYWMYWVRQVPGKGLEWVSAIDTGGGRTYYA DSVKGRFAISRVNAKNTMYLQMNSLRAEDTAV YYCARDEGGGTGWGVLKDWPYGLDAWGQGTL VTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKR VEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDW LNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	800
Prolgolimab Light Chain VL region is underlined.	QPVLTQPLSVSVALGQTARITCGGNNIGSK NVHWYQQKPGQAPVLVIYRDSNRPSGIPERFSGS NSGNTATLTISRAQAGDEADYYCQVWDSSTAVF GTGTKLTVLQRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTE QDSKDSTYSLSSTLTLSKADYEKHKVYACEVTH QGLSSPVTKSFNRGEC	801
Sasanlimab VH_CDR1	SYWIN	802
Sasanlimab VH_CDR2	NIYPGSSLTNYNEKFKN	803

Sasanlimab VH_CDR3	LSTGTFAY	804
Sasanlimab VL_CDR1	KSSQSLWDSGNQKNFLT	805
Sasanlimab VL_CDR2	WTSYRES	806
Sasanlimab VL_CDR3	QNDYFYPHT	807
Sasanlimab Heavy Chain VH region is underlined.	QVQLVQSGAEVKKPGASVKVSCKASGYT FTSYWINWVRQAPGQGLEWMGNIYPGSSLTNYN EKFKNRVTMTRDTSTSTVYMELSSLRSEDTAVY YCARLSTGTFAYWGQGTLVTVSSASTKGPSVFPL APCSRSTSESTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKT YTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEF LGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQ EDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYR VVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEK TISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD GSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHN HYTQKSLSLSLGK	808
Sasanlimab Light Chain VL region is underlined.	DIVMTQSPDSLAVSLGERATINCKSSQSLW DSGNQKNFLTWYQQKPGQPPKLLIYWTSYRESG VPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQND YFYPHTFGGGTKVEIKRTVAAPSVFIFPPSDEQLK SGTASVVCLLNNFYPREAKVQWKVDNALQSGN SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC	809
Zimberelimab VH_CDR1	STTYYWV	810
Zimberelimab VH_CDR2	SISYSGSTYYNPSLKS	811

Zimberelimab VH_CDR3	HLGYNGRYLPFDY	812
Zimberelimab VL_CDR1	TGTSSDVGFYNYVS	813
Zimberelimab VL_CDR2	DVSNRPS	814
Zimberelimab VL_CDR3	SSYTSISTWV	815
Zimberelimab Heavy Chain VH region is underlined.	QLQLQESGPG LVKPSETLTL TCTVSADSIS STTYYWVWIR QPPGKGLEWI GSISYSGSTY YNPSLKSRVT VSVDTSKNQF SLKLNSVAAT DTALYYCARH LGYNGRYLPF DYWGQGTLVT VSSASTKGPS VFPLAPCSRS TSESTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSSLG TKTYTCNVDH KPSNTKVDKR VESKYGPPCP PCPAPEFLGG PSVFLFPPKP KDTLMISRTP EVTCVVVDVS QEDPEVQFNW YVDGVEVHNA KTKPREEQFN STYRVVSVLT VLHQDWLNGK EYKCKVSNKG LPSSIEKTIS KAKGQPREPQ VYTLPPSQEE MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SRLTVDKSRW QEGNVFSCSV MHEALHNHYT QKSLSLSLGK	816
Zimberelimab Light Chain VL region is underlined.	QSALTQPASV SGSPGQSITI SCTGTSSDVG FYNYVSWYQQ HPGKAPELMI YDVSNRPSGV SDRFSGSKSG NTASLTISGL QAEDEADYYC SSYTSISTWV FGGGTKLTVL GQPKAAPSVT LFPPSSEELQ ANKATLVCLI SDFYPGAVTV AWKADSSPVK AGVETTTPSK QSNNKYAASS YLSLTPEQWK SHRSYSCQVT HEGSTVEKTV APTECS	817

Atezolizumab VH_CDR1	DSWIH	818
Atezolizumab VH_CDR2	WISPYGGSTYYADSVKG	819
Atezolizumab VH_CDR3	RHWPGGFDY	820
Atezolizumab VL_CDR1	RASQDVSTAVA	821
Atezolizumab VL_CDR2	SASFLYS	822
Atezolizumab VL_CDR3	QQYLYHPAT	823
Atezolizumab Heavy Chain VH region is underlined.	EVQLVESGGGLVQPGGSLRLSCAASGFTF SDSWIHWVRQAPGKGLEWVAWISPYGGSTYYA DSVKGRFTISADTSKNTAYLQMNSLRAEDTAVY YCARRHWPGGFDYWGQGTLVTVSSASTKGPSVF PLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPP CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YASTYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLSPGK	824
Atezolizumab Light Chain	DIQMTQSPSSLSASVGDRVTITCRASQDVS TAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSG SGSGTDFTLTISSLQPEDFATYYCQQYLYHPATFG QGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVC	825

VL region is underlined.	LLNNFYPREAKVQWKVDNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQ GLSSPVTKSFNRGEC	
Avelumab VH_CDR1	SYIMM	826
Avelumab VH_CDR2	SIYPSGGITFYADTVKG	827
Avelumab VH_CDR3	IKLGTVTTVDY	828
Avelumab VL_CDR1	TGTSSDVGGYNYVS	829
Avelumab VL_CDR2	DVSNRPS	830
Avelumab VL_CDR3	SSYTSSSTRV	831
Avelumab Heavy Chain VH region is underlined.	EVQLLESGGGLVQPGGSLRLSCAASGFTFS SYIMMWVRQAPGKGLEWVSSIYPSGGITFYADT VKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC ARIKLGTVTTVDYWGQGTLVTVSSASTKGPSVFP LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCP APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSRDELTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA LHNHYTQKSLSLSPG	832
Avelumab Light Chain VL region is underlined.	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYDVSNRPSGVSNRF SGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTR VFGTGTKVTVLGQPKANPTVTLFPPSSEELQANK ATLVCLISDFYPGAVTVAWKADGSPVKAGVETT KPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQV THEGSTVEKTVAPTECS	833

Durvalumab VH_CDR1	RYWMS	834
Durvalumab VH_CDR2	NIKQDGSEKYYVDSVKG	835
Durvalumab VH_CDR3	EGGWFGELAFDY	836
Durvalumab VL_CDR1	RASQRVSSSYLA	837
Durvalumab VL_CDR2	DASSRAT	838
Durvalumab VL_CDR3	QQYGSLPWT	839
Durvalumab Heavy Chain VH region is underlined.	EVQLVESGGGLVQPGGSLRLSCAASGFTF SRYWMSWVRQAPGKGLEWVANIKQDGSEKYY VDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCAREGGWFGELAFDYWGQGTLVTVSSASTK GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKT HTCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPASIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN YKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVF SCSVMHEALHNHYTQKSLSLSPGK	840
Durvalumab Light Chain	EIVLTQSPGTLSLSPGERATLSCRASQRVSS SYLAWYQQKPGQAPRLLIYDASSRATGIPDRFSG SGSGTDFTLTISRLEPEDFAVYYCQQYGSLPWTF GQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV	841

VL region is underlined.	CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQ GLSSPVTKSFNRGEC	
Adebrelimab VH_CDR1	SYWMH	842
Adebrelimab VH_CDR2	RIGPNSGFTSYNEKFKN	843
Adebrelimab VH_CDR3	GGSSYDYFDY	844
Adebrelimab VL_CDR1	RASESVSIHGTHLMH	845
Adebrelimab VL_CDR2	AASNLES	846
Adebrelimab VL_CDR3	QQSFEDPLT	847
Adebrelimab Heavy Chain VH region is underlined.	QVQLVQSGAEVKKPGASVKVSCKASGYT FTSYWMHWVRQAPGQGLEWMGRIGPNSGFTSY NEKFKNRVTMTRDTSTSTVYMELSSLRSEDTAV YYCARGGSSYDYFDYWGQGTTVTVSSASTKGPS VFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL GTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPC PAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSQEDPEVQFNWYVDGVEVHNAKTKPREEQF NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGL PSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHE ALHNHYTQKSLSLSLGK	848

Adebrelimab Light Chain VL region is underlined.	DIVLTQSPASLAVSPGQRATITCRASESVSI HGTHLMHWYQQKPGQPPKLLIYAASNLESGVPA RFSGSGSGTDFTLTINPVEAEDTANYYCQQSFED PLTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGT ASVVCLLNNFYPREAKVQWKVDNALQSGNSQE SVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC	849
Lodapolimab VH_CDR1	SYAIS	850
Lodapolimab VH_CDR2	GIIPIFGTANYAQKFQG	851
Lodapolimab VH_CDR3	SPDYSPYYYYGMDV	852
Lodapolimab VL_CDR1	SGSSSNIGSNTVN	853
Lodapolimab VL_CDR2	GNSNRPS	854
Lodapolimab VL_CDR3	QSYDSSLSGSV	855
Lodapolimab Heavy Chain VH region is underlined.	QVQLVQSGAEVKKPGSSVKVSCKASGGT FSSYAISWVRQAPGQGLEWMGGIIPIFGTANYAQ KFQGRVTITADKSTSTAYMELSSLRSEDTAVYYC ARSPDYSPYYYYGMDVWGQGTTVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTH TCPPCPAPEAEGAPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPSSIEKTISKAKGQPREPQVYTLPPSREEM	856

	TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPGK	
Lodapolimab Light Chain VL region is underlined.	QSVLTQPPSASGTPGQRVTISCSGSSSNIGS NTVNWYQQLPGTAPKLLIYGNSNRPSGVPDRFS GSKSGTSASLAISGLQSEDEADYYCQSYDSSLSGS VFGGGIKLTVLGQPKAAPSVTLFPPSSEELQANK ATLVCLISDFYPGAVTVAWKADSSPVKAGVETT TPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVT HEGSTVEKTVAPAECS	857
Envafolimab VH_CDR1	RRCMA	858
Envafolimab VH_CDR2	KLLTTSGSTYLADSVKG	859
Envafolimab VH_CDR3	DSFEDPTCTLVTSSGAFQY	860
Envafolimab single chain antibody VH region is underlined.	QVQLVESGGGLVQPGGSLRLSCAASGKM SSRRCMAWFRQAPGKERERVAKLLTTSGSTYLA DSVKGRFTISRDNSKNTVYLQMNSLRAEDTAVY YCAADSFEDPTCTLVTSSGAFQYWGQGTLVTVS SEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKD TLMISRTPEVTCVVVAVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKALPAGIEKTISKAKGQPREPQV YTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	861
Cosibelimab VH_CDR1	RSAIS	862

Cosibelimab VH_CDR2	VIIPAFGEANYAQKFQG	863
Cosibelimab VH_CDR3	GRQMFGAGIDF	864
Cosibelimab VL_CDR1	TRSSGSIDSNYVQ	865
Cosibelimab VL_CDR2	EDNQRPS	866
Cosibelimab VL_CDR3	QSYDSNNRHVI	867
Cosibelimab Heavy Chain VH region is underlined.	EVQLVQSGAEVKKPGSSVKVSCKASGGTF SRSAISWVRQAPGQGLEWMGVIIPAFGEANYAQ KFQGRVTITADESTSTAYMELSSLRSEDTAVYYC ARGRQMFGAGIDFWGQGTLVTVSSASTKGPSVF PLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPP CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLSPGK	868
Cosibelimab Light Chain VL region is underlined.	NFMLTQPHSVSESPGKTVTISCTRSSGSIDS NYVQWYQQRPGSAPTTVIYEDNQRPSGVPDRFS GSIDSSSNSASLTISGLKTEDEADYYCQSYDSNNR HVIFGGGTKLTVLGQPKAAPSVTLFPPSSEELQA NKATLVCLISDFYPGAVTVAWKADSSPVKAGVE	869

	TTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQ VTHEGSTVEKTVAPTECS	
Budigalimab heavy chain	EIQLVQSGAEVKKPGSSVKVSCKASGYTF THYGMNWVRQAPGQGLEWVGWVNTYTGEPTY ADDFKGRLTFTLDTSTSTAYMELSSLRSEDTAVY YCTREGEGLGFGDWGQGTTVTVSSASTKGPSVF PLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPP CPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLSPGK	870
Budigalimab light chain	DVVMTQSPLSLPVTPGEPASISCRSSQSIVH SHGDTYLEWYLQKPGQSPQLLIYKVSNRFSGVPD RFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHIP VTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQES VTEQDSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC	871
Ezabenlimab heavy chain	EVMLVESGGGLVQPGGSLRLSCTASGFTF SKSAMSWVRQAPGKGLEWVAYISGGGGDTYY SSSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVY YCARHSNVNYYAMDYWGQGTLVTVSS ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSS	872

	GLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKV DKRVESKYGPPCPPCPAPEFLGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIE KTISKAKGQPREPQVYTLPPSQEEMTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSRLTVDKSRWQEG NVFSCSVMHEALHNHYTQKSLSLSLG	
Ezabenlimab light chain	EIVLTQSPATLSLSPGERATMSCRASENID VSGISFMNWYQQKPGQAPKLLIYVASNQGS GIPARFSGSGSGTDFTLTISRLEPEDFAVYYCQQS KEVPWTFGQGTKLEIKRTVAAPSVF IFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSLS STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC	873
Finotonlimab heavy chain	EVQLVESGGGLVKPGGSLRLSCAASGFTF SSYGMSWVRQAPGKRLEWVATISGGGRDTYY SDSVKGRFTISRDNAKNNLYLQMNSLRAEDTAV YYCSRQYGTVWFFNWGQGTLVTVSSAS TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDK RVESKYGPPCPPCPAPEFLGGPSVFL FPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFN WYVDGVEVHNAKTKPREEQFNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQPREPQVYTLPPSQEEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP	874

	VLDSDGSFFLYSRLTVDKSRWQEGNV FSCSVMHEALHNHYTQKSLSLSLGK	
Finotonlimab light chain	EIVLTQSPATLSLSPGERATLSCRASESVDS YGNSFMHWYQQKPGQPPRLLIYAASNQGS GVPARFSGSGSGTDFTLTISSLEPEDFAMYFCQQS KEVPWTFGQGTKVEIKRTVAAPSVF IFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSLS STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC	875
Geptanolimab heavy chain	QIQLVQSGSELKKPGASVKVSCKASGYTF TNFGMNWVRQAPGQGLKWMGWISGYTREPTY AADFKGRFVISLDTSVSTAYLQISSLKAEDTAVY YCARDVFDYWGQGTLVTVSSASTKGP SVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVES KYGPPCPPCPAPEFLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTYRVVSVL TVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAK GQPREPQVYTLPPSQEEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS DGSFFLYSRLTVDKSRWQEGNVFSCS VMHEALHNHYTQKSLSLSLG	876
Geptanolimab light chain	DIVLTQSPASLAVSPGQRATITCRASESVD NYGYSFMNWFQQKPGQPPKLLIYRASNLES GVPARFSGSGSRTDFTLTINPVEADDTANYYCQQ SNADPTFGQGTKLEIKRTVAAPSVFI FPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV	877

	DNALQSGNSQESVTEQDSKDSTYSLSS TLTLSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC	
Lodapolimab heavy chain	QVQLVQSGAEVKKPGSSVKVSCKASGGT FSSYAISWVRQAPGQGLEWMGGIIPIFGTANY AQKFQGRVTITADKSTSTAYMELSSLRSEDTAVY YCARSPDYSPYYYYGMDVWGQGTTVT VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKRVEPKSCDKTHTCPPCPAPEA EGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPSSIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	878
Lodapolimab light chain	QSVLTQPPSASGTPGQRVTISCSGSSSNIGS NTVNWYQQLPGTAPKLLIYGNSNRPSGVP DRFSGSKSGTSASLAISGLQSEDEADYYCQSYDS SLSGSVFGGGIKLTVLGQPKAAPSVT LFPPSSEELQANKATLVCLISDFYPGAVTVAWKA DSSPVKAGVETTTPSKQSNNKYAASS YLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPA ECS	879
Penpulimab heavy chain	EVQLVESGGGLVQPGGSLRLSCAASGFAF SSYDMSWVRQAPGKGLDWVATISGGGRYTYY PDSVKGRFTISRDNSKNNLYLQMNSLRAEDTAL	880

	YYCANRYGEAWFAYWGQGTLVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP VTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAPEAAGAPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEV KFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSRDELT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPGK	
Penpulimab light chain	DIQMTQSPSSMSASVGDRVTFTCRASQDI NTYLSWFQQKPGKSPKTLIYRANRLVSGVPS RFSGSGSGQDYTLTISSLQPEDMATYYCLQYDEF PLTFGAGTKLELKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGE C	881
Pimivalimab heavy chain	QVQLVQSGAEVKKPGASVKVSCKASGYT FPSYYMHWVRQAPGQGLEWMGIINPEGGSTAY AQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAV YYCARGGTYYDYTYWGQGTLVTVSSAS TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDK RVESKYGPPCPPCPAPEFLGGPSVFL FPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFN WYVDGVEVHNAKTKPREEQFNSTYRV	882

	VSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQPREPQVYTLPPSQEEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLYSRLTVDKSRWQEGNV FSCSVMHEALHNHYTQKSLSLSLGK	
Pimivalimab light chain	DIQMTQSPSTLSASVGDRVTITCRASQSISS WLAWYQQKPGKAPKLLIYEASSLESGVPS RFSGSGSGTEFTLTISSLQPDDFATYYCQQYNSFP PTFGGGTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGE C	883
Pucotenlimab heavy chain	EVQLVQSGGGLVQPGGSLKLSCAASGFTF SSYGMSWVRQAPGKGLDWVATISGGGRDTYY PDSVKGRFTISRDNSKNNLYLQMNSLRAEDTAL YYCARQKGEAWFAYWGQGTLVTVSSAS TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDK RVESKYGPPCPPCPAPEFLGGPSVFL FPPKPKDTLMITRTPEVTCVVVDVSQEDPEVQFN WYVDGVEVHNAKTKPREEQFNSTYRV VSVLTPLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQPREPQVYTLPPSQEEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLYSRLTVDKSRWQEGNV FSCSVMHEALHAHYTQKSLSLSLGK	884
Pucotenlimab light chain	DIVLTQSPASLAVSPGQRATITCRASESVD NYGISFMNWFQQKPGQPPKLLIYAASNKGT	885

	GVPARFSGSGSGTDFTLNINPMEENDTAMYFCQ QSKEVPWTFGGGTKLEIKRTVAAPSVF IFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSLS STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC	
Serplulimab heavy chain	QVQLVESGGGLVKPGGSLRLSCAASGFTF SNYGMSWIRQAPGKGLEWSTISGGGSNIYYA DSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVY YCVSYYYGIDFWGQGTSVTVSSASKYG PSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVE SKYGPPCPPCPAPEFLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWY VDGVEVHNAKTKPREEQFNSTYRVVSV VLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISK AKGQPREPQVYTLPPSQEEMTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL DSDGSFFLYSRLTVDKSRWQEGNVFS CSVMHEALHNHYTQKSLSLSLGK	886
Serplulimab light chain	DIQMTQSPSSLSASVGDRVTITCKASQDVT TAVAWYQQKPGKAPKLLIYWASTRHTGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQQHYTIP WTFGGGTKLEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGE C	887

Sintilimab heavy chain	QVQLVQSGAEVKKPGSSVKVSCKASGGT FSSYAISWVRQAPGQGLEWMGLIIPMFDTAGY AQKFQGRVAITVDESTSTAYMELSSLRSEDTAVY YCARAEHSSTGTFDYWGQGTLVTVSS ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKV DKRVESKYGPPCPPCPAPEFLGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIE KTISKAKGQPREPQVYTLPPSQEEMTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSRLTVDKSRWQEG NVFSCSVMHEALHNHYTQKSLSLSLGK	888
Sintilimab light chain	DIQMTQSPSSVSASVGDRVTITCRASQGIS SWLAWYQQKPGKAPKLLISAASSLQSGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQQANHLP FTFGGGTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGE C	889
Toripalimab heavy chain	QGQLVQSGAEVKKPGASVKVSCKASGYT FTDYEMHWVRQAPIHGLEWIGVIESETGGTAY NQKFKGRVTITADKSTSTAYMELSSLRSEDTAVY YCAREGITTVATTYYWYFDVWGQGTT VTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPA VLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKP	890

	SNTKVDKRVESKYGPPCPPCPAPEFL GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQE DPEVQFNWYVDGVEVHNAKTKPREEQ FNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKG LPSSIEKTISKAKGQPREPQVYTLPPSQ EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYSRLTVDKS RWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK	
Toripalimab light chain	DVVMTQSPLSLPVTLGQPASISCRSSQSIV HSNGNTYLEWYLQKPGQSPQLLIYKVSNRF SGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCF QGSHVPLTFGQGTKLEIKRTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWK VDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF NRGEC	891
Zeluvalimab heavy chain	EVQLLESGGG LVQPGGSLRL SCAASGFTFS SYDMSWVRQA PGKGLEWVSL ISGGGSQTYY AESVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYFCASPS GHYFYAMDVW GQGTTVTVSS ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPCEEQYG STYRCVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSREE MTKNQVSLTC LVKGFYPSDI AVEWESNGQP	892

	ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK	
Zeluvalimab light chain	DIQMTQSPSS VSASVGDRVT ITCRASQGIS NWLAWYQQKP GKAPKLLIFA ASSLQSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ AESFPHTFGG GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC	893
Iparomlimab heavy chain	QVQLVQSGAE VKKPGASVKV SCKASGYTFT NYWIHWVRQA PGQGLEWMGE IDPYDSYTNY NQKFKGRVTM TVDKSTSTVY MELSSLRSED TAVYYCARPG FTYGGMDFWG QGTLVTVSSA STKGPSVFPL APCSRSTSES TAALGCLVKD YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTKTY TCNVDHKPSN TKVDKRVESK YGPPCPPCPA PEFLGGPSVF LFPPKPKDTL MISRTPEVTC VVVDVSQEDP EVQFNWYVDG VEVHNAKTKP REEQFNSTYR VVSVLTVLHQ DWLNGKEYKC KVSNKGLPSS IEKTISKAKG QPREPQVYTL PPSQEEMTKN QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTPPVLDSD GSFFLYSRLT VDKSRWQEGN VFSCSVMHEA LHNHYTQKSL SLSLGK	894
Iparomlimab light chain	DIQMTQSPSS LSASVGDRVT ITCKSSQSLF NSGNQKNYLA WYQQKPGKVP KLLIYGASTR DSGVPYRFSG SGSGTDFTLT ISSLQPEDVA	895

	TYYCQNDHYY PYTFGGGTKV EIKRTVAAPS VFIFPPSDEQ LKSGTASVVC LLNNFYPREA KVQWKVDNAL QSGNSQESVT EQDSKDSTYS LSSTLTLSKA DYEKHKVYAC EVTHQGLSSP VTKSFNRGEC	
Nofazinlimab heavy chain	QVQLVQSGAE VKKPGSSVKV SCKASGFTFT TYYISWVRQA PGQGLEYLGY INMGSGGTNY NEKFKGRVTI TADKSTSTAY MELSSLRSED TAVYYCAIIG YFDYWGQGTM VTVSSASTKG PSVFPLAPCS RSTSESTAAL GCLVKDYFPE PVTVSWNSGA LTSGVHTFPA VLQSSGLYSL SSVVTVPSSS LGTKTYTCNV DHKPSNTKVD KRVESKYGPP CPPCPAPEFL GGPSVFLFPP KPKDTLMISR TPEVTCVVVD VSQEDPEVQF NWYVDGVEVH NAKTKPREEQ FNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KGLPSSIEKT ISKAKGQPRE PQVYTLPPSQ EEMTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP PVLDSDGSFF LYSRLTVDKS RWQEGNVFSC SVMHEALHNH YTQKSLSLSL GK	896
Nofazinlimab light chain	DVVMTQSPLS LPVTLGQPAS ISCRSSQSLL DSDGGTYLYW FQQRPGQSPR RLIYLVSTLG SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCMQLTHWP YTFGQGTKLE IKRTVAAPSV FIFPPSDEQL KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL SSTLTLSKAD YEKHKVYACE VTHQGLLSPV TKSFNRGEC	897

Rulonilimab heavy chain	EVQLVESGGG LVKPGGSLRL SCAASGFTFS SYGMSWVRQT PEKRLEWVAT ISGGGRDTYY PDSVKGRFTI SRDNAKNNLY LQMSSLRSED TALYYCARQK DTSWFVHWGQ GTLVTVSSAS TKGPSVFPLA PSSKSTSGGT AALGCLVKDY FPEPVTVSWN SGALTSGVHT FPAVLQSSGL YSLSSVVTVP SSSLGTQTYI CNVNHKPSNT KVDKKVEPKS CDKTHTCPPC PAPELLGGPS VFLFPPKPKD QLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYAST YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSREEMT KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSK LTVDKSRWQQ GNVFSCSVLH EALHNHYTQK SLSLSPGK	898
Rulonilimab light chain	EIVLTQSPAT LAVSPGERAT ISCRASESVD DYGISFMNWF QQKPGQPPKL LIYVASNQGS GVPARFSGSG SGTDFTLNIH PMEEDDTAMY FCQQSKEVPW TFGGGTKLEI KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFYPREAKV QWKVDNALQS GNSQESVTEQ DSKDSTYSLS STLTLSKADY EKHKVYACEV THQGLSSPVT KSFNRGEC	899
Garivulimab heavy chain	EVQLVESGGGLVQPGGSLRLSCAVSGFSL TSYGVHWVRQAPGKGLEWVAVIWAGGSTNYA DSVKGRFTISKDTSKNTVYLQMNSLRAEDTAVY YCAKPYGTSAMDYWGQGTLVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK VEPKSCDKTHTCPPCPAPPAAGPSVF	900

	LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYNSTYR VVSVLTVLHQDWLNGKEYKCKVSNKALAAPIEK TISKAKGQPREPQVYTLPPSRDELTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPGK	
Garivulimab light chain	DIQMTQSPSSLSASVGDRVTITCKASQDVG IVVAWYQQKPGKAPKLLIYWASIRHTGVPS RFSGSGSGTEFTLTISSLQPDDFATYYCQQYSNYP LYTFGQGTKVEIKRTVAAPSVFIFP PSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG EC	901
Manelimab heavy chain	EVQLVESGGGVVRPGGSLRLSCAASGFTF DDYAMSWVRQAPGKGLEWVSDISWSGSNTNY ADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAL YHCARAPLLLAMTFGVGSWGQGTLVTV SSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK VDKRVEPKSCDKTHTCPPCPAPEAA GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	902

Manelimab light chain	QTVVTQEPSLSVSPGGTVTLTCGLSSGTVT AINYPGWYQQTPGQAPRTLIYNTNTRHSGV PDRFSGSISGNKAALTITGAQAEDEADYYCALYM GNGGHMFGGGTKLTVLGQPKAAPSVT LFPPSSEELQANKATLVCLISDFYPGAVTVAWKA DSSPVKAGVETTTPSKQSNNKYAASS YLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTE CS	903
Opucolimab heavy chain	EVQLVQSGGGLVKPGGSLRLSCAASGFTF SSYTMNWVRQAPGKGLEWVSSISSGSDYLYY ADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARNELRWYPQAGAFDRWGQGTMVT VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPEL LGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREE QYASTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	904
Opucolimab light chain	QSVVTQPPSMSAAPGQRVTISCSGSSSYIES SYVGWYQQLPGTAPRLLIYDDDMRPSGIP DRFSGSKSGTSATLAITGLQTGDEADYYCEIWRS GLGGVFGGGTKLTVLSQPKAAPSVTL FPPSSEELQANKATLVCLISDFYPGAVTVAWKAD SSPVKAGVETTTPSKQSNNKYAASSY LSLTPEQWKSHKSYSCQVTHEGSTVERTVALTEC	905

Pacmilimab heavy chain	EVQLLESGGGLVQPGGSLRLSCAASGFTFS SYAMSWVRQAPGKGLEWVSSIWRNGIVTVY ADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCAKWSAAFDYWGQGTLVTVSSASTK GPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRV ESKYGPPCPPCPAPEFLGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNW YVDGVEVHNAKTKPREEQFFNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIS KAKGQPREPQVYTLPPSQEEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSRLTVDKSRWQEGNVF SCSVMHEALHNHYTQKSLSLSLG	906
Pacmilimab light chain	QGQSGSGIALCPSHFCQLPQTGGGSSGGSG GSGGISSGLLSGRSDNHGGSDIQMTQSPSS LSASVGDRVTITCRASQSISSYLNWYQQKPGKAP KLLIYAASSLQSGVPSRFSGSGSGTD FTLTISSLQPEDFATYYCQQDNGYPSTFGGGTKV EIKRTVAAPSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQES VTEQDSKDSTYSLSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC	907
Sudubrilimab heavy chain	EVQLVESGGGLVQPGGSLRLSCAASGFTF SETWLHWVRQAPGKGLEWVAWVSPFGGSTYY ADSVKGRFTISADTSKNTAYLQMNSLRAEDTAV YYCARRHWPGGFDYWGQGTLVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP	908

	VTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAPELLGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEV KFNWYVDGVEVHNAKTKPREEQYAST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSREEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPG	
Sudubrilimab light chain	DIQMTQSPSSLSASVGDRVTITCRASQDVS TAVAWYQQKPGKAPKLLIYSASFLYSGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQQFLYHP ATFGQGTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGE C	909
Sugemalimab heavy chain	EVQLLESGGGLVQPGGSLRLSCAASGFTFS SYAMSWVRQAPGKGLEWVSGISGSGGFTYY ADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCAKPPRGYNYGPFDYWGQGTLVTVS SASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTK VDKRVESKYGPPCPPCPAPEFLGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEV QFNWYVDGVEVHNAKTKPREEQFNST YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSI EKTISKAKGQPREPQVYTLPPSQEEMT	910

	KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSRLTVDKSRWQE GNVFSCSVMHEALHNHYTQKSLSLSLGK	
Sugemalimab light chain	YVLTQPPSVSVAPGQTARITCGGNNIGSKS VHWYQQKPGQAPVLVVYDDSDRPSGIPERF SGSNSGNTATLTISRVEAGDEADYYCQVWDSSS DHVVFGGGTKLTVLGQPKAAPSVTLFP PSSEELQANKATLVCLISDFYPGAVTVAWKADSS PVKAGVETTTPSKQSNNKYAASSYLS LTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	911
Socazolimab heavy chain	EVQLVESGAE VKKPGSSVKV SCKASGGTFS SYAISWVRQA PGQGLEWMGG IIPIFGTANY AQKFQGRVTI TADESTSTAY MELSSLRSED TAVYYCARAP YYYYYMDVWG QGTTVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKP DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIETISK AKGQPREPQV YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLPGK	912
Socazolimab light chain	QSALTQPASV SGSLGQSVTI SCTGSSSDVG SYNLVSWYQQ HPGKAPNLMI YDVSKRSGVS NRFSGSKSGN TASLTISGLQ AEDEADYYCS SYTGISTVVF GGGTKLTVLG QPKAAPSVTL	913

	FPPSSEELQA NKATLVCLIS DFYPGAVTVA WKADSSPVKA GVETTTPSKQ SNNKYAASSY LSLTPEQWKS HRSYSCQVTH EGSTVEKTVA PTECS	
Tagitanlimab heavy chain	QVQLQESGPG LVKPSETLSI TCTVSGFSLS NYDISWIRQP PGKGLEWLGV IWTGGATNYN PALKSRLTIS RDNSKNQVSL KMSSVTAADT AVYYCVRDSN YRYDEPFTYW GQGTLVTVSS ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPEAAGA PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSRDE LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK	914
Tagitanlimab light chain	EIVLTQSPDT LSVTPKEKVT LTCRASQSIG TNIHWFQQKP GQSPKLLIKY ASESISGVPS RFSGSGSGTD FTLTINSVEA EDAATYYCQQ SNSWPYTFGQ GTKLEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC	915
ProC1239 Arm 1	QSGQTDVDYYREWSWTQVSGSSGGSLSGRSDNI GSGGSCDLPQTHSLGSRRTLMLLAQMRRISLFSC LKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIF NLFSTKDSSAAWDETLLDKFYTELYQQLNDLEA	916

	CVIQGVGVTETPLMKEDSILAVRKYFQRITLYLK EKKYSPCAWEVVRAEIMRSFSLSTNLQESLRSKE LSGRSDNICPPCPAPEFEGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVH NAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPP CQEEMTKNQVSLWCLVKGFYPSDIAVEWESNGQ PENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEG NVFSCSVMHEALHNHYTQKSLSLSLGK	
ProC1239 Arm 2	SDNICPPCPAPEFEGGPSVFLFPPKPKDTLMISRTP EVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKT KPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQVCTLPPSQEE MTKNQVSLSCAVKGFYPSDIAVEWESNGQPENN YKTTPPVLDSDGSFFLVSRLTVDKSRWQEGNVFS CSVMHEALHNRFTQKSLSLSLG	917
ProC1468 arm 2 heavy chain with a hole mutation	QVTLRESGPALVKPTQTLTLTCTFSGFSLSTSGMS VGWIRQPPGKALEWLADIWWDDKKDYNPSLKS RLTISKDTSKNQVVLKVTNMDPADTATYYCARS MITNWYFDVWGAGTTVTVSSASTKGPSVFPLAP CSRSTSESTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYT CNVDHKPSNTKVDKRVECPPCPAPEFEGGPSVFL FPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFN WYVDGVEVHNAKTKPREEQFNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKG QPREPQVCTLPPSQEEMTKNQVSLSCAVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSR LTVDKSRWQEGNVFSCSVMHEALHNRFTQKSLS LSLGK	918

palivizumab Heavy chain with a knob mutation	QVTLRESGPALVKPTQTLTLTCTFSGFSLSTSGMS VGWIRQPPGKALEWLADIWWDDKKDYNPSLKS RLTISKDTSKNQVVLKVTNMDPADTATYYCARS MITNWYFDVWGAGTTVTVSS	919
Pro1468 arm2 light chain with hole mutation	DIQMTQSPSTLSASVGDRVTITCKSQLSVGYMH WYQQKPGKAPKLLIYDTSKLASGVPSRFSGSGSG TEFTLTISSLQPDDFATYYCFQGSGYPFTFGGGTK LEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDS TYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC	920
palivizumab LIGHT chain with C25S mutation	DIQMTQSPSTLSASVGDRVTITCKSQLSVGYMH WYQQKPGKAPKLLIYDTSKLASGVPSRFSGSGSG TEFTLTISSLQPDDFATYYCFQGSGYPFTFGGGTK LEIK	921
human IgG4 CH1 domain	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTKTYTCNVDHKPSNTKVDKRVE	922
CM	LSGRSNI	923

The present disclosure includes the following non-limiting aspects and any combination of any of these aspects:

1. A method of treating a subject in need thereof comprising administering a combination of an activatable cytokine construct (ACC) and a PD-1/PD-L1 pathway inhibitor to the subject, wherein the ACC includes a first monomer construct and a second monomer construct, wherein:

(a) the first monomer construct comprises a first peptide mask (PM1), a first mature cytokine protein (CP1), a first and a third cleavable moieties (CM1 and CM3), and a first dimerization domain (DD1), wherein the CM1 is positioned between the CP1 and the DD1 and the CM3 is positioned between the PM1 and the CP1; and

(b) the second monomer construct comprises a second mature cytokine protein (CP2), a second cleavable moiety (CM2), and a second dimerization domain (DD2), wherein the CM2 is positioned between the CP2 and the DD2;

wherein the DD1 and the DD2 bind to each other thereby forming a dimer of the first monomer construct and the second monomer construct.

2. The method of aspect 1, wherein the second monomer construct further comprises a second peptide mask (PM2) and a fourth cleavable moiety (CM4), wherein the CM4 is positioned between the PM2 and the CP2.

3. The method of aspect 1 or 2, wherein the first monomer construct comprises a first polypeptide that comprises the PM1, the CM3, the CP1, the CM1, and the DD1.

4. The method of any one of aspects 1-3, wherein the second monomer construct comprises a second polypeptide that comprises the CP2, the CM2, and the DD2.

5. The method of aspect 2, wherein the second monomer construct comprises a second polypeptide that comprises the PM2, the CM4, the CP2, the CM2, and the DD2.

6. The method of any one of aspects 1-5, wherein the CP1 and/or the CP2 is/are each individually selected from the group consisting of: an interferon, an interleukin, GM-CSF, G-CSF, LIF, OSM, CD154, LT-β, TNF-α, TNF-β, 4-1BBL, APRIL, CD70, CD153, CD178, GITRL, LIGHT, OX40L, TALL-1, TRAIL, TWEAK, TRANCE, TGF-β1, TGF-β1, TGF-β3, Epo, Tpo, Flt-3L, SCF, M-CSF, and MSP, optionally wherein the CP1 and/or the CP2 is independently selected from IL-2, IL-7, IL-8, IL-10, IL-12, IL-15, IL-21, an IFN-alpha, an IFN beta, an IFN gamma, GM-CSF, TGF-beta, LIGHT, GITR-L, CD40L, CD27L, 4-1BB-L, OX40, and OX40L.

7. The method of any one of aspects 1-6, wherein:

the PM1 comprises a sequence selected from SEQ ID NOs: 297, 298, 292, and 299-336, and the CP1 is an interferon;

the PM1 comprises a sequence selected from SEQ ID NOs: 297, 298, 292, and 299-332, and the CP1 is an interferon alpha;

the PM1 comprises a sequence selected from SEQ ID NOs: 299-328, and 330-332, and the CP1 is an interferon beta;

the PM1 comprises a sequence selected from SEQ ID NOs: 299-328, and 333-336, and the CP1 is an interferon gamma;

the PM1 comprises a sequence selected from SEQ ID NOs: 337-341, and the CP1 is an IL-12;

the PM1 comprises a sequence selected from SEQ ID NOs: 342-349, 436-444, 478, and the CP1 is an IL-15;

the PM1 comprises a sequence selected from SEQ ID NOs: 350-435, 436-445, and the CP1 is an IL-2; or

the PM1 comprises a sequence selected from SEQ ID NOs: 445 and 446, and the CP1 is an IL-21.

8. The method of any one of aspects 2-7, wherein:

the PM2 comprises a sequence selected from SEQ ID NOs: 297, 298, 292, and 299-336, and the CP2 is an interferon;

the PM2 comprises a sequence selected from SEQ ID NOs: 297, 298, 292, and 299-332, and the CP2 is an interferon alpha;

the PM2 comprises a sequence selected from SEQ ID NOs: 299-328, and 330-332, and the CP2 is an interferon beta;

the PM2 comprises a sequence selected from SEQ ID NOs: 299-328, and 333-336, and the CP2 is an interferon gamma;

the PM2 comprises a sequence selected from SEQ ID NOs: 337-341, and the CP2 is an IL-12;

the PM2 comprises a sequence selected from SEQ ID NOs: 342-349, 436-444, 478, and the CP2 is an IL-15;

the PM2 comprises a sequence selected from SEQ ID NOs: 350-435, 436-445, and the CP2 is an IL-2; or

the PM2 comprises a sequence selected from SEQ ID NOs: 445 and 446, and the CP2 is an IL-21.

9. The method of any one of aspects 1 to 8, wherein the DD1 and the DD2 are a pair selected from the group consisting of: a pair of Fc domains; a sushi domain from an alpha chain of human IL-15 receptor (IL15Rα) and a soluble IL-15; barnase and barnstar; a PKA and an AKAP; adapter/docking tag modules based on mutated RNase I fragments; an epitope and sdAb; an epitope and scFv; and SNARE modules

based on interactions of the proteins syntaxin, synaptotagmin, synaptobrevin, and SNAP25; an antigen-binding domain and an epitope.

10. The method of aspect 9, wherein the DD1 and the DD2 are a pair of Fc domains.
11. The method of aspect 10, wherein the pair of Fc domains is a pair of human Fc domains.
12. The method of aspect 11, wherein the human Fc domains are human IgG1 Fc domains, human IgG2 Fc domains, human IgG3 Fc domains, or human IgG4 Fc domains.
13. The method of aspect 12, wherein the human Fc domains are human IgG4 Fc domains.
14. The method of aspect 11, wherein the human Fc domains comprise a sequence that is at least 80% identical to SEQ ID NO: 3.
15. The method of aspect 14, wherein the human Fc domains comprise a sequence that is at least 90% identical to SEQ ID NO: 3.
16. The method of aspect 15, wherein the human Fc domains comprise SEQ ID NO: 3.
17. The method of aspect 9, wherein the DD1 and the DD2 comprise SEQ ID NOs: 287 and 288, respectively.
18. The method of any one of aspects 1-16, wherein the DD1 and the DD2 are the same.
19. The method of aspect 9, wherein the DD1 comprises an antigen-binding domain and DD2 comprises a corresponding epitope.
20. The method of aspect 19, wherein the antigen-binding domain is an anti-His tag antigen-binding domain and wherein the DD2 comprises a His tag.
21. The method of aspect 19, wherein the antigen-binding domain is a single chain variable fragment (scFv).
22. The method of aspect 19, wherein the antigen-binding domain is a single domain antibody (sdAb).
23. The method of aspect 9, wherein at least one of the DD1 and the DD2 comprises a dimerization domain substituent selected from the group consisting of a non-polypeptide polymer and a small molecule.
24. The method of aspect 23, wherein the DD1 and the DD2 comprise non-polypeptide polymers covalently bound to each other.

25. The method of aspect 24, wherein the non-polypeptide polymer is a sulfur-containing polyethylene glycol, and wherein the DD1 and the DD2 are covalently bound to each other via one or more disulfide bonds.
26. The method of aspect 23, wherein at least one of the DD1 and the DD2 comprises a small molecule.
27. The method of aspect 26, wherein the small molecule is biotin.
28. The method of aspect 27, wherein DD1 comprises biotin and DD2 comprises an avidin.
29. The method of any one of aspects 1-28, wherein the CP1 and the CP2 are mature cytokines.
30. The method of any one of aspects 1-28, wherein the CP1 and the CP2 comprise a signal peptide.
31. The method of any one of aspects 1-30, wherein the CP1 and the CP2 are the same.
32. The method of any one of aspects 1-30 wherein the CP1 and the CP2 are different.
33. The method of any one of aspects 1-30, wherein the CP1 and/or the CP2 is/are an interferon.
34. The method of aspect 33, wherein the CP1 and the CP2 are an interferon.
35. The method of aspect 33, wherein the CP1 and the CP2 are different interferons.
36. The method of aspect 33, wherein the CP1 and the CP2 are the same interferon.
37. The method of any one of aspects 33-36, wherein the interferon(s) is/are a human wildtype mature interferon.
38. The method of any one of aspects 33-37, wherein the interferon(s) is/are selected from the group consisting of: interferon-alpha, interferon-beta, interferon-omega, and interferon-tau.
39. The method of aspect 38, wherein the interferons is/are an interferon-alpha.
40. The method of aspect 39, wherein the interferon(s) is/are selected from the group consisting of: interferon alpha-2a, interferon alpha-2b, and interferon alpha-n3.
41. The method of aspect 40, wherein the interferon(s) is/are interferon alpha-2b.
42. The method of aspect 41, wherein the CP1 and/or the CP2 comprises a sequence that is at least 80% identical to SEQ ID NO: 1.

43. The method of aspect 42, wherein the CP1 and/or the CP2 comprises a sequence that is at least 90% identical to SEQ ID NO: 1.
44. The method of aspect 43, wherein the CP1 and/or the CP2 comprises the sequence of SEQ ID NO: 1.
45. The method of aspect 38, wherein the interferon is an interferon beta.
46. The method of aspect 45, wherein the interferon beta is selected from the group consisting of interferon beta-1a, and interferon beta-1b.
47. The method of any one of aspects 1-46, wherein the CP1 and/or the CP2 comprises an IFab domain.
48. The method of any one of aspects 1-33, wherein the CP1 and/or the CP2 comprises an interleukin.
49. The method of aspect 48, wherein the interleukin is selected from the group consisting of IL-1α, IL-1β, IL-1RA, IL-18, IL-2, IL-4, IL-7, IL-9, IL-13, IL-15, IL-3, IL-5, IL-6, IL-11, IL-12, IL-10, IL-20, IL-21, IL-14, IL-16, and IL-17.
50. The method of any one of aspects 1-49, wherein each of the CM1 and the CM2 comprises a total of about 3 amino acids to about 15 amino acids.
51. The method of any one of aspects 1-50, wherein one or more of the CM1, the CM2, the CM3, and the CM4 comprise substrates for different proteases.
52. The method of any one of aspects 1-51, wherein the CM1, the CM2, and the CM3 comprise substrates for the same protease.
53. The method of any one of aspects 1-52, wherein the protease(s) is/are selected from the group consisting of: ADAM8, ADAM9, ADAM10, ADAM12, ADAM15, ADAM17/TACE, ADAMDEC1, ADAMTS1, ADAMTS4, ADAMTS5, BACE, Renin, Cathepsin D, Cathepsin E, Caspase 1, Caspase 2, Caspase 3, Caspase 4, Caspase 5, Caspase 6, Caspase 7, Caspase 8, Caspase 9, Caspase 10, Caspase 14, Cathepsin B, Cathepsin C, Cathepsin K, Cathespin L, Cathepsin S, Cathepsin V/L2, Cathepsin X/Z/P, Cruzipain, Legumain, Otubain-2, KLK4, KLK5, KLK6, KLK7, KLK8, KLK10, KLK11, KLK13, KLK14, Meprin, Neprilysin, PSMA, BMP-1, MMP-1, MMP-2, MMP-3, MMP-7, MMP-9, MMP-10, MMP-11, MMP-12, MMP-13, MMP-14, MMP-15, MMP-16, MMP-17, MMP-19, MMP-20, MMP-23, MMP-24, MMP-26, MMP-27, activated protein C, cathepsin A, cathepsin G, Chymase,

FVIIa, FIXa, FXa, FXIa, FXIIa, Elastase, Granzyme B, Guanidinobenzoatase, HtrA1, human neutrophil lyase, lactoferrin, marapsin, NS3/4A, PACE4, Plasmin, PSA, tPA, thrombin, tryptase, uPA, DESC1, DPP-4, FAP, Hepsin, Matriptase-2, MT-SP1/Matripase, TMPRSS2, TMPRSS3, and TMPRSS4.

54. The method of aspect 53, wherein the protease(s) is/are selected from the group consisting of: uPA, legumain, MT-SP1, ADAM17, BMP-1, TMPRSS3, TMPRSS4, MMP-2, MMP-9, MMP-12, MMP-13, and MMP-14.

55. The method of any one of aspect 1-52, wherein the CM1, CM2, CM3, and/or the CM4 comprise a sequence selected from the group consisting of: LSGRSDNH (SEQ ID NO: 5), TGRGPSWV (SEQ ID NO: 6), PLTGRSGG (SEQ ID NO: 7), TARGPSFK (SEQ ID NO: 8), NTLSGRSENHSG (SEQ ID NO: 9), NTLSGRSGNHGS (SEQ ID NO: 10), TSTSGRSANPRG (SEQ ID NO: 11), TSGRSANP (SEQ ID NO: 12), VHMPLGFLGP (SEQ ID NO: 13), AVGLLAPP (SEQ ID NO: 14), AQNLLGMV (SEQ ID NO: 15), QNQALRMA (SEQ ID NO: 16), LAAPLGLL (SEQ ID NO: 17), STFPFGMF (SEQ ID NO: 18), ISSGLLSS (SEQ ID NO: 19), PAGLWLDP (SEQ ID NO: 20), VAGRSMRP (SEQ ID NO: 21), VVPEGRRS (SEQ ID NO: 22), ILPRSPAF (SEQ ID NO: 23), MVLGRSLL (SEQ ID NO: 24), QGRAITFI (SEQ ID NO: 25), SPRSIMLA (SEQ ID NO: 26), SMLRSMPL (SEQ ID NO: 27), ISSGLLSGRSDNH (SEQ ID NO: 28), AVGLLAPPGGLSGRSDNH (SEQ ID NO: 29), ISSGLLSSGGSGGSLSGRSDNH (SEQ ID NO: 30), LSGRSGNH (SEQ ID NO: 31), SGRSANPRG (SEQ ID NO: 32), LSGRSDDH (SEQ ID NO: 33), LSGRSDIH (SEQ ID NO: 34), LSGRSDQH (SEQ ID NO: 35), LSGRSDTH (SEQ ID NO: 36), LSGRSDYH (SEQ ID NO: 37), LSGRSDNP (SEQ ID NO: 38), LSGRSANP (SEQ ID NO: 39), LSGRSANI (SEQ ID NO: 40), LSGRSDNI (SEQ ID NO: 41), MIAPVAYR (SEQ ID NO: 42), RPSPMWAY (SEQ ID NO: 43), WATPRPMR (SEQ ID NO: 44), FRLLDWQW (SEQ ID NO: 45), ISSGL (SEQ ID NO: 46), ISSGLLS (SEQ ID NO: 47), ISSGLL (SEQ ID NO: 48), ISSGLLSGRSANPRG (SEQ ID NO: 49), AVGLLAPPTSGRSANPRG (SEQ ID NO: 50), AVGLLAPPSGRSANPRG (SEQ ID NO: 51), ISSGLLSGRSDDH (SEQ ID NO: 52), ISSGLLSGRSDIH (SEQ ID NO: 53), ISSGLLSGRSDQH (SEQ ID NO: 54), ISSGLLSGRSDTH (SEQ ID NO: 55),

ISSGLLSGRSDYH (SEQ ID NO: 56), ISSGLLSGRSDNP (SEQ ID NO: 57), ISSGLLSGRSANP (SEQ ID NO: 58), ISSGLLSGRSANI (SEQ ID NO: 59), AVGLLAPPGGLSGRSDDH (SEQ ID NO: 60), AVGLLAPPGGLSGRSDIH (SEQ ID NO: 61), AVGLLAPPGGLSGRSDQH (SEQ ID NO: 62), AVGLLAPPGGLSGRSDTH (SEQ ID NO: 63), AVGLLAPPGGLSGRSDYH (SEQ ID NO: 64), AVGLLAPPGGLSGRSDNP (SEQ ID NO: 65), AVGLLAPPGGLSGRSANP (SEQ ID NO: 66), AVGLLAPPGGLSGRSANI (SEQ ID NO: 67), ISSGLLSGRSDNI (SEQ ID NO: 68), AVGLLAPPGGLSGRSDNI (SEQ ID NO: 69), GLSGRSDNHGGAVGLLAPP (SEQ ID NO: 70), GLSGRSDNHGGVHMPLGFLGP (SEQ ID NO: 71), LSGRSDNHGGVHMPLGFLGP (SEQ ID NO: 72), ISSGLSS (SEQ ID NO: 73), PVGYTSSL (SEQ ID NO: 74), DWLYWPGI (SEQ ID NO: 75), LKAAPRWA (SEQ ID NO: 76), GPSHLVLT (SEQ ID NO: 77), LPGGLSPW (SEQ ID NO: 78), MGLFSEAG (SEQ ID NO: 79), SPLPLRVP (SEQ ID NO: 80), RMHLRSLG (SEQ ID NO: 81), LLAPSHRA (SEQ ID NO: 82), GPRSFGL (SEQ ID NO: 83), GPRSFG (SEQ ID NO: 84), SARGPSRW (SEQ ID NO: 85), GGWHTGRN (SEQ ID NO: 86), HTGRSGAL (SEQ ID NO: 87), AARGPAIH (SEQ ID NO: 88), RGPAFNPM (SEQ ID NO: 89), SSRGPAYL (SEQ ID NO: 90), RGPATPIM (SEQ ID NO: 91), RGPA (SEQ ID NO: 92), GGQPSGMWGW (SEQ ID NO: 93), FPRPLGITGL (SEQ ID NO: 94), SPLTGRSG (SEQ ID NO: 95), SAGFSLPA (SEQ ID NO: 96), LAPLGLQRR (SEQ ID NO: 97), SGGPLGVR (SEQ ID NO: 98), PLGL (SEQ ID NO: 99), and SGRSDNI (SEQ ID NO: 100).

56. The method of aspect 55, wherein the CM1, the CM2, the CM3 and/or the CM4 comprises a sequence selected from the group consisting of: ISSGLLSGRSDNH (SEQ ID NO: 28), LSGRSDDH (SEQ ID NO: 33), ISSGLLSGRSDQH (SEQ ID NO: 54), SGRSDNI (SEQ ID NO: 100), and ISSGLLSGRSDNI (SEQ ID NO: 68).

57. The method of any one of aspects 1-56, wherein the protease(s) is/are produced by a tumor in a subject.

58. The method of aspect 57, wherein the subject has been diagnosed or identified as having a cancer.

59. The method of any one of aspects 1-58, wherein the CP1 and the CM1 directly abut each other in the first monomer construct.
60. The method of any one of aspects 1-59, wherein the CM1 and the DD1 directly abut each other in the first monomer construct.
61. The method of any one of aspects 1-60, wherein the CP2 and the CM2 directly abut each other in the second monomer construct.
62. The method of any one of aspects 1-61, wherein the CM2 and the DD2 directly abut each other in the second monomer construct.
63. The method of any one of aspects 1-58, wherein the first monomer construct comprises at least one linker.
64. The method of aspect 63, wherein the at least one linker is a linker L1 disposed between the PM1 and the CM3 and/or a linker L2 disposed between the CM3 and the CP1.
65. The method of aspect 63, wherein the second monomer construct comprises at least one linker.
66. The method of aspect 65, wherein the at least one linker is a linker L3 disposed between the PM2 and the CM4 and/or a linker L4 disposed between the CM4 and the CP2.
67. The method of aspect 66, wherein the first monomer construct comprises a linker L1 and the second monomer construct comprises a linker L3.
68. The method of aspect 67, wherein L1 and L3 are the same.
69. The method of aspect 66, wherein the first monomer construct comprises a linker L2 and the second monomer construct comprises a linker L4.
70. The method of aspect 69, wherein L2 and L4 are the same.
71. The method of any one of aspects 63-70, wherein each linker has a total length of 1 amino acid to about 15 amino acids.
72. The method of aspect 71, wherein each linker has a total length of at least 5 amino acids.
73. The method of aspect 63, wherein the first monomer construct comprises at least one linker, wherein each linker is independently selected from the group consisting of GSSGGSGGSGG (SEQ ID NO: 210); GGGS (SEQ ID NO: 2); GGGSGGGS (SEQ

ID NO: 211); GGGSGGGSGGGS (SEQ ID NO: 212); GGGGSGGGGSGGGGS (SEQ ID NO: 213); GGGGSGGGGSGGGGSGGGGSGGGGS (SEQ ID NO: 214); GGGGSGGGGS (SEQ ID NO: 215); GGGGS (SEQ ID NO: 216); GS; GGGGSGS (SEQ ID NO: 217); GGGGSGGGGSGGGGSGS (SEQ ID NO: 218); GGSLDPKGGGGS (SEQ ID NO: 219); PKSCDKTHTCPPCPAPELLG (SEQ ID NO: 220); SKYGPPCPPCPAPEFLG (SEQ ID NO: 221); GKSSGSGSESKS (SEQ ID NO: 222); GSTSGSGKSSEGKG (SEQ ID NO: 223); GSTSGSGKSSEGSGSTKG (SEQ ID NO: 224); GSTSGSGKPGSGEGSTKG (SEQ ID NO: 225); GSTSGSGKPGSSEGST (SEQ ID NO: 226); (GS)n, (GGS)n, (GSGGS)n (SEQ ID NO: 227), (GGGS)n (SEQ ID NO: 228), (GGGGS)n (SEQ ID NO: 216), wherein each n is an integer of at least one; GGSG (SEQ ID NO: 229); GGSGG (SEQ ID NO: 230); GSGSG (SEQ ID NO: 231; GSGGG (SEQ ID NO: 232); GGGSG (SEQ ID NO: 233); GSSSG (SEQ ID NO: 234); GGGGSGGGGSGGGGS (SEQ ID NO: 213); GGGGSGGGGSGGGGSGGGGS (SEQ ID NO: 214); GSTSGSGKPGSSEGST (SEQ ID NO: 226); SGGG (SEQ ID NO: 296); and SGGGG (SEQ ID NO: 459).

74. The method of aspect 73, wherein the linker comprises a sequence of GGGS (SEQ ID NO: 2).

75. The method of any one of aspects 1-74, wherein the first monomer construct comprises in a N- to C- terminal direction, the PM1, the CM3, the CP1, the CM1, and the DD1.

76. The method of any one of aspects 1-74, wherein the first polypeptide comprises in a C- to N-terminal direction, the PM1, the CM3, the CP1, the CM1, and the DD1.

77. The method of any one of aspects 1-76, wherein the second polypeptide comprises in a N- to C-terminal direction, the CP2, CM2, and the DD2.

78. The method of any one of aspects 1-77, wherein the second polypeptide comprises in a C- to N-terminal direction, the CP2, CM2, and the DD2.

79. The method of any one of aspects 1-31, 33, 34, or 36-78, wherein the first monomer construct and the second monomer construct are the same.

80. The method of any one of aspects 1-74, wherein the first monomer construct comprises in a N- to C- terminal direction, the PM1, an optional linker, the CM3, an

optional linker, the CP1, the CM1, and the DD1, wherein the CP1 and the CM1 directly abut each other, wherein the CM1 and the DD1 directly abut each other, wherein the CM1 is a peptide of not more than 10 amino acids, wherein the second monomer construct is the same as the first monomer construct, and wherein the first and second monomer constructs are covalently bound to each other via at least two disulfide bonds.

81. The method of aspect 80, wherein the DD1 and the DD2 are each a human Fc domain having an N-terminus at Cysteine 216, as numbered according to EU numbering.

82. The method of aspect 80 or 81, wherein the CM1 is a peptide of not more than 7 amino acids.

83. The method of any one of aspect 80-82, wherein the CP1 and the CP2 comprise an amino acid sequence that is at least 90% identical to SEQ ID NO: 1.

84. The method of any one of aspects 1-83, wherein the ACC is characterized by having a reduced level of at least one CP1 and/or CP2 activity as compared to a control level of at least one CP1 and/or CP2 activity.

85. The method of aspect 84, wherein the at least one of the CP1 and the CP2 activity is a level of proliferation of lymphoma cells.

86. The method of aspect 84, wherein the at least one of the CP1and the CP2 activity is the level of JAK/STAT/ISGF3 pathway activation in a lymphoma cell.

87. The method of aspect 84, wherein the at least one activity is a level of SEAP production in a lymphoma cell.

88. The method of aspect 84, wherein the ACC is characterized by at least a 2-fold reduction in at least one of the CP1 and the CP2 activity as compared to the control level.

89. The method of aspect 88, wherein the ACC is characterized by at least a 5-fold reduction in at least one CP1 and/or the CP2 activity as compared to the control level.

90. The method of aspect 89, wherein the ACC is characterized by at least a 10-fold reduction in at least one activity of the CP1 and/or the CP2 as compared to the control level.

91. The method of aspect 90, wherein the ACC is characterized by at least a 500-fold reduction in at least one CP1 and/or the CP2 activity as compared to the control level.

92. The method of any one of aspects 84-91, wherein the control level of the at least one activity of the CP1 and/or the CP2, is the activity of the CP1 and/or the CP2 in the ACC following exposure of the ACC to the protease(s).

93. The method of any one of aspects 84-92, wherein the control level of the at least one CP1 and/or CP2, is the corresponding CP1 and/or the CP2 activity of a corresponding wildtype mature cytokine.

94. The method of any one of aspects 84-93, wherein the ACC is characterized by generating a cleavage product following exposure to the protease(s), wherein the cleavage product comprises the at least one activity of the CP1 and/or the CP2.

95. The method of aspect 94, wherein the at least one activity of the CP1 and/or the CP2 is anti-proliferation activity.

96. The method of aspect 95, wherein the control level is an EC50 value, and wherein ratio of EC50 (cleavage product) to EC50 (control level) is less than about 10, or less than about 9, or less than about 8, or less than about 7, or less than about 6, or less than about 5, or less than about 4, or less than about 3, or less than about 2, or less than about 1.5, or less than about 1.0.

97. The method of any one of aspects 84-96, wherein the at least one of the CP1 and the CP2 activity is a binding affinity of the CP1 and/or the CP2 for its cognate receptor as determined using surface plasmon resonance.

98. A method of treating a subject in need thereof comprising administering a combination of an activatable cytokine construct (ACC) and a PD-1/PD-L1 pathway inhibitor to the subject, wherein the ACC comprises a first monomer construct and a second monomer construct, wherein:

(a) the first monomer construct is a polypeptide comprising a first peptide mask (PM1), a first mature cytokine protein (CP1), a first and a third cleavable moieties (CM1 and CM3), and a first dimerization domain (DD1);

(b) the second monomer construct is a polypeptide comprising a second peptide mask (PM2), a second mature cytokine protein (CP2), a second and a fourth cleavable moieties (CM2 and CM4), and a second dimerization domain (DD2);

(c) the first monomer construct comprises, in an N- to C- terminal direction, the PM1, the CM3, the CP1, the CM1, and the DD1;

and

(d) the ACC is characterized by having a reduced level of interferon activity as compared to a corresponding wildtype interferon or a corresponding pegylated interferon.

99. The method of aspect 98, wherein the ACC is further characterized by at least one of:

(i) the PM1 comprises no more than 20 amino acids and binds to the CP1;

(ii) the CM1 and the DD1 directly abut each other;

(iii) the CP1 and the CM1 directly abut each other;

(iv) the CM1 comprises no more than 12 amino acids;

(v) the CM1 and the CM3 each functions as a substrate for a protease; and

(vi) the CP1 is a mature interferon.

100. The method of aspect 98 or aspect 99, wherein

(i) the DD1 and the DD2 are a pair of human IgG Fc domains;

(ii) the DD1 and the DD2 bind to each other via at least one disulfide bond, thereby forming a homodimer of the first monomer construct and the second monomer construct; or

(iii) both (i) and (ii).

101. The method of any one of aspects 98-100, wherein the CP1 is a mature interferon-alpha and the PM1 comprises a sequence that is at least 85% identical to SEQ ID NO: 292.

102. The method of any one of aspects 98-101, wherein the CM1 and the CM3 each independently functions as a substrate of urokinase (uPa) and/or a matrix metalloproteinase (MMP).

103. The method of aspect 102, wherein the CM1 and the CM3 each independently functions as a substrate of urokinase (uPa) and/or MMP-14.

104. The method of any one of aspects 99-103, wherein the mature interferon is a mature human interferon alpha.

105. The method of any one of aspects 99-104, wherein the mature interferon alpha is mature interferon alpha-2b.

106. The method of any one of aspects 99-105, wherein the mature interferon alpha is a truncated form of a wildtype mature interferon alpha-2b.

107. The method of any one of aspects 99-106, wherein the mature interferon comprises a sequence that is at least 95% identical to SEQ ID NO: 1.

108. The method of any one of aspects 99-107, wherein the mature interferon comprises the sequence of SEQ ID NO: 1.

109. The method of any one of aspects 99-108, wherein the CM1 and the CM3 each comprises no more than 8 amino acids.

110. The method of any one of aspects 99-109, wherein the CM1 and the CM3 are the same.

111. The method of any one of aspects 99-110, wherein the CM1 and the CM3 each comprises a sequence that is at least 85% identical to SEQ ID NO: 41.

112. The method of any one of aspects 99-111, wherein the CM1 and the CM3 each comprises a sequence selected from the group consisting of SEQ ID NO: 41, SEQ ID NO: 68, and SEQ ID NO: 100.

113. The method of any one of aspects 99-112, wherein the DD1 and the DD2 are a pair of human IgG4 Fc domains.

114. The method of aspect 113, wherein the DD1 and the DD2 are a pair of human IgG4 Fc domains truncated at N-terminus to Cysteine 226 as numbered by EU numbering.

115. The method of aspect 113 or 114, wherein the human IgG4 Fc domains comprise a S228P mutation as numbered by EU numbering.

116. The method of any one of aspects 99-115, wherein the DD1 and the DD2 each comprises a sequence that is at least 95% identical to SEQ ID NO: 3.

117. The method of any one of aspects 99-116, wherein the DD1 and the DD2 each comprises the sequence of SEQ ID NO: 3.

118. The method of any one of aspects 99-117, wherein the first and second monomer constructs are covalently bound to each other via at least two disulfide bonds.

119. The method of aspect 118, wherein the first and second monomer constructs are covalently bound to each other via at least three disulfide bonds.

120. The method of any one of aspects 99-119, wherein:

the first monomer construct further comprises a first signal sequence at the N-terminus, and the second monomer construct further comprises a second signal sequence at the N-terminus.

121. The method of aspect 120, wherein the first and second signal sequences each comprises a sequence that is at least 95% identical to SEQ ID NO: 470.

122. The method of aspect 121, wherein the first and second signal sequences each comprises the sequence of SEQ ID NO: 470.

123. The method of any one of aspects 120-122, wherein:

the first monomer construct further comprises a first spacer positioned between the first signal sequence and the PM1, and the second monomer construct further comprises a second spacer positioned between the second signal sequence and the PM2.

124. The method of aspect 123, wherein the first and second spacers each comprises a sequence that is at least 80% identical to SEQ ID NO: 480.

125. The method of aspect 124, wherein the first and second spacers each comprises a sequence of SEQ ID NO: 480.

126. The method of any one of aspects 99-125, further comprising a linker L1 between the PM1 and the CM3, and/or a linker L2 between the CM3 and the CP1, wherein each of L1 and L2 independently comprises a sequence that is at least 80% identical to SEQ ID NO: 27 (wherein n=1), a sequence that is at least 80% identical to SEQ ID NO: 293, or is absent.

127. The method of aspect 126, wherein the L1 comprises the sequence SEQ ID NO: 27 (wherein n=1) and L2 comprises the sequence of SEQ ID NO: 293.

128. The method of any one of aspects 99-127, comprising a Linking Region comprising no more than 12 amino acids.

129. The method of aspect 128, wherein the Linking Region comprises 7 to 12 amino acids.

130. The method of aspect 129, wherein the Linking Region comprises 7 amino acids.

131. The method of any one of aspects 99-130, wherein the ACC is characterized by at least a 2000-fold reduction in interferon alpha activity as compared to wildtype interferon alpha.

132. The method of aspect 131, wherein the ACC is characterized by at least a 4000-fold reduction in interferon alpha activity as compared to wildtype interferon alpha.

133. The method of aspect 132, wherein the ACC is characterized by at least a 5000-fold reduction in interferon alpha activity as compared to wildtype interferon alpha.

134. The method of any one of aspects 99-130, wherein the ACC is characterized by at least a 2000-fold reduction in interferon alpha activity as compared to pegylated interferon alpha.

135. The method of any one of aspects 99-134, wherein the reduction in interferon activity is determined by comparing the EC50 of the ACC with the EC50 of the wildtype interferon or the pegylated interferon in an anti-proliferation assay in lymphoma cells.

136. The method of any one of aspects 99-135, wherein the reduction in interferon activity is determined by comparing the EC50 of the ACC with the EC50 of the wildtype interferon or the pegylated interferon in an assay of induction of secreted embryonic alkaline phosphatase production in interferon-responsive HEK293 cells.

137. The method of any of aspects 99-136, wherein the ACC is further characterized by generating a cleavage product following exposure to the protease(s) for which CM1 and CM3 function as a substrate, wherein the ratio of the interferon activity of the corresponding wildtype interferon to the cleavage product is less than about 2.

138. The method of aspect 137, wherein the EC50 of the cleavage product is approximately the same as the EC50 of the corresponding wildtype interferon.

139. The method of aspect 99, wherein the first and second monomer constructs each comprises a sequence that is at least 95% identical to SEQ ID NO: 290, wherein the ACC is characterized by at least a 1000-fold reduction in interferon activity as compared to wildtype interferon alpha-2b, and wherein the ACC is further characterized by generating a cleavage product following exposure to uPA, wherein the cleavage product has approximately the same interferon activity as wildtype interferon alpha-2b, wherein interferon activity is measured in an anti-proliferation assay in lymphoma cells or in an assay of induction of secreted embryonic alkaline phosphatase production in interferon-responsive HEK293 cells.

140. A method of treating a subject in need thereof comprising administering a combination of an activatable cytokine construct (ACC) and a PD-1/PD-L1 pathway inhibitor to the subject, wherein the ACC comprises a first monomer construct and a second monomer construct, wherein:

(a) the first monomer construct comprises a first peptide mask (PM1), a first mature cytokine protein (CP1), a first and a third cleavable moieties (CM1 and CM3), and a first dimerization domain (DD1);

(b) the second monomer construct is a polypeptide comprising a second peptide mask (PM2), a second mature cytokine protein (CP2), a second and a fourth cleavable moieties (CM2 and CM4), and a second dimerization domain (DD2);

(c) the first monomer construct is a polypeptide comprising, in an N- to C- terminal direction, the PM1, the CM3, the CP1, the CM1, and the DD1, further wherein:

(i) the PM1 comprises a sequence that is at least 85% identical to SEQ ID NO: 292,

(ii) the CM1 and the DD1 directly abut each other,

(iii) the CM1 comprises a sequence that is at least 85% identical to SEQ ID NO: 41, and

(iv) the CP1 comprises a sequence that is at least 85% identical to SEQ ID NO: 1;

(d) further wherein:

(i) the second monomer construct is the same as the first monomer construct,

(ii) the DD1 and DD2 are a pair of human IgG4 Fc domains;

(e) the DD1 and the DD2 covalently bind to each other via at least one disulfide bond, thereby forming a homodimer of the first monomer construct and the second monomer construct; and

(f) the ACC is characterized by having a reduced level of interferon alpha activity as compared to the interferon alpha activity of PEGylated interferon alpha-2b.

141. The method of aspect 140, wherein the first and second monomer constructs each comprises a sequence that is at least 95% identical to SEQ ID NO: 290 or wherein each of the first and second monomer constructs comprises the sequence of SEQ ID NO: 290, wherein the ACC exhibits lower toxicity in vivo compared to either wildtype interferon alpha-2b or PEGylated interferon alpha-2b.

142. The method of any one of aspects 1-141, wherein the CM1 and the CM3 each functions as a substrate for a protease that is over-expressed in a tumor tissue.

143. The method of any one of aspects 1-142, wherein the PD1/PD-L1 pathway inhibitor is selected from a PD-1 antibody, an activatable PD-1 antibody, a PD-L1 antibody, or an activatable PD-L1 antibody.

144. The method of aspect 143, wherein the activatable PD-1 antibody or the activatable PD-L1 antibody comprises: (i) an antibody or an antigen binding fragment thereof (AB) that specifically binds to PD-1 or PD-L1; (ii) a masking moiety (MM) that, when the activatable antibody is in an uncleaved state, inhibits the binding of the AB to PD-1 or PD-L1; and (iii) a cleavable moiety (CM) coupled to the AB, wherein the CM is a polypeptide that functions as a substrate for a protease; and optionally a first linking peptide and/or a second linking peptide.

145. The method of any one of aspects 1-142, wherein the PD1/PD-L1 pathway inhibitor comprises nivolumab, pembrolizumab, tislelizumab, spartalizumab, camrelizumab, cetrelimab, Balstilimab, Dostarlimab, Prolgolimab, Sasanlimab, zimberelimab, Atezolizumab, Avelumab, Durvalumab, adebrelimab, Lodapolimab, Envafolimab, Cosibelimab, budigalimab, ezabenlimab, finotonlimab, geptanolimab, lodapolimab, penpulimab, pimivalimab, pucotenlimab, serplulimab. Sintilimab, toripalimab, zeluvalimab, iparomlimab, nofazinlimab, rulonilimab, garivulimab, manelimab, opucolimab, sudubrilimab, sugemalimab, socazolimab, or tagitanlimab.

146. The method of any one of aspects 1-142 or 145, wherein the PD1/PD-L1 pathway inhibitor comprises pacmilimab (CX-072), CX-075, CX-171, or CX-188.

147. The method of any one of aspects 1-146, wherein the subject is in need of reducing, inhibiting, and/or delaying the onset or progression of PD-1 or PD-L1 in the subject.

148. The method of any one of aspects 1-146, wherein the subject is in need of alleviating a symptom associated with aberrant expression and/or activity of PD-1 or PD-L1 in the subject.

149. The method of any one of aspects 1-148, wherein the subject has been identified or diagnosed as having a cancer.

150. The method of aspect 149, wherein the cancer is a lymphoma.

151. The method of aspect 150, wherein the lymphoma is Burkitt's lymphoma.

152. The method of any one of aspects 1-151, wherein the method comprises augmenting or potentiating therapeutic efficacy and/or therapeutic index relative to a conventional cytokine therapy in the subject.

153. The method of any one of aspects 1-151, wherein the method comprises augmenting or potentiating therapeutic efficacy and/or therapeutic index relative to a conventional PD1/PDL1 inhibitor therapy in the subject.

154. The method of any one of aspects 1-151, wherein the method comprises augmenting or potentiating therapeutic efficacy and/or therapeutic index relative to a conventional cytokine and PD1/PDL1 inhibitor combination therapy in the subject.

155. The method of any one of aspects 1-149, wherein the method comprises augmenting or potentiating therapeutic efficacy and/or therapeutic index relative to administering the ACC alone.

156. A combination or composition comprising the ACC and the PD-1/PD-L1 pathway inhibitor as aspected in any one of aspects 1-148.

157. The combination or composition of aspect 156, wherein the combination or composition is a pharmaceutical composition.

158. The combination or composition of aspect 156, wherein the combination or composition is for use in therapy.

159. The combination of composition of aspect 156, wherein the combination or composition is for use in treating cancer.

160. The combination or composition of aspect 156, wherein the combination or composition is for use in treating an infection.

161. A container, vial, syringe, injector pen, or kit comprising at least one dose of the combination or composition of aspects 156-160.

162. A method of treating a subject in need thereof comprising administering a combination of an activatable cytokine construct (ACC) and a PD-1/PD-L1 pathway inhibitor to the subject, wherein the ACC includes a first monomer construct and a second monomer construct, wherein:

(a) the first monomer construct comprises a first mature cytokine protein (CP1), a first cleavable moiety (CM1), and a first dimerization domain (DD1),

wherein the CM1 is positioned between the CP1 and the DD1; and

(b) the second monomer construct comprises a second mature cytokine protein (CP2), a second cleavable moiety (CM2), and a second dimerization domain (DD2),

wherein the CM2 is positioned between the CP2 and the DD2; or

(a) the first monomer construct comprises a first mature cytokine protein (CP1), a first dimerization domain (DD1), and

(b) the second monomer construct comprises a second mature cytokine protein (CP2), a cleavable moiety (CM), and a second dimerization domain (DD2), wherein the CM is positioned between the CP2 and the DD2, wherein the CM functions as a substrate for a protease; or

(a) the first monomer construct comprises a first mature cytokine protein (CP1), a cleavable moiety (CM), and a first dimerization domain (DD1), wherein the CM is positioned between the CP1 and the DD1, and

(b) the second monomer construct comprises a second mature cytokine protein (CP2), and a second dimerization domain (DD2),

wherein the CM functions as a substrate for a protease; or

(a) the first monomer construct comprises a first mature cytokine protein (CP1), and a first dimerization domain (DD1), and

(b) the second monomer construct comprises a second mature cytokine protein (CP2), and a second dimerization domain (DD2), wherein the CP1, the CP2, or both CP1 and CP2 include(s) an amino acid sequence that functions as a substrate for a protease;

further wherein (c) the DD1 and the DD2 bind each other thereby forming a dimer of the first monomer construct and the second monomer construct; and

further wherein (d) the ACC is characterized by having a reduced level of at least one CP1 and/or CP2 activity as compared to a control level of the at least one CP1 and/or CP2 activity.

163. The method of aspect 162, wherein the first monomer construct comprises a first polypeptide that comprises the CP1, the CM1, and the DD1.

164. The method of aspect 162 or 163, wherein the second monomer construct comprises a second polypeptide that comprises the CP2, the CM2, and the DD2.

165. The method of any one of aspects 162-164, wherein the DD1 and the DD2 are a pair selected from the group consisting of: a pair of Fc domains, a sushi domain from an alpha chain of human IL-15 receptor (IL15Rα) and a soluble IL-15; barnase and barnstar; a PKA and an AKAP; adapter/docking tag modules based on mutated RNase I fragments; an epitope and sdAb; an epitope and scFv; and SNARE modules based on interactions of the proteins syntaxin, synaptotagmin, synaptobrevin, and SNAP25, an antigen-binding domain and an epitope.

166. The method of any one of aspects 162-165, wherein the DD1 and the DD2 are a pair of Fc domains.

167. The method of aspect 166, wherein the pair of Fc domains is a pair of human Fc domains.

168. The method of aspect 167, wherein the human Fc domains are human IgG1 Fc domains, human IgG2 Fc domains, human IgG3 Fc domains, or human IgG4 Fc domains.

169. The method of aspect 168, wherein the human Fc domains are human IgG4 Fc domains.

170. The method of aspect 167, wherein the human Fc domains comprise a sequence that is at least 80% identical to SEQ ID NO: 3.

171. The method of aspect 167, wherein the human Fc domains comprise a sequence that is at least 90% identical to SEQ ID NO: 3.

172. The method of aspect 167, wherein the human Fc domains comprise SEQ ID NO: 3.

173. The method of aspect 162, wherein the DD1 and the DD2 comprise SEQ ID NOs: 287 and 288, respectively.

174. The method of any one of aspects 162-173, wherein the DD1 and the DD2 are the same.

175. The method of aspect 165, wherein the DD1 comprises an antigen-binding domain and DD2 comprises a corresponding epitope.

176. The method of aspect 175, wherein the antigen-binding domain is an anti-His tag antigen-binding domain and wherein the DD2 comprises a His tag.

177. The method of aspect 175, wherein the antigen-binding domain is a single chain variable fragment (scFv).

178. The method of aspect 175, wherein the antigen-binding domain is a single domain antibody (sdAb).

179. The method of aspect 165, wherein at least one of the DD1 and the DD2 comprises a dimerization domain substituent selected from the group consisting of a non-polypeptide polymer and a small molecule.

180. The method of aspect 179, wherein the DD1 and the DD2 comprise non-polypeptide polymers covalently bound to each other.

181. The method of aspect 180, wherein the non-polypeptide polymer is a sulfur-containing polyethylene glycol, and wherein the DD1 and the DD2 are covalently bound to each other via one or more disulfide bonds.

182. The method of aspect 179, wherein at least one of the DD1 and the DD2 comprises a small molecule.

183. The method of aspect 182, wherein the small molecule is biotin.

184. The method of aspect 183, wherein DD1 comprises biotin and DD2 comprises an avidin.

185. The method of any one of aspects 162-184, wherein the CP1 and the CP2 are mature cytokines.

186. The method of any one of aspects 162-184, wherein the CP1 and the CP2 comprise a signal peptide.

187. The method of any one of aspects 162-186, wherein the CP1 and the CP2 are the same.

188. The method of any one of aspects 162-186, wherein the CP1 and the CP2 are different.

189. The method of any one of aspects 162-186, wherein the CP1 and/or the CP2 is/are an interferon.

190. The method of aspect 189, wherein the CP1 and the CP2 are an interferon.

191. The method of aspect 189, wherein the CP1 and the CP2 are different interferons.

192. The method of aspect 189, wherein the CP1 and the CP2 are the same interferon.

193. The method of any one of aspects 189-192, wherein the interferon(s) is/are a human wildtype mature interferon.

194. The method of any one of aspects 189-193, wherein the interferon(s) is/are selected from the group consisting of: interferon-alpha, interferon-beta, interferon-omega, and interferon-tau.

195. The method of aspect 194, wherein the interferons is/are an interferon-alpha.

196. The method of aspect 195, wherein the interferon(s) is/are selected from the group consisting of: interferon alpha-2a, interferon alpha-2b, and interferon alpha-n3.

197. The method of aspect 196, wherein the interferon(s) is/are interferon alpha-2b.

198. The method of aspect 197, wherein the CP1 and/or the CP2 comprises a sequence that is at least 80% identical to SEQ ID NO: 1.

199. The method of aspect 198, wherein the CP1 and/or the CP2 comprises a sequence that is at least 90% identical to SEQ ID NO: 1.

200. The method of aspect 199, wherein the CP1 and/or the CP2 comprises the sequence of SEQ ID NO: 1.

201. The method of aspect 194, wherein the interferon is an interferon beta.

202. The method of aspect 201, wherein the interferon beta is selected from the group consisting of interferon beta-1a, and interferon beta-1b.

203. The method of any one of aspects 162-202, wherein the CP1 and/or the CP2 comprises an IFab domain.

204. The method of any one of aspects 162-189, wherein the CP1 and/or the CP2 comprises an interleukin.

205. The method of aspect 204, wherein the interleukin is selected from the group consisting of IL-1α, IL-1β, IL-1RA, IL-18, IL-2, IL-4, IL-7, IL-9, IL-13, IL-15, IL-3, IL-5, IL-6, IL-11, IL-12, IL-10, IL-20, IL-21, IL-14, IL-16, and IL-17.

206. The method of any one of aspects 162-205, wherein each of the CM1 and the CM2 comprises a total of about 3 amino acids to about 15 amino acids.

207. The method of any one of aspects 162-206, wherein one or more of the CM1, the CM2, the CM3, and the CM4 comprise substrates for different proteases.

208. The method of any one of aspects 162-207, wherein the CM1, the CM2, and the CM3 comprise substrates for the same protease.

209. The method of any one of aspects 162-208, wherein the protease(s) is/are selected from the group consisting of: ADAM8, ADAM9, ADAM10, ADAM12, ADAM15, ADAM17/TACE, ADAMDEC1, ADAMTS1, ADAMTS4, ADAMTS5, BACE, Renin, Cathepsin D, Cathepsin E, Caspase 1, Caspase 2, Caspase 3, Caspase 4, Caspase 5, Caspase 6, Caspase 7, Caspase 8, Caspase 9, Caspase 10, Caspase 14, Cathepsin B, Cathepsin C, Cathepsin K, Cathespin L, Cathepsin S, Cathepsin V/L2, Cathepsin X/Z/P, Cruzipain, Legumain, Otubain-2, KLK4, KLK5, KLK6, KLK7, KLK8, KLK10, KLK11, KLK13, KLK14, Meprin, Neprilysin, PSMA, BMP-1, MMP-1, MMP-2, MMP-3, MMP-7, MMP-9, MMP-10, MMP-11, MMP-12, MMP-13, MMP-14, MMP-15, MMP-16, MMP-17, MMP-19, MMP-20, MMP-23, MMP-24, MMP-26, MMP-27, activated protein C, cathepsin A, cathepsin G, Chymase, FVIIa, FIXa, FXa, FXIa, FXIIa, Elastase, Granzyme B, Guanidinobenzoatase, HtrA1, human neutrophil lyase, lactoferrin, marapsin, NS3/4A, PACE4, Plasmin, PSA, tPA, thrombin, tryptase, uPA, DESC1, DPP-4, FAP, Hepsin, Matriptase-2, MT-SP1/Matripase, TMPRSS2, TMPRSS3, and TMPRSS4.

210. The method of aspect 209, wherein the protease(s) is/are selected from the group consisting of: uPA, legumain, MT-SP1, ADAM17, BMP-1, TMPRSS3, TMPRSS4, MMP-2, MMP-9, MMP-12, MMP-13, and MMP-14.

211. The method of any one or combination of aspect 162-208, wherein the CM1, CM2, CM3, and/or the CM4 comprise a sequence selected from the group consisting of: LSGRSDNH (SEQ ID NO: 5), TGRGPSWV (SEQ ID NO: 6), PLTGRSGG (SEQ ID NO: 7), TARGPSFK (SEQ ID NO: 8), NTLSGRSENHSG (SEQ ID NO: 9), NTLSGRSGNHGS (SEQ ID NO: 10), TSTSGRSANPRG (SEQ ID NO: 11), TSGRSANP (SEQ ID NO: 12), VHMPLGFLGP (SEQ ID NO: 13), AVGLLAPP (SEQ ID NO: 14), AQNLLGMV (SEQ ID NO: 15), QNQALRMA (SEQ ID NO: 16), LAAPLGLL (SEQ ID NO: 17), STFPFGMF (SEQ ID NO: 18), ISSGLLSS (SEQ ID NO: 19), PAGLWLDP (SEQ ID NO: 20), VAGRSMRP (SEQ ID NO: 21), VVPEGRRS (SEQ ID NO: 22), ILPRSPAF (SEQ ID NO: 23), MVLGRSLL (SEQ ID NO: 24), QGRAITFI (SEQ ID NO: 25), SPRSIMLA (SEQ ID NO: 26), SMLRSMPL (SEQ ID NO: 27), ISSGLLSGRSDNH (SEQ ID NO: 28), AVGLLAPPGGLSGRSDNH (SEQ ID NO: 29), ISSGLLSSGGSGGSLSGRSDNH

(SEQ ID NO: 30), LSGRSGNH (SEQ ID NO: 31), SGRSANPRG (SEQ ID NO: 32), LSGRSDDH (SEQ ID NO: 33), LSGRSDIH (SEQ ID NO: 34), LSGRSDQH (SEQ ID NO: 35), LSGRSDTH (SEQ ID NO: 36), LSGRSDYH (SEQ ID NO: 37), LSGRSDNP (SEQ ID NO: 38), LSGRSANP (SEQ ID NO: 39), LSGRSANI (SEQ ID NO: 40), LSGRSDNI (SEQ ID NO: 41), MIAPVAYR (SEQ ID NO: 42), RPSPMWAY (SEQ ID NO: 43), WATPRPMR (SEQ ID NO: 44), FRLLDWQW (SEQ ID NO: 45), ISSGL (SEQ ID NO: 46), ISSGLLS (SEQ ID NO: 47), ISSGLL (SEQ ID NO: 48), ISSGLLSGRSANPRG (SEQ ID NO: 49), AVGLLAPPTSGRSANPRG (SEQ ID NO: 50), AVGLLAPPSGRSANPRG (SEQ ID NO: 51), ISSGLLSGRSDDH (SEQ ID NO: 52), ISSGLLSGRSDIH (SEQ ID NO: 53), ISSGLLSGRSDQH (SEQ ID NO: 54), ISSGLLSGRSDTH (SEQ ID NO: 55), ISSGLLSGRSDYH (SEQ ID NO: 56), ISSGLLSGRSDNP (SEQ ID NO: 57), ISSGLLSGRSANP (SEQ ID NO: 58), ISSGLLSGRSANI (SEQ ID NO: 59), AVGLLAPPGGLSGRSDDH (SEQ ID NO: 60), AVGLLAPPGGLSGRSDIH (SEQ ID NO: 61), AVGLLAPPGGLSGRSDQH (SEQ ID NO: 62), AVGLLAPPGGLSGRSDTH (SEQ ID NO: 63), AVGLLAPPGGLSGRSDYH (SEQ ID NO: 64), AVGLLAPPGGLSGRSDNP (SEQ ID NO: 65), AVGLLAPPGGLSGRSANP (SEQ ID NO: 66), AVGLLAPPGGLSGRSANI (SEQ ID NO: 67), ISSGLLSGRSDNI (SEQ ID NO: 68), AVGLLAPPGGLSGRSDNI (SEQ ID NO: 69), GLSGRSDNHGGAVGLLAPP (SEQ ID NO: 70), GLSGRSDNHGGVHMPLGFLGP (SEQ ID NO: 71), LSGRSDNHGGVHMPLGFLGP (SEQ ID NO: 72), ISSGLSS (SEQ ID NO: 73), PVGYTSSL (SEQ ID NO: 74), DWLYWPGI (SEQ ID NO: 75), LKAAPRWA (SEQ ID NO: 76), GPSHLVLT (SEQ ID NO: 77), LPGGLSPW (SEQ ID NO: 78), MGLFSEAG (SEQ ID NO: 79), SPLPLRVP (SEQ ID NO: 80), RMHLRSLG (SEQ ID NO: 81), LLAPSHRA (SEQ ID NO: 82), GPRSFGL (SEQ ID NO: 83), GPRSFG (SEQ ID NO: 84), SARGPSRW (SEQ ID NO: 85), GGWHTGRN (SEQ ID NO: 86), HTGRSGAL (SEQ ID NO: 87), AARGPAIH (SEQ ID NO: 88), RGPAFNPM (SEQ ID NO: 89), SSRGPAYL (SEQ ID NO: 90), RGPATPIM (SEQ ID NO: 91), RGPA (SEQ ID NO: 92), GGQPSGMWGW (SEQ ID NO: 93), FPRPLGITGL (SEQ ID NO: 94), SPLTGRSG (SEQ ID NO: 95), SAGFSLPA (SEQ ID NO: 96),

LAPLGLQRR (SEQ ID NO: 97), SGGPLGVR (SEQ ID NO: 98), PLGL (SEQ ID NO: 99), and SGRSDNI (SEQ ID NO: 100).

212. The method of aspect 211, wherein the CM1, the CM2, the CM3 and/or the CM4 comprises a sequence selected from the group consisting of: ISSGLLSGRSDNH (SEQ ID NO: 28), LSGRSDDH (SEQ ID NO: 33), ISSGLLSGRSDQH (SEQ ID NO: 54), SGRSDNI (SEQ ID NO: 100), and ISSGLLSGRSDNI (SEQ ID NO: 68).

213. The method of any one of aspects 162-211, wherein the protease(s) is/are produced by a tumor in a subject.

214. The method of aspect 213, wherein the subject has been diagnosed or identified as having a cancer.

215. The method of any one of aspects 162-214, wherein the CP1 and the CM1 directly abut each other in the first monomer construct.

216. The method of any one of aspects 162-215, wherein the CM1 and the DD1 directly abut each other in the first monomer construct.

217. The method of any one of aspects 162-217, wherein the CP2 and the CM2 directly abut each other in the second monomer construct.

218. The method of any one of aspects 162-217, wherein the CM2 and the DD2 directly abut each other in the second monomer construct.

219. The method of any one of aspects 162-214, wherein the first monomer construct comprises at least one linker.

220. The method of aspect 219, wherein the at least one linker is a linker L1 disposed between the PM1 and the CM3 and/or a linker L2 disposed between the CM3 and the CP1.

221. The method of aspect 219, wherein the second monomer construct comprises at least one linker.

222. The method of aspect 221, wherein the at least one linker is a linker L3 disposed between the PM2 and the CM4 and/or a linker L4 disposed between the CM4 and the CP2.

223. The method of aspect 222, wherein the first monomer construct comprises a linker L1 and the second monomer construct comprises a linker L3.

224. The method of aspect 223, wherein L1 and L3 are the same.

225. The method of aspect 222, wherein the first monomer construct comprises a linker L2 and the second monomer construct comprises a linker L4.

226. The method of aspect 225, wherein L2 and L4 are the same.

227. The method of any one of aspects 219-226, wherein each linker has a total length of 1 amino acid to about 15 amino acids.

228. The method of aspect 227, wherein each linker has a total length of at least 5 amino acids.

229. The method of any one of aspects 219-225, wherein each linker is independently selected from the group consisting of GSSGGSGGSGG (SEQ ID NO: 210); GGGS (SEQ ID NO: 2); GGGSGGGS (SEQ ID NO: 211); GGGSGGGSGGGS (SEQ ID NO: 212); GGGGSGGGGSGGGGS (SEQ ID NO: 213); GGGGSGGGGSGGGGSGGGGSGGGGS (SEQ ID NO: 214); GGGGSGGGGS (SEQ ID NO: 215); GGGGS (SEQ ID NO: 216); GS; GGGGSGS (SEQ ID NO: 217); GGGGSGGGGSGGGGSGS (SEQ ID NO: 218); GGSLDPKGGGGS (SEQ ID NO: 219); PKSCDKTHTCPPCPAPELLG (SEQ ID NO: 220); SKYGPPCPPCPAPEFLG (SEQ ID NO: 221); GKSSGSGSESKS (SEQ ID NO: 222); GSTSGSGKSSEGKG (SEQ ID NO: 223); GSTSGSGKSSEGSGSTKG (SEQ ID NO: 224); GSTSGSGKPGSGEGSTKG (SEQ ID NO: 225); GSTSGSGKPGSSEGST (SEQ ID NO: 226); (GS)n, (GGS)n, (GSGGS)n (SEQ ID NO: 227), (GGGS)n (SEQ ID NO: 228), (GGGGS)n (SEQ ID NO: 216), wherein each n is an integer of at least one; GGSG (SEQ ID NO: 229); GGSGG (SEQ ID NO: 230); GSGSG (SEQ ID NO: 231; GSGGG (SEQ ID NO: 232); GGGSG (SEQ ID NO: 233); GSSSG (SEQ ID NO: 234); GGGGSGGGGSGGGGS (SEQ ID NO: 213); GGGGSGGGGSGGGGSGGGGS (SEQ ID NO: 214); GSTSGSGKPGSSEGST (SEQ ID NO: 226); SGGG (SEQ ID NO: 296); and SGGGG (SEQ ID NO: 459).

230. The method of aspect 229, wherein the linker comprises a sequence of GGGS (SEQ ID NO: 2).

231. The method of any one of aspects 162-230, wherein the first monomer construct comprises in a N- to C- terminal direction, the PM1, the CM3, the CP1, the CM1, and the DD1.

232. The method of any one of aspects 162-230, wherein the first polypeptide comprises in a C- to N-terminal direction, the PM1, the CM3, the CP1, the CM1, and the DD1.

233. The method of any one of aspects 162-232, wherein the second polypeptide comprises in a N- to C-terminal direction, the CP2, CM2, and the DD2.

234. The method of any one of aspects 162-233, wherein the second polypeptide comprises in a C- to N-terminal direction, the CP2, CM2, and the DD2.

235. The method of any one of aspects 162-187, 189, 190, or 192-234, wherein the first monomer construct and the second monomer construct are the same.

236. The method of any one of aspects 162-230, wherein the first monomer construct comprises in a N- to C- terminal direction, the PM1, an optional linker, the CM3, an optional linker, the CP1, the CM1, and the DD1, wherein the CP1 and the CM1 directly abut each other, wherein the CM1 and the DD1 directly abut each other, wherein the CM1 is a peptide of not more than 10 amino acids, wherein the second monomer construct is the same as the first monomer construct, and wherein the first and second monomer constructs are covalently bound to each other via at least two disulfide bonds.

237. The method of aspect 236, wherein the DD1 and the DD2 are each a human Fc domain having an N-terminus at Cysteine 216, as numbered according to EU numbering.

238. The method of aspect 236 or 237, wherein the CM1 is a peptide of not more than 7 amino acids.

239. The method of any one or combination of aspect 236-238, wherein the CP1 and the CP2 comprise an amino acid sequence that is at least 90% identical to SEQ ID NO: 1.

240. The method of any one of aspects 162-239, wherein the ACC is characterized by having a reduced level of at least one CP1 and/or CP2 activity as compared to a control level of at least one CP1 and/or CP2 activity.

241. The method of aspect 240, wherein the at least one of the CP1 and the CP2 activity is a level of proliferation of lymphoma cells.

242. The method of aspect 240, wherein the at least one of the CP1and the CP2 activity is the level of JAK/STAT/ISGF3 pathway activation in a lymphoma cell.

243. The method of aspect 240, wherein the at least one activity is a level of SEAP production in a lymphoma cell.

244. The method of aspect 240, wherein the ACC is characterized by at least a 2-fold reduction in at least one of the CP1 and the CP2 activity as compared to the control level.

245. The method of aspect 244, wherein the ACC is characterized by at least a 5-fold reduction in at least one CP1 and/or the CP2 activity as compared to the control level.

246. The method of aspect 245, wherein the ACC is characterized by at least a 10-fold reduction in at least one activity of the CP1 and/or the CP2 as compared to the control level.

247. The method of aspect 246, wherein the ACC is characterized by at least a 500-fold reduction in at least one CP1 and/or the CP2 activity as compared to the control level.

248. The method of any one of aspects 240-247, wherein the control level of the at least one activity of the CP1 and/or the CP2, is the activity of the CP1 and/or the CP2 in the ACC following exposure of the ACC to the protease(s).

249. The method of any one of aspects 240-248, wherein the control level of the at least one CP1 and/or CP2, is the corresponding CP1 and/or the CP2 activity of a corresponding wildtype mature cytokine.

250. The method of any one of aspects 240-249, wherein the ACC is characterized by generating a cleavage product following exposure to the protease(s), wherein the cleavage product comprises the at least one activity of the CP1 and/or the CP2.

251. The method of aspect 250, wherein the at least one activity of the CP1 and/or the CP2 is anti-proliferation activity.

252. The method of aspect 251, wherein the control level is an EC50 value, and wherein ratio of EC50 (cleavage product) to EC50 (control level) is less than about 10, or less than about 9, or less than about 8, or less than about 7, or less than about 6, or less than about 5, or less than about 4, or less than about 3, or less than about 2, or less than about 1.5, or less than about 1.0.

253. The method of any one of aspects 240-252, wherein the at least one of the CP1 and the CP2 activity is a binding affinity of the CP1 and/or the CP2 for its cognate receptor as determined using surface plasmon resonance.

254. The method of aspect 162, wherein the first and second monomer constructs each comprises a sequence that is at least 95% identical to SEQ ID NO: 290 or wherein each of the first and second monomer constructs comprises the sequence of SEQ ID NO: 290, wherein the ACC exhibits lower toxicity in vivo compared to either wildtype interferon alpha-2b or PEGylated interferon alpha-2b.

255. The method of any one of aspects 162-254, wherein the CM1 and the CM2 each functions as a substrate for a protease that is over-expressed in a tumor tissue.

256. The method of any one of aspects 162-255, wherein the PD1/PD-L1 pathway inhibitor is selected from a PD-1 antibody, an activatable PD-1 antibody, a PD-L1 antibody, or an activatable PD-L1 antibody.

257. The method of aspect 256, wherein the activatable PD-1 antibody or the activatable PD-L1 antibody comprises: (i) an antibody or an antigen binding fragment thereof (AB) that specifically binds to PD-1 or PD-L1; (ii) a masking moiety (MM) that, when the activatable antibody is in an uncleaved state, inhibits the binding of the AB to PD-1 or PD-L1; and (iii) a cleavable moiety (CM) coupled to the AB, wherein the CM is a polypeptide that functions as a substrate for a protease; and optionally a first linking peptide and/or a second linking peptide.

258. The method of any preceding aspect, wherein the PD1/PD-L1 pathway inhibitor comprises nivolumab, pembrolizumab, tislelizumab, spartalizumab, camrelizumab, cetrelimab, Balstilimab, Dostarlimab, Prolgolimab, Sasanlimab, zimberelimab, Atezolizumab, Avelumab, Durvalumab, adebrelimab, Lodapolimab, Envafolimab, Cosibelimab, budigalimab, ezabenlimab, finotonlimab, geptanolimab, lodapolimab, penpulimab, pimivalimab, pucotenlimab, serplulimab. Sintilimab, toripalimab, zeluvalimab, iparomlimab, nofazinlimab, rulonilimab, garivulimab, manelimab, opucolimab, sudubrilimab, sugemalimab, socazolimab, or tagitanlimab.

259. The method of any preceding aspect, wherein the PD1/PD-L1 pathway inhibitor comprises pacmilimab (CX-072), CX-075, CX-171, or CX-188.

260. The method of any preceding aspect, wherein the PD1/PD-L1 pathway inhibitor is a PD-1 pathway inhibitor, optionally a PD-1 antibody or an activatable PD-1 antibody, optionally wherein the PD-1 pathway inhibitor is an antibody comprising one or more sequences in Tables 7-9 of WO2017011580A2.

261. The method of any preceding aspect, wherein the PD1/PD-L1 pathway inhibitor is a PD-L1 pathway inhibitor, optionally a PD-L1 antibody or an activatable PD-L1 antibody, optionally wherein the PD-L1 pathway inhibitor is an antibody comprising one or more sequences in Tables 15-17 of WO2016149201A2.

262. The method of aspect 256, wherein the activatable PD-1 antibody or the activatable PD-L1 antibody comprises: (i) an antibody or an antigen binding fragment thereof (AB) that specifically binds to PD-1 or PD-L1; (ii) a masking moiety (MM) that, when the activatable antibody is in an uncleaved state, inhibits the binding of the AB to PD-1 or PD-L1; and (c) a cleavable moiety (CM) coupled to the AB, wherein the CM is a polypeptide that functions as a substrate for a protease; and optionally a first linking peptide and/or a second linking peptide.

263. The method of aspect 262, wherein the activatable anti-PD-1 antibody comprises a MM comprising an amino acid sequence selected from the group consisting of AMSGCSWSAFCPYLA (SEQ ID NO: 550), DVNCAIWYSVCITVP (SEQ ID NO: 551), LVCPLYALSSGVCMG (SEQ ID NO: 552), SVNCRIWSAVCAGYE (SEQ ID NO: 553), MLVCSLQPTAMCERV (SEQ ID NO: 554), APRCYMFASYCKSQY (SEQ ID NO: 555), VGPCELTPKPVCNTY (SEQ ID NO: 556), ETCNQYERSSGLCFA (SEQ ID NO: 557), APRTCYTYQCSSFYT (SEQ ID NO: 558), GLCSWYLSSSGLCVD (SEQ ID NO: 559), VPWCQLTPRVMCMWA (SEQ ID NO: 560), NWLDCQFYSECSVYG (SEQ ID NO: 561), SCPLYVMSSFGGCWD (SEQ ID NO: 562), MSHCWMFSSSCDGVK (SEQ ID NO: 563), VSYCTWLIEVICLRG (SEQ ID NO: 564), VLCAAYALSSGICGG (SEQ ID NO: 565), TTCNLYQQSSMFCNA (SEQ ID NO: 566), APRCYMFASYCKSQY (SEQ ID NO: 567), PCDQNPYFYPYVCHA (SEQ ID NO: 568), SVCPMYALSSMLCGA (SEQ ID NO: 569), LSVECYVFSRCSSLP (SEQ ID NO: 570), FYCTYLVSLTCHPQ (SEQ ID NO: 571), SMAGCQWSSFCVQRD (SEQ ID NO: 572), IYSCYMFASRCTSDK (SEQ ID NO: 573), SRCSVYEVSSGLCDW (SEQ ID

NO: 574), GMCSAYAYSSKLCTI (SEQ ID NO: 575), MTTNTCNLLCQQFLT (SEQ ID NO: 576), FQPCLMFASSCFTSK (SEQ ID NO: 577), WNCHPAGVGPVFCEV (SEQ ID NO: 578), ALCSMYLASSGLCNK (SEQ ID NO: 579), NYLSCQFFQNCYETY (SEQ ID NO: 580), GWCLFSDMWLGLCSA (SEQ ID NO: 581), EFCARDWLPYQCSSF (SEQ ID NO: 582), and TSYCSIEHYPCNTHH (SEQ ID NO: 583).

264. The method of aspect 262, wherein the activatable anti-PD-L1 antibody comprises a masking moiety (MM) comprising an amino acid sequence selected from the group consisting of YCEVSELFVLPWCMG (SEQ ID NO: 584), SCLMHPHYAHDYCYV (SEQ ID NO: 585), LCEVLMLLQHPWCMG (SEQ ID NO: 586), IACRHFMEQLPFCHH (SEQ ID NO: 587), FGPRCGEASTCVPYE (SEQ ID NO: 588), LYCDSWGAGCLTRP (SEQ ID NO: 589), GIALCPSHFCQLPQT (SEQ ID NO: 590), DGPRCFVSGECSPIG (SEQ ID NO: 591), LCYKLDYDDRSYCHI (SEQ ID NO: 592), PCHPHPYDARPYCNV (SEQ ID NO: 593), PCYWHPFFAYRYCNT (SEQ ID NO: 594), VCYYMDWLGRNWCSS (SEQ ID NO: 595), LCDLFKLREFPYCMG (SEQ ID NO: 596), YLPCHFVPIGACNNK (SEQ ID NO: 597), FCHMGVVVPQCANY (SEQ ID NO: 598), ACHPHPYDARPYCNV (SEQ ID NO: 599), PCHPAPYDARPYCNV (SEQ ID NO: 600), PCHPHAYDARPYCNV (SEQ ID NO: 601), PCHPHPADARPYCNV (SEQ ID NO: 602), PCHPHPYAARPYCNV (SEQ ID NO: 603), PCHPHPYDAAPYCNV (SEQ ID NO: 604), PCHPHPYDARPACNV (SEQ ID NO: 605), PCHPHPYDARPYCAV (SEQ ID NO: 606), PCHAHPYDARPYCNV (SEQ ID NO: 607), and PCHPHPYDARAYCNV (SEQ ID NO: 608).

265. The method of any one of aspects 162-264, wherein the subject is in need of reducing, inhibiting, and/or delaying the onset or progression of PD-1 or PD-L1 in the subject.

266. The method of any one of aspects 162-264, wherein the subject is in need of alleviating a symptom associated with aberrant expression and/or activity of PD-1 or PD-L1 in the subject.

267. The method of any one of aspects 162-266, wherein the subject has been identified or diagnosed as having a cancer.

268. The method of aspect 267, wherein the cancer is a lymphoma.

269. The method of aspect 268, wherein the lymphoma is Burkitt's lymphoma.

270. The method of any one of aspects 162-269, wherein the method comprises augmenting or potentiating therapeutic efficacy and/or therapeutic index relative to a conventional cytokine therapy in the subject.

271. The method of any one of aspects 162-269, wherein the method comprises augmenting or potentiating therapeutic efficacy and/or therapeutic index relative to a conventional PD1/PDL1 inhibitor therapy in the subject.

272. The method of any one of aspects 162-269, wherein the method comprises augmenting or potentiating therapeutic efficacy and/or therapeutic index relative to a conventional cytokine and PD1/PDL1 inhibitor combination therapy in the subject.

273. The method of any one of aspects 162-269, wherein the method comprises augmenting or potentiating therapeutic efficacy and/or therapeutic index relative to administering the ACC alone.

274. A combination or composition comprising the ACC and the PD-1/PD-L1 pathway inhibitor as aspected in any one of aspects 162-262.

275. The combination or composition of aspect 274, wherein the combination or composition is a pharmaceutical composition.

276. A container, vial, syringe, injector pen, or kit comprising at least one dose of the combination or composition of aspects 274 or 275.

277. The method of any preceding aspect, wherein the ACC and the PD-1/PD-L1 pathway inhibitor are administered simultaneously or sequentially.

278. The method of any preceding aspect, wherein the ACC and the PD-1/PD-L1 pathway inhibitor are administered separately.

279. A method of treating a subject in need thereof comprising administering a combination of an activatable cytokine construct (ACC) and a PD-1/PD-L1 pathway inhibitor to the subject, wherein the ACC comprises a first monomer construct and a second monomer construct, wherein:

(a) the first monomer construct comprises a first peptide mask (PM1), a first mature cytokine protein (CP1), a first and a third cleavable moieties (CM1 and CM3), and a

first dimerization domain (DD1), wherein the CM1 is positioned between the CP1 and the DD1 and the CM3 is positioned between the PM1 and the CP1; and

(b) the second monomer construct comprises a second mature cytokine protein (CP2), a second cleavable moiety (CM2), and a second dimerization domain (DD2), wherein the CM2 is positioned between the CP2 and the DD2;

wherein the DD1 and the DD2 bind to each other thereby forming a dimer of the first monomer construct and the second monomer construct,

the ACC is characterized in that it has at least one of the following characteristics:

(i) a structural arrangement in an N- to C-terminal direction comprising: PM1-CM3-CP1-CM1-DD1 and CP2-CM2-DD2, wherein DD1 and DD2 are dimerized;

(ii) wherein the first monomer construct is characterized in that the CP1 and the DD1 are linked by a linking region of no more than 18 amino acids such that the linking region of no more than 18 amino acids includes the CM3;

(iii) wherein the second monomer construct is characterized in that the CP2 and the DD2 are linked by a linking region of no more than 18 amino acids such that the linking region of no more than 18 amino acids includes the CM2;

(iv) wherein each of PM1 and PM2 is less than 40 amino acids;

(v) wherein each of PM1 and PM2 is between 13 and 49 amino acids; and/or

(vi) wherein each of PM1 and PM2 is not a receptor for the CP1 and the CP2 and wherein each of PM1 and PM2 is not a fragment of receptor for the CP1 and the CP2.

280. The method of aspect 279, wherein the first monomer construct is characterized in that the CP1 and the DD1 are linked by a linking region of no more than 12 amino acids such that the linking region of no more than 12 amino acids includes the CM3.

281. The method of aspects 279-280, wherein the second monomer construct is characterized in that the CP2 and the DD2 are linked by a linking region of no more than 12 amino acids such that the linking region of no more than 12 amino acids includes the CM2.

282. The method of any preceding aspect, comprising a mask linking region between PM1 and CP1 that comprises 15, 16, 17, 18, 19, 20, 21, or 22 amino acids.

283. The method of any preceding aspect, comprising a mask linking region between PM2 and CP2 that comprises 15, 16, 17, 18, 19, 20, 21, or 22 amino acids.

284. The method of any preceding aspect, wherein the first monomer construct has only one peptide mask.

285. The method of any preceding aspect, wherein the second monomer construct has only one peptide mask.

286. The method of any preceding aspect, wherein the first monomer construct has only one peptide mask and the second monomer construct has only one peptide mask.

EXAMPLES

The invention is further described in the following examples, which do not limit the scope of the invention described in the claims.

Example 1: *In vitro* characterization of example cytokine constructs

An activatable cytokine construct ProC440 was prepared by recombinant methods. The 1st and 2nd monomer constructs of the ProC440 were identical, with each being a polypeptide having the amino acid sequence of SEQ ID NO: 286 and a signal sequence at its N-terminus. Each of the 1st and 2nd monomer constructs comprises, from N-terminus to C-terminus, a signal sequence (e.g., SEQ ID NO: 470), a mature cytokine protein that corresponds to human interferon alpha-2b (SEQ ID NO: 1), a cleavable moiety having the amino acid sequence of SEQ ID NO: 100, and a dimerization domain corresponding to human IgG4 Fc, truncated at Cys226 (according to EU numbering) and including an S228P mutation (SEQ ID NO: 3).

The polypeptide was prepared by transforming a host cell with a polynucleotide having the sequence of SEQ ID NO: 286, followed by cultivation of the resulting recombinant host cells. Dimerization of the resulting expressed polypeptides yielded the cytokine construct ProC440.

The activity of ProC440 was tested in vitro using IFN-responsive HEK293 cells and Daudi cells. See Figs. 7A and 7B, respectively.

IFN-responsive HEK293 cells were generated by stable transfection with the human STAT2 and IRF9 genes to obtain a fully active type I IFN signaling pathway. The cells also feature an inducible SEAP (secreted embryonic alkaline phosphatase) reporter gene under the control of the IFNα/β inducible ISG54 promoter. To maintain

transgene expression, cells were cultured in DMEM GlutaMax media supplemented with 10% FBS, Pen/Strep, 30 μg/mL of blasticidin, 100 μg/ml of zeocin and 100 μg/mL of normocin. The addition of type I IFN to these cells activates the JAK/STAT/ISGF3 pathway and subsequently induces the production of SEAP which can be readily assessed in the supernatant using Quanti-Blue solution, a colorimetric detection for alkaline phosphatase activity.

The Daudi cell is a cell line of human B-cell lymphoblastic origin. Daudi cells were prepared at a concentration of 2×10^5 cells/mL in RPMI-1640 media supplemented with 10% FBS and 50 μL aliquots were pipetted into wells of a white flat-bottom 96-well plate (10K/well). The tested ProC440 or controls were diluted in RPMI 1640 media supplemented with 10% FBS. Duplicate five-fold serial dilutions were generated from which 50 μL was added to the each well. After 3 days of incubation at 37 °C, a viability kit was used to measure the levels of intracellular ATP as an indirect estimate of the number of viable cells remaining. 100 μL of cell-titer go was directly added to the plates which were then placed on an orbital shaker for 10 minutes. Following this incubation, the luminescent signal was directly measured using an Envision plate reader. Dose-response curves were generated and EC50 values were obtained by sigmoidal fit non-linear regression using Graph Pad Prism software.

In both of the assays using HEK293 cells and Daudi cells, the activity of ProC440 was reduced at least 1,000X as compared to Stem Cell IFNα-2b (human recombinant IFN-alpha2b, available from StemCell Technologies, Catalog #78077.1) (Figs. 7A and 7B). This indicates that the fusion of a cleavable dimerization domain corresponding to human IgG Fc provided steric masking to IFNα-2b in the ProC440 construct. Protease activation with uPa restored activity to a level comparable to the recombinant cytokine. EC50 values for ProC440, ProC440 + uPA, and Stem Cell IFNα-2b were computed from the IFNα/β assay results and are provided below in Table 8.

Table 8. EC50: IFNα/β Reporter Assay

	ProC440	ProC440 + uPA	Stem Cell IFNα-2b
EC50	7643	4.333	10.88

EC50 values for ProC440, ProC440 + uPA, and Stem Cell IFNα-2b were computed from the Daudi apoptosis assay results and are provided below in Table 9.

Table 9. EC50: Daudi Apoptosis Assay

	ProC440	ProC440 + uPA	Stem Cell IFNα-2b
EC50	264.2	0.1842	0.3530

Cleavage with uPa at the expected site in the cleavable moiety was confirmed by electrophoresis and Mass spectrometry analysis (Figs. 6A and 6B). The results suggest that the uPa protease was effective at cleaving the cleavable moieties in the ProC440 activatable cytokine construct. In addition to sensitivity to uPa activation, ProC440 was cleaved by MMP14 (Figs. 6A to 6C). Fig. 6A depicts the gel electrophoresis results; the left column shows ProC440 that has not been exposed to protease, the middle column shows ProC440 exposed to protease uPA, and the far right column shows ProC440 exposed to MMP14. Analysis by Mass spectrometry identified an MMP14 cleavage site at the C-terminal extremity of IFNα-2b, near the cleavable moiety (Fig. 6B). Protease activation with MMP14 also restored activity to a level comparable to the recombinant cytokine (Figs. 6C). The data indicate that ProC440 recovered full activity after cleavage of intrinsic and engineered cleavable moieties by proteases such as uPa or MMP14.

Activatable cytokine construct ProC732 was prepared by recombinant methods. The 1st and 2nd monomer constructs of this ACC were identical, with each being a polypeptide having the amino acid sequence shown in Fig. 8 (SEQ ID NO: 290 with an exemplary optional signal sequence (QSGQ)). Each of the 1st and 2nd monomer constructs comprises, from N-terminus to C-terminus, a signal sequence, a spacer (QSGQ SEQ ID NO: 480) sequence, an IFNalpha-2b masking peptide (SEQ ID NO: 292), a linker (SEQ ID NO: 293), a cleavable moiety having the amino acid sequence of SEQ ID NO: 41 (LSGRSDNI), a linker (SEQ ID NO: 227, wherein n=1), a mature cytokine protein that corresponds to human interferon alpha-2b (SEQ ID NO:1), a cleavable moiety having the amino acid sequence of SEQ ID NO: 41, and a DD corresponding to human IgG4 S228P Fc, truncated to Cys226 (according to EU numbering) (SEQ ID NO:3).

Another activatable cytokine construct, ProC733, was prepared by recombinant methods. The 1st and 2nd monomer constructs of this ACC were identical, with each being a polypeptide having the amino acid sequence shown in Fig. 9 (SEQ ID NO: 291 with an exemplary optional signal sequence). Each of the 1st and 2nd monomer constructs comprises, from N-terminus to C-terminus, a signal sequence, a spacer (e.g., QSGQ) sequence, an IFNalpha-2b masking peptide (SEQ ID NO: 292), a linker (SEQ ID NO: 293), a cleavable moiety having the amino acid sequence of SEQ ID NO: 41, a linker (SEQ ID NO: 227, wherein n=1), a mature cytokine protein that corresponds to human interferon alpha-2b (SEQ ID NO:1), and a DD corresponding to human IgG4 S228P Fc, including the full hinge sequence (SEQ ID NO: 4). Because the ProC733 construct lacks a cleavable moiety between the cytokine sequence and the DD, it is only partially activatable, as discussed below.

The masked cytokine constructs ProC732 and ProC733 were prepared by transforming a host cell with polynucleotides encoding the sequence of SEQ ID NOs: 290 and 291, respectively, followed by cultivation of the resulting recombinant host cells. Dimerization of the resulting expressed polypeptides yielded the cytokine constructs ProC732 and ProC733, respectively.

The activity of ProC732, ProC733 and ProC440 was tested *in vitro* using IFN-responsive HEK293 cells as previously described. The activity of ProC732 and ProC733 was further reduced as compared to ProC440 (Figs. 10A and 10B). This indicates that the addition of a peptide mask provided additional masking strength even though the cytokine activity was already significantly reduced in ProC440 by steric masking through the dimerization domains. Surprisingly, it appears that the addition of a masking peptide (PM) does not interfere with steric masking by the DD, nor does the DD appear to interfere with masking by the PM. Protease activation with uPa restored the activity of ProC732 to a level comparable to the level of ProC440 after protease activation with uPa. This indicates that ProC732, upon protease activation, recovered the full strength of activity of an unmasked IFNalpha-2b.

ProC733 contains an affinity peptide mask attached to IFNalpha-2b via a cleavable moiety, with the C-terminus of IFNα-2b fused directly to human IgG Fc (without a cleavable moiety interposed between the cytokine and the Fc region). Protease

activation with uPa restored the activity of ProC733 to a level comparable to the level of unactivated ProC440. This further indicates that in addition to the steric masking provided by the cleavable human IgG Fc, or constraint by IFN□-2b dimerization, a cleavable affinity peptide mask provides additional masking strength to IFN□-2b. EC50 values for ProC440, ProC440 + uPa, ProC732, ProC732 + uPa, ProC733, and ProC733 + uPa were computed from the IFNα/β assay results and are provided below in Table 10.

Table 10. EC50: IFNα/β Reporter Assay

	ProC440	ProC440 + uPA	ProC732	ProC732 + uPA	ProC733	ProC733 + uPA
EC50	0.6344	0.0004	40.69	0.0005	21.83	0.2977

The masking efficiencies of ACCs in a HEK reporter assay (as measured by comparing the EC50 of the uncleaved ACC to the EC50 of the cleaved ACC) were as follows:

ProC440: 1358X

ProC732: 7380X

ProC733: 60X

Thus, high levels of masking efficiency (e.g., > 5,000x) can be achieved in ACCs that include both a peptide mask and steric masking through dimerization domains.

As shown in Figs. 38A-38D, each of the peptide masks (Fig. 38A (no peptide mask) vs. Fig. 38B (peptide masked)) and the Fc masks (Fig. 38C (no Fc mask) vs. 38D (Fc masked)) affect binding of the ACC to the receptor. In view of the data, synergistic activity has been obtained through the use of the dual masking structure of the ACCs of the present disclosure. The activity of recombinant IFNa2b, monomeric IFNa2b/Fc, activated homodimeric IFNa2b/Fc, and homodimeric IFNa2b/Fc was tested *in vitro* using IFN-responsive HEK293 cells as previously described. Recombinant IFNa2b, monomeric IFNa2b/Fc, activated homodimeric IFNa2b/Fc, and homodimeric IFNa2b/Fc were prepared as described above. The activity of homodimeric IFNa2b/Fc was substantially reduced compared to recombinant IFNa2b, but was rescued by protease activation to a level commensurate with recombinant IFNa2b (Fig. 27). Fig. 31 also

shows that monomeric IFNa2b/Fc exhibited activity at an approximate midpoint between the activity observed for activated and unactivated homodimeric IFNa2b/Fc.

Additionally, ProC440 shows substantially reduced acitivty compared to uPA treated ProC440 (Fig. 35A). The same molecule, but with a NSUB substrate has restored activity in response to MMP indicating the presence of a cryptic cleavage site (Fig. 39A). The activity of both ProC732 and ProC1299 (deletion of L161) was rescued by uPA (Fig. 39B). Deletion of L161 (in the MMP14 cleavage site) prevents activation of ProC1301 (NSUB substrate) even in the presence of MMP14 or uPA (Fig. 39C).

The activity of ProC732 and ProC733 was further reduced as compared to ProC440 (Figs. 10A and 10B). This indicates that the addition of a peptide mask provided additional masking strength even though the cytokine activity was already significantly reduced in ProC440 by steric masking through the dimerization domains. Surprisingly, it appears that the addition of a masking peptide (PM) does not interfere with steric masking by the DD, nor does the DD appear to interfere with masking by the PM. Protease activation with uPa restored the activity of ProC732 to a level comparable to the level of ProC440 after protease activation with uPa**.** This indicates that ProC732, upon protease activation, recovered the full strength of activity of an unmasked IFNalpha-2b.

The activity of recombinant IFNa2b, monomeric IFNa2b/Fc, activated homodimeric IFNa2b/Fc, and homodimeric IFNa2b/Fc was tested *in vitro* using IFN-responsive HEK293 cells as previously described. Recombinant IFNa2b, monomeric IFNa2b/Fc, activated homodimeric IFNa2b/Fc, and homodimeric IFNa2b/Fc were prepared as described above. The activity of homodimeric IFNa2b/Fc was substantially reduced compared to recombinant IFNa2b, but was rescued by protease activation to a level commensurate with recombinant IFNa2b (**Fig. 27**). Fig. 27 also shows that monomeric IFNa2b/Fc exhibited activity at an approximate midpoint between the activity observed for activated and unactivated homodimeric IFNa2b/Fc.

Additionally, the activity of activated and unactivated masked IFNa2b and activated and unactivated dual mask IFNa2b was tested *in vitro* using IFN-responsive HEK293 cells in an uncleaved state and after protease activation (**Fig. 32**). Activated and unactivated masked IFNa2b and activated and unactivated dual mask IFNa2b were

prepared as described above. As shown in Fig. 32, masked IFNa2b exhibited ~700x lower the activity compared to protease activated masked IFNa2b and dual masked IFNa2b exhibited ~1400x lower the activity compared to protease activated dual masked IFNa2b.

Example 2: *In vivo* tolerability of cytokine constructs

Human IFNα-2b cross-reacts with hamster IFNα receptor and has been previously shown to be active in hamster (Altrock et al, Journal of Interferon Research, 1986). To assess the tolerability of IFNα-2b-containing cytokine constructs, Syrian Gold Hamsters were dosed with a starting dose of 0.4 mg/kg. Animals received one dose of test article and kept on study up to 7 days post dose, unless non-tolerated toxicities were identified. The starting dose (0.4mpk) represents an equivalent dose of IFNalpha-con (recombinant interferon alpha, a non-naturally occurring type-I interferon manufactured by Amgen under the name Infergen®) expected to induce body weight lost, decreased food consumption and bone marrow suppression in a hamster (125gr). In cyno, 0.1 mg/kg/day of INFalpha-con was associated with body weight lost, decreased food consumption and bone marrow suppression (equal to 1.25-2.5 x 10^7 U for a 125 gram hamster). If the starting dose was tolerated, animals were moved up to a "medium dose" of 2 mg/kg and received three doses of test article unless not tolerated. If tolerated, animals were moved up to a "high dose" of 10 mg/kg and received three doses of test article unless not tolerated. If tolerated, animals were moved up to a "higher dose" of 15 mg/kg. At each stage, if the test dose was not tolerated, the animal was moved down to the next lower dose. If the starting dose was not tolerated, the animal was moved down to a "lower dose" of 0.08 mg/kg. Animals were also dosed with the unmasked IFN□□ 2b Fc fusion constructs ProC286. As a negative control, animals were dosed with a human IgG4. The negative control did not induce any toxicity in the animals, as expected.

ProC286 (ChIgG4 5AA 1204DNIdL IFNa2b) was also prepared by recombinant methods. The 1st and 2nd monomer constructs were identical, with each being a polypeptide having the amino acid sequence of SEQ ID NO: 295 and a signal sequence at its N-terminus. Each of the 1st and 2nd monomer constructs comprises, from N-terminus to C-terminus, a signal sequence, a DD corresponding to human IgG4 S228P Fc

including the ESKYGPP hinge sequence (SEQ ID NO:4), a linker (SEQ ID NO: 296), a cleavable moiety having the amino acid sequence of SEQ ID NO:100, a linker (SEQ ID NO: 228), and a mature cytokine protein that corresponds to human interferon alpha-2b (SEQ ID NO:1).

ProC291 (NhIgG4 5AA 1204DNIdL IFNa2b) was also prepared by recombinant methods. The 1st and 2nd monomer constructs were identical, with each being a polypeptide having the amino acid sequence of SEQ ID NO: 463 and a signal sequence at its N-terminus. Each of the 1st and 2nd monomer constructs comprises, from N-terminus to C-terminus, a signal sequence, a mature cytokine protein that corresponds to human interferon alpha-2b (SEQ ID NO: 1), a linker (SEQ ID NO: 459), a CM (SEQ ID NO: 100), a linker (GGGS SEQ ID NO: 2), and a human IgG4 Fc region including the ESKYGPP (SEQ ID NO: 524) hinge sequence (SEQ ID NO: 4).

The activity of ProC286 and ProC291 were compared to the activity of Sylatron® (PEG-IFN-alpha2b) in the Daudi apoptosis assay (Figs. 11A-11B). In this assay, ProC286 and Sylatron® show similar levels of activity as shown in Fig. 11A. This indicates that ProC286 has similar activity to commercially-available pegylated IFN-alpha2b, and could be used as surrogate Sylatron control to evaluate the tolerability of IFN□-2b in the hamster study. ProC291 showed reduced activity compared to ProC286 and Sylatron®, indiciating that the structural orientation of the IFN N-terminal to the Fc was important for reduction in activity. That is, when the DD is a pair of Fc domains, positioning the cytokine N-terminal to the DD (as in ProC291) may provide greater reduction of cytokine activity than when the cytokine is positioned C-terminal to the DD (as in ProC286).

Animal were dosed on day 1 with the 0.4 mg/kg starting dose. Animals were kept on study for one week, unless a non-tolerated dose (DLT) was reached. Clinical observations, body weights & temperature were measured prior to dosing, and at 6h, 24h, 72h, 7d post-dose for each animal. Blood samples for Hematology and Chemistry analysis were collected at 72h, 7d post-dose for each animal. Hematology and Chemistry analysis were performed right after sampling. For the Hematology analysis, blood smear, differential white blood cell count, hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular volume, platelet count, red blood cell (erythrocyte) count,

red blood cell distribution width, reticulocyte count and white blood cell (leukocyte) count were evaluated. The clinical chemistry panel included measurement of alanine aminotransferase, albumin, albumin/globulin ratio, alkaline phosphatase, aspartate aminotransferase, calcium, chloride, cholesterol, creatine kinase, creatine, gamma glutamytransferase, globulin, glucose, inorganic phosphorus, potassium, sodium, total bilirubin, total protein, triglycerides, urea, nitrogen, and C-reactive protein. The evidence of toxicities in the tolerability study are summarized in Figs.13A-13C, 14, and 15.

Overall, animals dosed with the ProC286 constructs showed on average 5 % body weight loss when dosed at 2mpk (i.e., 2 mg/kg), and 15% body weight loss when dosed at 10mpk and 15mpk (Figs. 13A-13C). One animal dosed with ProC286 at 15mpk showed 20% body weight loss at 7 days post-dose (end of study). This is considered a non-tolerated dose. In contrast, animals dosed with ProC440 and ProC732 at 2mpk and 10mpk did not show body weight lost (Figs. 13A-13B). Animals dosed with ProC440 at 15mpk showed on average 5% body weight loss (Figs. 13A-13C). Animals dosed with ProC732 at 15mpk showed no body weight loss (Fig. 13C). This indicates that the masking of IFNα-2b to its receptor in the context of ProC440 limits IFNα-2b mediated bodyweight lost. Animals dosed with unmasked IFNa2b/Fc at 15mpk showed elevated ALP (and increased ALP detected at 0.4 mpk) compared to animals dosed with masked and dual masked IFNa2b/Fc. The results indicate that the masked IFNa2b/Fc is well tolerated up to 15 mg/kg in the hamster toxicity model.

Without wishing to be bound by theory, it is believed that positioning the interferon N-terminal of the DD and using a relatively short LR inhibits cytokine activity in the context of ProC440, reducing the toxicity of the interferon in comparison to PEGylated IFNα-2b (Sylatron®) or ProC286. Unexpectedly, the addition of a peptide affinity mask at the N-terminus of the cytokine in the context of ProC732 fully abrogates IFNα-2b mediated bodyweight lost at a dose of at least 15mpk. The use of both a cleavable peptide mask and a cleavable dimerization domain thus lowers toxicity and allows dosing at higher levels, potentially resulting in an improved therapeutic window for this cytokine therapeutic.

In terms of clinical chemistry, animals dosed with ProC286 showed significant elevation of Alkaline Phosphatase (ALP) at all doses (0.4mpk, 2mpk, 10mpk and

15mpk), 7 days post-dose (end of study) (Fig. 14). No significant increase of ALP was measured when animals were dosed with 10mpk or 15mpk of ProC440 or ProC732 (Fig. 14). Elevation of ALT is a marker of liver toxicity. IFNα-2b has been shown to induce liver toxicities. This indicates that the masking of IFNα-2b from binding to its receptor in the context of ProC440 and ProC732 limit IFNa-2b mediated liver toxicities.

In terms of hematology, 3 days post-dose and 7 days post-dose (end of study), animals dosed with ProC286 at 2mpk, 10mpk and 15mpk showed significant reduction level of Reticulocyte count, Neutrophyle count and White Blood Cells (WBC) count (Fig. 15). These reductions are reminiscent of IFNa-2b mediated bone-marrow toxicities. Three days post-dose, animals dosed with ProC440 and ProC732 showed reduction level of Reticulocyte count, Neutrophyle count and White Blood Cells (WBC) count (Fig. 15). Overall, the reduction level of hematopoietic cells observed in animals dosed with ProC440 and ProC732 is not as significant as the reduction levels observed in animals dosed with ProC286. At 7 days post-dose (end of study), in animals dosed with ProC732 and ProC440, the overall level of Reticulocyte count, Neutrophyle count and White Blood Cells (WBC) count is back to normal levels, or to a similar level that what observed in animals dosed with the negative control IgG4 (Fig. 15). In animals dosed with ProC286, the level of Reticulocyte count, Neutrophyle count and White Blood Cells (WBC) count remains low. This indicates that the masking of IFNα-2b to its receptor in the context of ProC440 and ProC732 limit IFNa-2b mediated bone marrow toxicities.

Example 3. *In vitro* anti-proliferative effect of cytokine constructs with linkers of various lengths on cancer cells

The anti-proliferative effects of IFNa-2b-hIgG4 Fc fusion constructs with varying linker lengths or without a linker between the IFNa-2b and the hIgG4 Fc were tested *in vitro* using Daudi cells. The test was performed using the Daudi cell assay described in Example 1.

The fusion proteins tested in this experiment include, in an N- to C-terminal direction, the mature IFNalpha-2b cytokine sequence, an optional linker and/or cleavable moiety, and the Fc domain of human IgG4 of SEQ ID NO: 4 (including the full hinge region such that the N-terminus of the Fc sequence begins with the amino acid sequence ESKYGPPCPPC (SEQ ID NO: 926)…). The ESKYGPP (SEQ ID NO: 524) sequence

contributes 7 amino acids to the "linking region" of these constructs. The first construct (Linking Region = 7) construct has no linker or cleavable moiety; its sequence in the N- to C-terminal direction consists of SEQ ID NO: 1 fused to SEQ ID NO: 4. The second construct (Linking Region = 12) construct has a 5 amino acid linker SGGGG (SEQ ID NO: 459) and no CM; its sequence in the N- to C-terminal direction consists of SEQ ID NO: 1 fused to SEQ ID NO: 459 fused to SEQ ID NO: 4. The third construct (Linking Region = 18) includes a 7 amino acid CM (SGRSDNI, SEQ ID NO: 100) and a 4 amino acid linker GGGS (SEQ ID NO: 2); its sequence in the N- to C-terminal direction consists of SEQ ID NO: 1 fused to SEQ ID NO: 100 fused to SEQ ID NO: 2 fused to SEQ ID NO: 4. The fourth construct (Linking Region = 23) includes a 5 amino acid linker, a 7 amino acid CM, and a 4 amino acid linker; its sequence in the N- to C-terminal direction consists of SEQ ID NO: 1 fused to SEQ ID NO: 459 fused to SEQ ID NO: 100 fused to SEQ ID NO: 2 fused to SEQ ID NO: 4. The fifth construct (Linking Region = 24) includes a 13 amino acid CM (ISSGLLSGRSDNI, SEQ ID NO: 68) and a 4 amino acid linker; its sequence in the N- to C-terminal direction consists of SEQ ID NO: 1 fused to SEQ ID NO: 68 fused to SEQ ID NO: 2 fused to SEQ ID NO: 4.

Fig. 16 shows the activities of the above ACCs in Daudi cells. The ACCs tested in this example did not have a peptide affinity mask attached thereto. The data indicates that the length of the flexible linkers and the length of the Linking Region (LR) between the cytokine and the Fc domain had an impact on the activity of the (uncleaved) ACCs. Constructs with zero linkers, or short linkers, and a correspondingly short LR display reduced cytokine activity, whereas contructs with longer linkers and thus a longer LR have a higher level of cytokine activity.

Example 4. *In vitro* characterization of additional activatable cytokine constructs

Additional activatable cytokine constructs without a peptide mask were also prepared by recombinant methods. The 1st and 2nd monomer constructs of these ACCs were identical. Each of the 1st and 2nd monomer constructs comprises, from N-terminus to C-terminus, a signal sequence, a mature cytokine protein that corresponds to human interferon alpha-2b (SEQ ID NO: 1), a cleavable moiety (CM) having the amino acid sequence of SEQ ID NO: 100 (SGRSDNI), and a dimerization domain corresponding to human IgG4 S228P Fc (comprising SEQ ID NO: 3). In addition, these ACCs include or

not a linker having the amino acid sequence SGGGG (SEQ ID NO: 459) between the CP and the CM. These ACCs include or not a linker having the amino acid sequence GGGS between the CM and DD. These ACCs also contain or not portions of the hinge of the DD that are N-terminal to Cysteine 226 (by EU numbering). These additional activable cytokines constructs are described in Table 11.

Table 11: Activable cytokines having different lengths of the linking region

Name	Alternative Name	Linker between CP and CM	Linker between CM and DD	Fc Hinge N-terminal residues	Linking Region Length
ProC288	IFNa2b 1204DNI 0AA Fc	SGGGG (SEQ ID NO: 459)	absent	absent	12
ProC289	IFNa2b 1204DNI 3AA Fc	SGGGG (SEQ ID NO: 459)	absent	GPP	15
ProC290	IFNa2b 1204DNI 7AA Fc	SGGGG (SEQ ID NO: 459)	absent	ESKYGPP (SEQ ID NO: 524)	19
ProC291	IFNa2b 1204DNI 11AA Fc	SGGGG (SEQ ID NO: 459)	GGGS	ESKYGPP (SEQ ID NO: 524)	23
ProC440	N IFNa2b 0 1204DNIdL 0AA Fc	absent	absent	absent	7
ProC441	N IFNa2b 0 1204DNIdL 3AA Fc	absent	absent	GPP	10
ProC442	N IFNa2b 0 1204DNIdL 7AA Fc	absent	absent	ESKYGPP (SEQ ID NO: 524)	14
ProC443	N IFNa2b 0 1204DNIdL 11AA Fc	absent	GGGS	ESKYGPP (SEQ ID NO: 524)	18

The activity of ProC440, an ACC with no flexible linkers and an IgG4 Fc region truncated to Cys226 (i.e., comprising a linking region of 7 amino acids), and the activity of additional ACCs containing various flexible linkers and Fc region sequences (i.e., comprising linking regions having more than 7 amino acids) was tested *in vitro* using IFN-responsive HEK293 cells and Daudi cells as previously described. In both assays, the activity (*e.g.*, anti-proliferative effects) of ProC440 was reduced as compared to all other ACCs with longer linking regions, which contain various additional sequences between the cytokine and the first amino acid that binds the DD to the corresponding

second monomer (*i.e.*, Cys226 of IgG4 by EU numbering). EC50 values for the ACCs were computed from the IFNα/β assay results and are provided below in Table 12.

Table 12. EC50: IFNα/β Reporter Assay

	Pro C288	Pro C289	Pro C290	Pro C291	Pro C440	Pro C441	Pro C442	Pro C443
EC50	34.34	17.93	10.33	8.743	41.37	6.28	6.637	1.687

EC50 values for the ACCs were computed from the Daudi apoptosis assay results and are provided below in Table 13.

Table 13. EC50: Daudi Apoptosis Assay

	Pro C288	Pro C289	Pro C290	Pro C291	Pro C440	Pro C441	Pro C442	Pro C443
EC50	112.8	64.55	23.04	13.39	2078	1053	642.9	478

The data in Tables 7-8 also shows that the activity of the (uncleaved) ACCs could be modulated by varying the length of the Linking Region.

The ACCs tested in this Example do not comprise a peptide mask. Based on the experimental results reported herein comparing ProC440 with ProC732, the activity of the uncleaved ACCs may be further decreased by adding a cleavable moiety and peptide mask to the N-terminus of the cytokine construct. Likewise, based on the data herein comparing ProC440 and ProC732, ACCs further comprising a CM and a PM at the N-terminus may have increased masking efficiency compared to ACCs that do not comprise a PM.

Example 5. Universal cytokine constructs

A universal activatable cytokine construct was prepared by recombinant methods described herein. The universal ACC has a universal interferon sequence (ProC859) having activity on both human and mouse cells as shown in Fig. 29. The universal ACC is a dimer. The 1st and 2nd monomer constructs of this ACC were identical, with each being a polypeptide having the amino acid sequence of SEQ ID NO: 447 with a signal sequence at its N-terminus. Each of the 1st and 2nd monomer constructs comprises, from N-terminus to C-terminus, a signal sequence, a mature cytokine protein that corresponds

to a universal interferon molecule that is a hybrid of IFN alpha 1 and IFN alpha 2a (SEQ ID NO: 488), a cleavable moiety having the amino acid sequence of SEQ ID NO: 100, and a dimerization domain corresponding to human IgG Fc (SEQ ID NO: 3).

The activity of the universal cytokine construct was tested *in vitro* using IFN-responsive HEK293 cells and B16 mouse melanoma cells. The activity of ProC859 was reduced at least 150X as compared to mouse IFNa4. Protease activation with uPa restored activity to a level that is comparable to mouse IFNa4 as shown in Fig. 29. EC50 values for ACC ProC859, ACC ProC859 + uPA, and mouse IFNα4 were computed from the assay results and are provided in Fig. 29.

EC50: B16 IFNα/β Reporter Assay

	ProC859 (ACC)	ProC859 (ACC) + uPA	IFNa4
EC50	293.7	1.951	1.966

An ACC with universal IFN and a peptide mask according to the present disclosure may be prepared by recombinant methods described herein. The peptide masks are coupled to the universal interferon to further reduce the cytokine activity of the ACC compared to ProC859. The 1st and 2nd monomer constructs of this ACC are identical, with each being a polypeptide having the amino acid sequence. Each of the 1st and 2nd monomer constructs comprises, from N-terminus to C-terminus, a signal sequence (for example, one of SEQ ID NOs: 468-470), a masking peptide (e.g., any one PM selected from SEQ ID NOs: 292, and 297-446), an optional linker (e.g., any one selected from SEQ ID NO:2, or SEQ ID Nos: 210-236), a cleavable moiety (e.g., any one selected from SEQ ID NOs: 5-100, and 237-252), an optional linker (e.g., any one selected from SEQ ID NOs: 2, 210-236, 293, 294, and 296), a mature cytokine protein that corresponds to a universal interferon molecule that is a hybrid of IFN alpha 1 and IFN alpha 2a (SEQ ID NO: 448), a cleavable moiety having the amino acid sequence of SEQ ID NO: 100, and a dimerization domain corresponding to human IgG Fc (SEQ ID NO: 3). The activity of the universal ACC is tested in vitro using IFN-responsive HEK293 cells and B16 mouse melanoma cells. Based on the experimental results

reported herein comparing ProC440 with ProC732, it is expected that the presence of the affinity mask (PM) will further decrease the cytokine activity of the uncleaved ACC relative to ProC859, but will permit full recovery of cytokine activity when the CMs are cleaved by protease, thereby further reducing toxicity and improving the therapeutic window.

Without wishing to be bound by theory, based on the results presented herein, the inventors envisage that use of an affinity mask (PM) at the N-terminus of a cytokine in addition to the use of a DD with a relatively short LR at the C-terminus of the cytokine will provide significant masking of cytokine activity for cytokines in addition to the interferon-alpha cytokines exemplified in the foregoing specific examples. As described above, the invention described herein encompasses activatable cytokine constructs that include various cytokine proteins discussed herein. As non-limiting examples, the CP used in the ACCs of the invention may be any of those listed in SEQ ID NOs: 101 to 209, and variants thereof. In particular, monomeric cytokines are suited to use in the ACCs described herein. Based on the results provided herein, it is believed that the ACCs of the invention will exhibit reduced cytokine activity relative to the corresponding wildtype cytokine, and that upon cleavage of the ACC by the relevant protease(s), the cleavage product will recover cytokine activity similar to that of the corresponding wildtype cytokine.

Example 6: *In vivo* characterization of conditionally active INFa-A/D or IFNa2b alone or in combination with anti-PD-L1

Dual masked INFa-A/D (SEQ ID NO: 493, ProC1023) and its modified version with potentially reduced cleavability (SEQ ID NO: 494, ProC1549) were prepared as described in Example 1. CX-171 (SEQ ID NOs: 504 or 505– HC, SEQ ID NO: 506– LC) is the monoclonal mAb binding to PD-L1 ("PD-L1 mAb") expressed by human and mouse cells. CX-171 features mouse IgG2a Fc portion to facilitate interactions with the murine immune system in vivo. The c-terminal lysine may or may not be present in the CX-171 antibody following expression.

The antitumor activity of the masked IFNa-A/D was tested in vivo using the MC38 tumor model. Mice (N=5 per group) were implanted subcutaneously with $1.5x10^6$ MC38 cells in serum-free medium. Body weights and tumor measurements were

recorded twice weekly for the duration of the study. When the average tumor volume reached 80 mm^3, mice were dosed two times per week by subcutaneous injections of masked IFNa-A/D (ProC1023), or masked uncleavable IFNa-A/D (ProC1549), or PD-L1 mAb (CX-171) one time per week intraperitoneally, or the combination of masked IFNa-A/D with PD-L1 (ProC1023 + CX-171) at the indicated dose levels.

Masked IFNa-A/D demonstrated antitumor activity in the 50-200 ug dose level. Administration of 50 ug resulted in significant tumor growth inhibition, while administration of 200 ug also resulted in rejection of the tumors by 60% of the animals (**Fig. 18A**). Antitumor effect of the masked IFNa-A/D (ProC1023) was dependent on proteolytic activation, because the uncleavable construct (ProC1549) did not mediate similar responses (**Fig. 18B**).

The combination of 50 ug/dose of masked IFNa-A/D with 200 ug/dose of PD-L1 mAb resulted in enhanced antitumor effects as compared to either molecule alone (**Fig. 18C**).

Masked IFNa2b reduced tumor volume at increasing doses. Masked IFNa2b was prepared as described above. Masked IFNa2b/Fc prevented tumor progression at a dose of 0.02 mg/kg and induced tumor regression at a dose of 0.1 mg/kg (**Figs. 28, 51**). As shown in Fig. 28 and Fig. 51, masked IFNa2b/Fc exhibited antitumor activity similar to peginterferon and the unmasked Fc-IFN-a2b control.

Additionally, masked IFNa2b showed anti-tumor activity at 20 µg and 200 µg compared to control (**Fig. 33**). The antitumor activity of the masked IFNa-A/D was tested as described above with doses on days 1, 4, 8, 11, and 15. Tumor volume was assessed at times indicated in the graph of Fig. 23.

As shown in Fig. 33, dual masked IFNa AD reduced tumor volume compared to a non-cleavable version at doses of 10, 50, and 200 µg (**Fig. 33A**). The combination of dual masked IFNa AD with PD-L1 monoclonal antibody reduced tumor volume compared to dual masked IFNa AD alone at doses of 10 and 50 µg or PD-L1 monoclonal antibody alone at 200 µg (**Fig. 33B**). The antitumor activity was tested as described above with doses on days 1, 4, 7, and 11. PD-L1 monoclonal antibody alone was administered on days 1 and 7.

As shown in **Fig. 34A**, Pro IFNa A/D (ProC1023) inhibited tumor volume growth in a dose-dependent manner. The inhibition requires activation as shown in **Fig. 34B)**, where IFNa A/D NSUB (ProC1549) at 200 µg showed reduced antitumor activity compared to Pro IFNa A/D (ProC1023) at the same dose.

Pro IFNa A/D (ProC1023) reduced tumor volume growth at 10 µg, 50 µg, and 200 µg compared to PBS control (**Fig. 35A**). IFNa A/D NSUB (ProC1549) at 50 and 200 µg had reduced antitumor activity compared to Pro IFNa A/D (ProC1023) over the same time-period (**Fig. 35B**). The antitumor activity of the masked IFNa-A/D was tested as described above with doses on days 1, 4, 7, 11, and 15. CX-171 was dosed on days 1, 7, and 15. Tumor volume was assessed at times indicated in the graph of Figs. 35A and 35B.

Table 14. Example Sequences

SEQ ID NO.	NAME	SEQUENCE
924	Monomeric IFNa-2b/Fc ProC657 first monomer (knob mutation) without signal sequence	CDLPQTHSLGSRRTLMLLAQMRRISLFSCLKDRHDFGFP QEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWDE TLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKEDSI LAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSFSLS TNLQESLRSKESGRSDNICPPCPAPEFEGGPSVFLFPPKP KDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEV HNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKC KVSNKGLPSSIEKTISKAKGQPREPQVYTLPPCQEEMTK NQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL DSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNH YTQKSLSLSLG
925	Monomeric IFNa-2b/Fc ProC657 second monomer (hole	SDNICPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQPREPQVCTLPPSQEEMTKNQVSLSCAVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSRLTVD KSRWQEGNVFSCSVMHEALHNRFTQKSLSLSLG

	mutation) without signal sequence	

Example 7. Immune memory in IFNa-A/D treated mice.

Naïve mice (N=5; **Fig. 19A**) or mice that rejected MC38 tumor after IFNa-A/D treatment with a 200 microgram dose of ProC1023 (N=3; **Fig. 19B**) were re-challenged with 1.5 x 10^6 MC38 cells at day 56 after initial treatment. Tumor growth was monitored twice weekly. Mice that rejected tumor after treatment with 200 ug/dose IFNa-A/D were re-challenged with MC38 tumor 56 days after the initial treatment. The mice were not administered any treatment during the re-challenge period. After the challenge, MC38 tumors progressively grew in all five control animals (**Fig. 19A**), however only one out of three previously IFNa-A/D-treated mice developed the tumor, and the tumor in that mouse exhibited significantly slower growth consistent with the formation of antitumor immune memory in these mice that had been previously treated the 200 micrograms dose of ProC1023 (**Fig. 19B**).

The results indicate that masked IFNa-A/D suppresses MC38 tumor growth in activation-dependent, immune mediated manner. Combinatorial activity of IFNa-A/D with PD-L1 mAb indicate non-redundant mechanisms of antitumor effect of the two treatments.

Example 8: Unmasked INF-a2b activates tumor immune infiltrate in vitro

Dual masked INFa-a2b (SEQ ID NO: 290, ProC732) was activated by treatment with uPA as described previously. Pegylated IFN-a2b (Merck, USA) was purchased from a vendor and used as a control. In this example, CX-075 (SEQ ID NO: 496– HC, SEQ ID NO: 497– LC) is the monoclonal mAb that binds to human PD-L1 expressed by human immune and tumor cells. CX-075 features a human IgG4 Fc portion.

Dissociated tumor and PBMC from a patient with renal carcinoma were obtained from a vendor as a cryopreserved, single-cell suspension with at least 50% viability after thawing. PBMC or dissociated tumor cells were treated with masked IFNa-2b (uncleaved ProC732), unmasked IFNa-2b (ProC732 treated with uPA protease), Peg-IFN-a2b, or a combination of unmasked IFN-a2b with PD-L1 mAb (CX-075) for 24 hours at ProC732 dosages of 0.1 ng/mL, 10 ng/mL or 1000 ng/mL. Interferon gamma release (the sensitive

biomarker induced by type I IFNs and PD-1:PD-L1 axis blockade) was measured by MSD multiplex assay.

Treatment with masked IFN-a2b (uncleaved ProC732) did not result in measurable changes in interferon gamma supernatant concentrations as compared to untreated controls. Treatment with activated IFN-a2b (uPA-treated ProC732) demonstrated dose-dependent increase in the level of interferon gamma released by dissociated tumor and PBMC (**Fig. 20**). Both the character and magnitude of the changes were similar to Peg-IFN-a2b benchmark control. While treatment with PD-L1 mAb (CX-075) did not result in increased level of interferon gamma release, combination of activated IFN-a2b with PD-L1 mAb increased release of the biomarker in a dose-dependent manner in dissociated tumor cells but not PBMC.

Observed results are consistent with activation of tumor immune infiltrate by activated IFN-a2b. Combinatorial activity of activated IFN-a2b with PD-L1 mAb suggest non-redundant mechanisms of immune activation. Differences between activity of masked and unmasked forms of IFN-a2b indicate attenuation of its function by the dual masked structure.

Additionally, the biological effects and masking of IFN are evident in dissociated tumor. Dissociated tumor and PBMC from a patient with renal carcinoma were obtained as described above. As shown in Fig. 31, IFN-gamma release saturates at 10 ng/mL (PD-L1 mAb was administered at a single dose). As shown in Fig. 31, the combination of activated IFNa2b and PD-L1 mAb increased IFN-gamma release over activated IFNa2b or PD-L1 mAb alone.

Example 9: Activation-dependent induction of type I interferon signature by unmasked IFN-a2b

Dual masked INFa-a2b (SEQ ID NO: 290, ProC732) was activated by treatment with uPA as described previously. Pegylated IFN-a2b (Merck, USA) was purchased from a vendor.

PBMCs from four healthy donors were purchased from a vendor as a cryopreserved, single-cell suspensions with at least 80% viability after thawing. PBMCs from each donor were treated in vitro with 1 ug/mL (high dose) of masked IFN-a2b (uncleaved ProC732), or 10 ng/mL of masked IFN-a2b (uncleaved ProC732), unmasked

IFN-a2b (uPA-treated ProC732), or Peg-IFN-a2b (Sylatron® - Merck, USA) for 24 hours. Bulk mRNA from treated cells was subjected to paired-end 150c RNAseq high-throughput sequencing. Unique gene hit counts were calculated by using Subread package v.1.5.2. Using DESeq2, a comparison of gene expression between the indicated groups of samples was performed. The Wald test was used to generate p-values and log2 fold changes. Genes with an adjusted p-value < 0.05 and absolute log2 fold change > 1 were called as differentially expressed genes for each comparison.

Table 15. Pair-wise comparison of gene expression profiles

	Untreated	**ProC732**	**ProC732 high dose**	**ProC732 + uPA**	**Sylatron** (Peg-IFN-a2b)
Untreated		↑ 1 ↓ 0	↑ 248 ↓ 36	↑ 418 ↓ 77	↑ 480 ↓ 86
ProC732			↑ 8 ↓ 1	↑ 71 ↓ 10	↑ 125 ↓ 17
ProC732 high dose				↑ 1 ↓ 0	↑ 0 ↓ 0
ProC732 + uPA					↑ 0 ↓ 0

Treatment of PBMCs with masked IFN-a2b did not result in gene expression changes, while activated IFN-a2b consistently upregulated and downregulated large number of genes in all four donors (**Fig. 21**). The results demonstrate statistically significant increases in the expression of 418 genes, whereas 77 genes were downregulated (**Table 15**). Gene ontology analysis revealed a pattern associated with activation of type I interferon signaling, including enhanced expression of known targets of IFN-a2b such as CXCL10, TRAIL and 2'OAS. Treatment with pegylated IFN-a2b induced and suppressed similar number of genes in all donors. Direct comparison between expression profile of PBMC treated with activated IFN-a2b and Peg-IFN-a2b revealed no difference between two treatments.

The results are consistent with activation dependent induction of interferon signaling in primary human immune cells by unmasked IFN-a2b. Minimal changes

between gene expression induced by high dose of masked IFN-a2b and the unmasked interferon indicate that dual masking reduced signaling potential of the cytokine without creating new interactions with the receptor.

Example 10: Pharmacokinetic properties of masked IFN-a2b in rodents

Dual masked INFa-a2b (SEQ ID NO: 290, ProC732), steric masked IFN-a2b (SEQ ID NO: 286, ProC440), its uncleavable control (SEQ ID NO: 507, ProC659), or Fc-IFN-a2b fusion molecule (SEQ ID NO: 295, ProC286) were administered to golden Syrian hamsters as described previously. Blood samples were obtained at 6, 24, 72 hours or 7 days after administration. Concentrations of IFN-a2b were measured using ELISA (Mabtech, USA). Non-compartmental pharmacokinetic analysis was performed using WinNonlin software (Certara, USA).

Pharmacokinetic profiles of all tested molecules demonstrate increased serum concentrations proportional to the administered dose (**Fig. 22**). At each dose level, drug exposure was comparable between masked IFN-a2b and control proteins. Non-compartmental analysis revealed average circulation half-life of 4.3 days – ranging 1.98 to 6.38 days (**Table 16**).

The results indicate linear pharmacokinetic properties of IFN-a2b in vivo and extended half-life compared to published data for unmodified IFN-a2b (2.3 hours) and Peg-IFN-a2b conjugated with a 12kDa PEG molecule (4.3 hours).

Pharmacokinetics profiles of all tested molecules indicate increased serum concentrations proportional to the administered dosages.

Table 16. Summary of non-compartmental analysis of IFN-a2b pharmacokinetics

Test_Article	Dose	Tmax	Cmax	AUClast	HL_Lambda_z (half life)
	mg/kg	day	ng/mL	day*ng/mL	day
ProC286	0.4	0.25	2913	10371	4.3499
ProC286	2	1	8225	30936	
ProC286	2	1	8863	39595	
ProC286	2	1	7685	29731	
ProC286	10	3	19443	104368	
ProC286	10	1	37673	79286	
ProC286	10	1	24036	118866	
ProC286	15	0.25	41340	187894	1.9774
ProC286	15	1	63075	250384	
ProC286	15	1	74989	259900	

ProC286	15	3	45546	219676	
ProC440	0.4	1	401	1791	4.3952
ProC440	2	1	4718	18986	
ProC440	2	1	7137	27274	
ProC440	2	1	8968	40329	
ProC440	10	1	36860	161885	
ProC440	10	1	31851	152170	
ProC440	15	0.25	53422	214393	5.1186
ProC440	15	1	44331	226428	
ProC440	15	0.25	37551	122954	4.5772
ProC440	15	1	18738	109485	
ProC659	0.4	1	686	3143	5.0481
ProC659	2	3	9842	48705	
ProC659	2	0.25	12284	44567	
ProC659	2	0.25	15715	36674	5.7591
ProC659	10	1	51601	303538	
ProC659	10	1	57389	315392	
ProC659	10	1	51022	241447	
ProC732	10	1	21019	128288	
ProC732	10	1	34498	182458	
ProC732	10	1	34191	179881	
ProC732	15	0.25	33121	186676	6.3841
ProC732	15	1	54723	164326	
ProC732	15	1	27760	157575	
ProC732	15	1	33898	177802	

Beige/SCID mice (n=15 per group) were treated with single administration of indicated doses of Pb-IFN-a2b. Plasma for PK studies was collected at 1, 2, 3, 6, 24, 48, 72, 120 hours, 7 and 14 days after the administration. Samples were analyzed by MSD assay using anti-human IFN-a2b-specific capture and detection antibodies (Mabtech, USA).

Pharmacokinetic profiles of all tested molecules demonstrate increased concentrations proportional to the administered dose (**Fig. 52**).

Example 11: *In vitro* characterization of example Universal cytokine constructs

A universal activatable cytokine construct was prepared by recombinant methods described herein. The universal ACC has a universal interferon sequence (ProC1023) having activity on both human and mouse cells. The universal ACC is a dimer. The 1st and 2nd monomer constructs of this ACC were identical, with each being a polypeptide

having the amino acid sequence of SEQ ID NO: 493 with a signal sequence at its N-terminus. Each of the 1st and 2nd monomer constructs comprises, from N-terminus to C-terminus a signal sequence, a spacer (QSGQ, SEQ ID NO: 480) sequence, an IFNalpha-2b masking peptide (TDVDYYREWSWTQVS) (SEQ ID NO: 292), a linker (GSSGGS) (SEQ ID NO: 293), a cleavable moiety having the amino acid sequence of SEQ ID NO: 41 (LSGRSDNI), a linker (GS)n, (GGS)n, (GSGGS)n (SEQ ID NO: 227, wherein n=1), a mature cytokine protein that corresponds to a universal interferon molecule that is a hybrid of IFN alpha 1 and IFN alpha 2a (SEQ ID NO: 448), a cleavable moiety having the amino acid sequence of SEQ ID NO: 41, and a DD corresponding to human IgG4 S228P Fc, truncated to Cys226 (according to EU numbering) (SEQ ID NO: 3).

Another universal cytokine construct, ProC1549, was prepared by recombinant methods. The 1st and 2nd monomer constructs of this ACC were identical, with each being a polypeptide having the amino acid sequence of SEQ ID NO: 494 (having an exemplary optional signal sequence). Each of the 1st and 2nd monomer constructs comprises, from N-terminus to C-terminus, a signal sequence, a spacer (e.g., QSGQ, SEQ ID NO: 480) sequence, an IFNalpha-2b masking peptide (TDVDYYREWSWTQVS) (SEQ ID NO: 292), a linker (GSSGGS) (SEQ ID NO: 293), a non-cleavable moiety having the amino acid sequence of SEQ ID NO: 211, a linker (GS)n, (GGS)n, (GSGGS)n (SEQ ID NO: 227, wherein n=1), a mature cytokine protein that corresponds to a universal interferon molecule that is a hybrid of IFN alpha 1 and IFN alpha 2a (SEQ ID NO: 481), a non-cleavable moiety having the amino acid sequence of (GGSGGGGS) SEQ ID NO: 495, and a DD corresponding to human IgG4 S228P Fc, including the full hinge sequence (SEQ ID NO: 3). Because the ProC1549 construct lacks cleavable moieties between the masking peptide and the cytokine, as well between the cytokine sequence and the DD, it is not activatable, as discussed below.

Another universal activatable cytokine construct, ProC859, was prepared by recombinant methods described herein. ProC859 has a universal interferon sequence having activity on both human and mouse cells. ProC859 is a dimer. The 1st and 2nd monomer constructs of this ProC859 were identical, with each being a polypeptide having the amino acid sequence of SEQ ID NO: 447 with a signal sequence at its N-terminus. Each of the 1st and 2nd monomer constructs comprises, from N-terminus to C-

terminus, a signal sequence, a mature cytokine protein that corresponds to a universal interferon molecule that is a hybrid of IFN alpha 1 and IFN alpha 2a (SEQ ID NO: 448), a cleavable moiety having the amino acid sequence of (SGRSDNI) SEQ ID NO: 100, and a dimerization domain corresponding to human IgG Fc (SEQ ID NO: 3). Unlike ProC1023, ProC859 does not comprise a peptide masking moiety.

The activity of the universal cytokine constructs ProC1023 (SEQ ID NO: 493) and proC859 (SEQ ID NO: 447) was tested *in vitro* using B16 mouse melanoma cells. The activity of ProC1023 was further reduced as compared to ProC859 (Fig. 24A). This indicates that the addition of a peptide mask provided additional masking strength even though the cytokine activity was already significantly reduced in ProC859 by steric masking through the dimerization domains. Surprisingly, it appears that the addition of a masking peptide (PM) does not interfere with steric masking by the DD, nor does the DD appear to interfere with masking by the PM. Protease activation with uPa restored the activity of ProC1023 to a level comparable to the level of ProC859 after protease activation with uPa**.** This indicates that ProC1023, upon protease activation, recovered the full strength of activity of an unmasked universal IFNalpha.

The masking efficiencies of ACCs in a HEK reporter assay (as measured by comparing the EC50 of the uncleaved ACC to the EC50 of the cleaved ACC) were as follows:

ProC1023: 1387X

ProC859: 700X

The activity of the universal cytokine constructs ProC1023 and ProC1549 was tested *in vitro* using B16 mouse melanoma cells. In the un-activated state, ProC1023 and ProC1549 showed similar reduction of signaling activity (Figs. 24B and 24C). Upon Protease activation with either uPa or MMP14, activity of the non-cleavable ProC1549 remains low and similar to ProC1549 without protease activation, while activity of ProC1023 was significantly increased after protease activation as compare ProC1023 and ProC1549 without protease activation (Figs. 24B and 24C). This indicates that ProC1549 is resistant to Protease activation, and it can be used as a control to demonstrate protease-dependent activation of universal activatable cytokine constructs.

Example 12: *In vitro* characterization of additional heterodimeric ACCs

ACC ProC1239 (Pro-IFN 49CS 1204 IFNa2b 0 1204 0 G4 Knob Stub Hole) was also prepared by recombinant methods. The 1st monomer construct of this ACC is a polypeptide having the amino acid sequence of ProC1239 Arm 1 SEQ ID NO: 792 and a signal sequence at its N-terminus. The 1st monomer construct of this ACC comprises, from N-terminus to C-terminus a signal sequence, a spacer (QSGQ, SEQ ID NO: 480) sequence, an IFNalpha-2b masking peptide (TDVDYYREWSWTQVS) (SEQ ID NO: 292), a linker (GSSGGS) (SEQ ID NO:293), a cleavable moiety having the amino acid sequence of SEQ ID NO: 41 (LSGRSDNI), a linker (GS)n, (GGS)n, (GSGGS)n (SEQ ID NO: 227, wherein n=1), a mature cytokine protein that corresponds to human interferon alpha-2b (SEQ ID NO:1), a cleavable moiety having the amino acid sequence of SEQ ID NO: 41, and a DD corresponding to human IgG Fc with a knob mutation, truncated to Cys226 (according to EU numbering) (SEQ ID NO: 287). The 2nd monomer construct of this ACC is a polypeptide having the amino acid sequence of ProC1239 Arm 2 SEQ ID NO: 793 and a signal sequence at its N-terminus. The 2nd monomer construct has, from N-terminus to C-terminus, a signal sequence, a stub moiety (SDNI) (SEQ ID NO: 289), and a dimerization domain corresponding to human IgG Fc with a hole mutation (SEQ ID NO: 288).

The activity of ProC1239 and ProC732 was tested in vitro using IFN-responsive HEK293 cells as previously described. The activity of ProC1239 was moderately reduced as compared to ProC732 (Fig. 25).

Example 13: *In vitro* characterization of additional ACCs with various cleavable linkers

Additional activatable cytokine constructs with varying cleavable linkers were also prepared by recombinant methods. The 1st and 2nd monomer constructs of these ACCs were identical. Each of the 1st and 2nd monomer constructs comprises, from N-terminus to C-terminus, a signal sequence, a spacer (QSGQ, SEQ ID NO: 480) sequence, an IFNalpha-2b masking peptide (TDVDYYREWSWTQVS) (SEQ ID NO: 292), a linker (GSSGGS) (SEQ ID NO: 293), a cleavable moiety, a linker (GS)n, (GGS)n, (GSGGS)n (SEQ ID NO: 227, wherein n=1), a mature cytokine protein that corresponds to human interferon alpha-2b (SEQ ID NO: 1), a cleavable moiety, and a DD corresponding to

human IgG4 S228P Fc, truncated to Cys226 (according to EU numbering) (SEQ ID NO: 3). The various cleavable linkers are described in the following table:

Table 17. Activable cytokines having different cleavable linkers between

Name	Alternative Name	CM between CP and Cytokine moiety	CM between Cytokine Moiety and DD
ProC732	Pro-IFN 49CS 1204 IFNa2b 0 1204 0 (-ESKYGPP) G4	LSGRSDNI (SEQ ID NO: 41)	LSGRSDNI (SEQ ID NO: 41
ProC1550	Pro-IFN 49CS 1205 IFNa2b 0 1205 0 (-ESKYGPP) G4	LSGRSNI (SEQ ID NO: 799)	LSGRSNI (SEQ ID NO: 799)
ProC1552	Pro-IFN 49CS 559 IFNa2b 0 559 0 (-ESKYGPP) G4	QNQALRMA (SEQ ID NO: 16)	QNQALRMA (SEQ ID NO: 16)

The activity of ProC732, ProC1550 and ProC1552 were tested *in vitro* using IFN-responsive HEK293 cells as previously described. Upon protease activation with either uPa or MTSP1, all activable cytokine constructs showed a similar increase of activity, indicating that all activated cytokines constructs recover the same level of activity upon protease treatment as shown in Fig. 26.

Example 14: Masked IFNa-A/D elicit tumor growth delay in CT26 and B16 syngeneic tumor models

The antitumor activity of the masked IFNa-A/D (ProC1023) was tested in vivo using B16 and CT26 tumor models. Mice (N=6 per group) were implanted subcutaneously with tumor cells in serum-free medium. Body weights and tumor measurements were recorded twice weekly for the duration of the study. When the average tumor volume has reached 80 mm^3, mice were dosed 2 times per week by subcutaneous injections of masked Pb-IFNa-A/D and/or PD-1 or PD-L1 mAb 1 time per week intraperitoneally.

Masked IFNa-A/D demonstrate antitumor activity in the 50 ug dose level in both model systems. Administration of Pb-IFNa-A/D resulted in statistically significant tumor growth inhibition, while PD-1 and PD-L1 mAbs did not significantly affected tumor growth. Combination of masked IFNa-A/D with 200 ug/dose of PD-L1 mAb resulted in enhanced antitumor effects as compared to either molecule alone (Fig. 37). In B16 tumor model combination of Pb-IFNa-A/D with PD-L1 resulted in statistically significant improvement of survival.

The results indicate that masked IFNa-A/D suppresses tumor growth in multiple tumor models. Combination with Pb-IFNa-A/D enables therapeutic activity of PD-L1 mAb in the CPI-resistant B16 tumor model.

Example 15: Binding of activated Pb-IFN-a2b to interferon alpha receptors in vitro

Pb-INF-a2b was activated *in vitro* with uPA, and the active fraction was purified by chromatography (ProC1640). Interferon alpha receptor 1 human (ProC1822) and cyno (ProC1824), as well as IFNAR2 human (ProC1823) and cyno (ProC1825) were expressed as recombinant proteins and purified. Binding was performed *in vitro* using the surface plasmon resonance approach. The ligands were captured on a chip coated with immobilized anti-human Fc or anti-histidine antibodies. Regeneration conditions to permit multi-cycle kinetic measurements were established. Different concentrations of analytes were flowed over the ligand-captured chip to generate multi-cycle kinetic sensorgrams that were analyzed to obtain the kinetic rate constants and the affinity constant using a 1:1 binding model.

ProC1640 binds to human and cyno IFNAR1, however affinity and specificity of the interaction could not be determined with current method due to extremely slow dissociation of the molecules. Binding of the activated fraction of the IFN-a2b to human IFNAR2 and cyno IFNAR2 was detected. As shown in Figs. 40A-40D, ProC732 binds to human and cynomolgus monkey interferon alpha receptor IFNAR2 with similar affinity. Fig. 40A shows human IFNAR1 response over time. Fig. 40B shows cynomolgus monkey IFNAR1 response over time. Fig. 40C shows human IFNAR2 response over time. Fig. 40D shows cynomolgus monkey IFNAR2 response over time.

Affinity to hIFNAR2 was 2.7 nM, cyno – 9.3 nM as shown in the following table:

Table 18 Summary of binding studies with IFN-a2b molecules

Ligand	**Analyte**	**ka (1/Ms)**	**kd (1/s)**	**KD (nM)**
ProC1823	ProC1640	4.374E+06	1.195E-02	2.731
ProC1825	ProC1640	2.674E+06	2.501E-02	9.353
ProC1823	ProC1976	8.985E+04	1.175E-02	130.8
ProC1718	ProC1640	5.177E+06	1.214E-02	2.344

ProC440	ProC1718	2.055E+05	2.077E-02	101.1

For confirmatory studies, binding of the activated Pb-IFN-a2b (ProC1640) to Fc-tagged dimeric IFNAR2 (ProC1718) was analyzed. The Kd of the interaction of ProC1640 with ProC1718 was 2.3 nM.

Therefore, human IFN-a2b binds to human and cynomolgus monkey IFNAR2 with similar affinity. The format and valency of the ligand did not affect measurement results.

Example 16: Binding of single masked Pb-IFN-a2b molecules to IFNAR2

Binding of masked Pb-INF-a2b to human IFNAR2 was performed as described above. Direct comparison of the peptide masked IFN-a2b (ProC1976) with its unmasked version (ProC1640) demonstrated ~50x affinity differential (130.8 nM vs 2.7 nM, respectively). Furthermore, sterically masked molecule (ProC440) binds to IFNAR2 with significantly reduced affinity (kD = 101.1 nM) compared to the unmasked molecule. As shown in Figs. 38A-38D, each of the peptide masks (Fig. 38A (no peptide mask) vs. Fig. 38B (peptide masked)) and the Fc masks (Fig. 38C (no Fc mask) vs. 38D (Fc masked)) affect binding of the ACC to the receptor. In view of the data, synergistic activity has been obtained through the use of the dual masking structure of the ACCs of the present disclosure. Therefore, both affinity and steric masking decreases binding of the IFN-a2b to IFNAR2.

Example 17: Activation of ACCs by tumor tissues

Fluorescently labeled ProC732 was incubated with enzymatically active tumor samples or low-activity control tissues at 37°C as shown in Fig. 41A as described in (Howng, B, Winter, MB, LePage, C, et al. Novel Ex Vivo Zymography Approach for Assessment of Protease Activity in Tissues with Activatable Antibodies. Pharmaceutics 2021;13:1390). Proteins recovered after 2 or 16 hours of incubation were analyzed for activation status (capillary electrophoresis) and bioactivity (HEK-blue reporter assay). Recovered solution was then analyzed through capillary electrophoresis enabling quantification of active molecules or low-activity control tissue (Fig. 41B) or using HEK-blue IFNA reporter model (Fig. 41C). Enzymatically inactive samples were used as

control tissues. The results demonstrate the activation of ProC732 in the tumor microenvironment.

Incubation with breast carcinoma tumor samples but not low-activity control tissues resulted in appearance of protein products corresponding to molecules expected to be generated after release of steric (Fc fragment) and affinity (CS49 peptide) masks (Fig. 41B). Release of the peptide mask was detected earlier while separation of the Fc mask was more pronounced at the later time point. Pb-IFN-a2b samples incubated with the breast carcinoma tissues, but not control tissues demonstrated increased potency in the IFN pathway activation assay (Fig. 41C). 16h incubation resulted in higher potency as compared to 2h.

The observation is consistent with time-dependent release of the steric and peptide masks from the Pb-IFN-a2b molecule, and therefore, proteolytic activation of Pb-IFN-a2b by tumor tissues.

Example 18: Changes in bioactivity of the interferon molecules after incubation with tumor tissues.

Fully masked Pb-INF-a2b (ProC732) or *in vitro* activated (ProC1640) IFN-a2b proteins were incubated with tumor samples. Proteins recovered after 2, 6 or 24 hours of incubation were analyzed for bioactivity using HEK-blue reporter assay.

Incubation with enzymatically active tumor tissues resulted in activation and enhanced bioactivity of Pb-IFN-a2b. On contrary, incubation with tumor tissues reduced bioactivity of the unmasked interferon, potentially by proteolytic degradation of the molecule. Bioactivity of control samples of both Pb-IFN-a2b and unmasked IFN-a2b did not change upon incubation in the absence of tumor. As shown in Figs. 42A-42C, ProC732 or recombinant IFN-a2b were incubated on TNBC and head and neck ("H&N") tumor tissue sections or in tumor-free glass area at 37°C. Recovered solutions were then analyzed by HEK-blue IFNA reporter model. Figs. 42A and 42B show the fold change of bioactivity of 10 ng/mL ProC732 or 1 ng/mL of recombinant IFN-a2b calculated relative to 0 hour values. Fig. 42C shows bioactivity of ProC732 and IFN-a2b proteins incubated in the absence of tumor tissues for 24h. Each line connects an individual sample (concentration range 100-0.01 ng/mL) analyzed before and after 24h incubation.

The results suggest that exposure to tumor tissue could degrade unmasked interferon molecules in vitro. Masked Pb-IFN-a2b retains and enhances its bioactivity after tumor exposure.

Example 19: Pharmacodynamics of the masked INF-a2b and control molecules in non-human primates

To understand PK/PD properties of the Pb-IFN-a2b in cynomolgus monkey, animals (N=2 per group) were treated with a single dose subcutaneous administration of Pb-IFN-a2b at 0.03, 0.3, 3 or 15 mg/kg. Plasma samples were collected at indicated time points and analyzed for total Pb-IFN-a2b concentration. Concentrations of IP-10 in the serum were measured by the MesoScale Discovery MSD V-plex assay.

Administration of ProC732 resulted in dose-dependent increase in plasma concentrations of the drug starting from the first measurement at 24h after administration (Fig. 43). Plasma concentrations of the Pb-IFN-a2b were maintained for at least 2 weeks after the administration.

Elevated serum concentrations of IP-10 were detected in treated animals as early as 24h after the administration (Fig. 44A). Magnitude of the increase was correlated with dose level; 15 and 3 mg/kg administrations resulted in IP-10 concentrations above 8 and 4 ng/mL respectively. Seven days after the administration, serum levels of IP-10 came back to the physiological concentration in all animals except the monkeys treated with the highest dose level. Concentrations of circulating Pb-IFN-a2b and IP-10 plotted against each other at day 1 and day 7 after administration (Fig. 44B).

The results are consistent with extended half-life of Pb-IFN-a2b in hon-human primates. Transient increase in IP-10 after treatment with high dose of Pb-IFN-a2b indicates that the molecule can activate the type I IFN signaling pathway in non-human primates then given at high dose levels.

Example 20: Gene expression profile changes induced by Pb-INF-a2b non-human primates

Cynomolgus monkeys were treated with Pb-IFN-a2b as described previously. PBMC were isolated from whole blood at 24h after the administration. Gene expression profile changes induced by ProC732 in cynomolgus monkeys were analyzed. Cynomolgus monkey (N=2 per group) were treated with a single dose subcutaneous

administration of ProC732 at 0.03, 0.3, 3 or 15 mg/kg. Bulk mRNA from isolated cells was subjected to paired-end 150c RNAseq high-throughput sequencing. Unique gene hit counts were calculated by using Subread package v.1.5.2. Using DESeq2, a comparison of gene expression between the indicated groups of samples was performed. The Wald test was used to generate p-values and log2 fold changes. Genes with an adjusted p-value < 0.05 and absolute fold change > 3 were called as differentially expressed genes for each comparison.

Administration of Pb-IFN-a2b at all dose levels was associated with upregulation of 35 genes in circulating leucocytes (Fig. 45). Additional numbers of genes (3, 12, and 47) were upregulated by increased dose level of administered Pb-IFN-a2b (0.3, 3, and 15 mg/kg), respectively. Many of the upregulated genes belong to the group identified as ISG, or interferon-stimulated genes, known to be induced by type I interferons. Analysis of individual upregulated genes indicated dose-dependent pattern of induction where most evident changes were associated with the top dose level of the Pb-IFN-a2b. Fig. 46 shows the dose-dependent changes in gene expression. Genes were called differentially expressed if number of reads changes were >3.

The results are consistent with in vivo activation of type I IFN signaling by Pb-IFN-a2b.

Example 21: In vivo characterization of Pb-INFa-A/D

The antitumor activity of the masked IFNa-A/D (ProC1023) was tested in vivo using MC38 tumor model. Mice (N=10 per group) were be implanted subcutaneously with $1.5x10^6$ MC38 cells in serum-free medium. Body weights and tumor measurements were recorded twice weekly for the duration of the study. When the average tumor volume has reached 80 mm^3, mice were dosed with the indicated amounts of ProC1023 by a single subcutaneous injection. Previously we established that masked IFNa-A/D demonstrate antitumor activity in the 50-200 ug dose level. Administration of 50 ug resulted in significant tumor growth inhibition, while administration of 200 ug also resulted in rejection of the tumors by 60% of the animals. In this experiment, animals were euthanized 6 days after the administration and tumors, tumor-draining lymph nodes, and spleens were collected and processed into single-cell suspensions. Composition and

activation of tumor immune infiltrate was analyzed by flow cytometry performed with total cells and gated on viable CD45+CD3+ subsets.

In mice treated with Pb-IFNa-A/D, CD8+ T cell subset in tumor microenvironment (TME), but not in peripheral tissues demonstrated enhanced activation, including production of effector molecules associated with tumoricidal activity (Fig. 47). Granzyme B is an effector molecule of cytotoxic T cells that could be induced by type I interferon signaling. Administration of Pb-IFNa-A/D was associated with significant increase in frequency of Granzyme B positive and CD69 positive CD8+ T cells in tumors, while where was no major changes in peripheral tissues, including tumor-draining lymph nodes.

Thus, the data show that Pb-IFNa-A/D mediates immune activation in tumor but not in periphery. The pattern of immune activation was generally consistent with published effects of type I interferon. The tumor-preferred manner of immune activation shows activation of the ACCs by tumors through proteolytic cleavage. The observation is in agreement with immune-mediated mechanism of MC38 tumor growth suppression by Pb-IFNa-A/D.

Example 22: *In vivo* tolerability of the Pb-IFN-a2b

Human IFNα-2b cross-reacts with hamster IFNα receptor and has been previously shown to be active in hamsters (Altrock et al, Journal of Interferon Research, 1986). Improved tolerability of the ProC732 compared to unmasked IFN-a2b-Fc fusion (ProC286) or single (sterically) masked IFN-a2b (ProC440) in hamsters after single administration was shown in Example 2. In this example, tolerability of the Pb-IFNα-2b in Syrian Gold Hamsters was determined after multiple administrations.

Animals (N=5 per group) were dosed with ProC732 15, 30 or 60 mg/kg dose level or unmasked IFN-a2b-Fc fusion protein (ProC286) at 7.5 or 15 mg/kg dose level, i.p. once weekly for total 3 administrations. Clinical observations, body weights & temperature were measured prior to dosing, and twice weekly thereafter. Animals dosed with the unmasked IFN molecules (ProC286) showed significant body weight loss as early as 3 days after first administration (Fig. 48). The first animal dosed with 15 mg/kg ProC286 was euthanized at day 10 due to excessive weight loss (>25%) and all the other animals were either euthanized due to excessive weight loss, inactivity and lethargy or

were found dead between days 11 and 19. Similar observations were made for the animals treated with lower (7.5 mg/kg) dose of the unmasked INF-a2b. In contrast, none of the animals treated with ProC732 up to 30 mg/kg demonstrated significant loss of weight or morbidity.

Table 19. The survival of the animals is shown in Fig. 48 and the table below

	3.75 mg/kg	**7.5 mg/kg**	**15 mg/kg**	**30 mg/kg**	**60 mg/kg**
Pb-IFN-a2b (masked)			tolerated	tolerated	tolerated
Fc-IFN-a2b (unmasked)	tolerated	3/5 survival	0/5 survival		

The results are in agreement with increased safety of Pb-IFN-a2b due to the use of the dual masking structure used in the present disclosure.

Example 23: Reduced cytokine and chemokine release in cynomolgus monkey tretad with single dose administration of the Pb-IFN-a2b

To understand effect of masking of the Pb-IFN-a2b in cynomolgus monkeys, animals (N=2 per group) were treated with a single dose subcutaneous administration of Pb-IFN-a2b (ProC732) at 1 mg/kg of unmasked control molecule ProC286 at 1 or 0.1 mg/kg. Plasma samples were collected at indicated time points and analyzed for IP-10, MIP-1b and IL-12p70 concentrations using the multiplex MSD V-plex assay.

As shown in Fig. 49, administration of ProC732 resulted in elevation of the plasma IP-10 and MIP-1b level 6 hours after the administration. Plasma concentrations of all measured molecules were higher in animals treated with unmasked molecule at high and low dose level. 24 hours after the administration only slight elevation of IP-10 was noted in animals treated with ProC732. On contrary, animals received 1 mg/kg of ProC286 demonstrated highly elevated IP-10 levels. IP-10 elevation observed 24 hours after administration of 0.1 mg/kg ProC286 was greater than such induced by 10-fold higher dose of ProC732.

The results indicate attenuated induction of biomarkers of type I interferon response in non-human primates treated with ProC732 as compared to unmasked cytokine-Fc fusion. The observation is in agreement with masking effects.

Example 24: Tolerability of the multiple administrtions of the Pb-IFN-a2b in non-human primates

The objectives of this study were to determine the potential toxicity of Pb-IFN-a2b (ProC732) when administered by intravenous infusion or subcutaneous injection once weekly for 3 weeks to cynomolgus monkeys (3 total doses). In addition, the pharmacokinetics of the test article, Pb-IFN-a2b were investigated (see Example 25).

The study design was as follows:

Table 20

Group No.[c]	Test Article	Dose Level (mg/kg)[a]	Dose Volume (mL/kg)	Dose Concentration (mg/mL)	Dose Administration Route	No. of Animals[b]	
						Males	Females
1	ProC732	7.5	10	0.75	IV	2	2
2	ProC732	15	10	1.5	IV	2	2
3	ProC732	30	10	3	IV	2	2
4	ProC732	30	10	3	SC	1	1
5	ProC732	60	12	5	IV	2	2

IV = intravenous infusion; SC = subcutaneous injection.
[a] Based on the most recent body weight measurement.
[b] Animals were euthanized on Day 18.
[c] Groups 3 and 4 were dosed 7 days following Day 1 of Groups 1 and 2. Group 5 was dosed 20 days following Day 1 of Groups 3 and 4.

The following parameters and end points were evaluated in this study: mortality, clinical observations, body weights, body temperature, qualitative food consumption, clinical pathology parameters (hematology and clinical chemistry), peripheral blood mononuclear cells collection, organ weights, and macroscopic and microscopic examinations.

Observations summary was as follows:

Table 21

	7.5 mg/kg	15 mg/kg	30 mg/kg	60 mg/kg
Adverse effects	-	-	-	-
CRP elevation	+/-	+	++	++
WBC reduction	+	+/-	++	++
IP-10 elevation	++	++	++	++

All animals survived until the scheduled necropsy on Day 18. There were no drug-related changes in body weights, qualitative food consumption, or body temperature. There were no definitive Pb-IFN-a2b-related clinical observations and no changes in food consumption. Decreases in the total WBC count and/or 1 or more WBC subsets were observed in 1 or more animals at various time points at all doses and lacked a dose response. These decreases included minimal to marked decreases in neutrophils (except in males and females at 30 mg/kg SC, and females at 15 mg/kg IV) with evidence of accelerated neutrophil maturation and release (band forms, Döhle bodies, and/or cytoplasmic basophilia) in individual animals, including some that lacked decreases in neutrophils and minimally to mildly decreased lymphocytes in males and females at 7.5 and 30 mg/kg IV and in the male at 30 mg/kg SC. There were also decreases in monocytes and/or eosinophils at all doses except females at 30 mg/kg SC. There were also minimal to mild increases in CRP in males and females at all doses except females at 7.5 mg/kg IV indicating a mild acute phase response that may have contributed to the decrease in albumin.

In conclusion, administration of Pb-IFN-a2b once weekly for 3 weeks (3 total doses) by IV infusion at levels of 7.5, 15, 30 and 60 mg/kg or SC injection at a dose level of 30 mg/kg were clinically tolerated in cynomolgus monkeys. Clinical pathology changes were observed at all doses at 1 or more time point, but they lacked a dose response, most were minimal to mild in magnitude and often found in individual animals. These changes were generally of higher magnitude and incidence on Days 11 and/or 18. Pb-IFN-a2b-related microscopic findings were observed in most of the tissues evaluated and at all dose levels and both dose routes evaluated.

Example 25: Pharmacokinetics of Pb-IFN-a2b during multiple administrtions of the Pb-IFN-a2b to non-human primates

The objectives of this study were to determine the pharmacokinetics of Pb-IFN-a2b (ProC732) when administered by intravenous infusion or subcutaneous injection once weekly for 3 weeks to cynomolgus monkeys (3 total doses). In addition, the potential toxicity of the test article, Pb-IFN-a2b were investigated (see Example 24).

The study design was as follows:

Table 22

Group No.[c]	Test Article	Dose Level (mg/kg)[a]	Dose Volume (mL/kg)	Dose Concentration (mg/mL)	Dose Administration Route	No. of Animals[b]	
						Males	Females
1	ProC732	7.5	10	0.75	IV	2	2
2	ProC732	15	10	1.5	IV	2	2
3	ProC732	30	10	3	IV	2	2
4	ProC732	30	10	3	SC	1	1
5	ProC732	60	12	5	IV	2	2

IV = intravenous infusion; SC = subcutaneous injection.
[a] Based on the most recent body weight measurement.
[b] Animals were euthanized on Day 18.
[c] Groups 3 and 4 were dosed 7 days following Day 1 of Groups 1 and 2. Group 5 was dosed 20 days following Day 1 of Groups 3 and 4.

Bioanalysis (stability of Pb-IFN-a2b investigated by LC-MS) and pharmacokinetic parameters were evaluated in this study.

As indicated in Fig. 53, Pb-IFN-a2b demonstrates extended, dose-proportional PK profile. Expectected differences were observed between subcutaneous and intravenous administration. Time to maximal plasma concentrations was delayed and magnitude of the peak was reduced after subcutaneous administration as compared to intravenous.

There were no significant differences between the detected concentrations of total and intact forms of Pb-IFN-a2b. This observation is consistent with preservation of masking properties of Pb-IFN-a2b in non-human primates during 15-days circulation.

Example 26: Antitumor efficacy of the multiple administrtions of the Pb-IFN-a2b in RPMI 1846 melanoma-bearing hamsters

Human IFNα-2b cross-reacts with hamster IFNα receptor and has been previously shown to be active in hamsters (Altrock et al, Journal of Interferon Research, 1986). Improved tolerability of the Pb-IFN-a2b (ProC732) compared to the unmasked IFN-a2b-Fc fusion (ProC286) in hamsters was shown in Examples 2 and 22. In this example, antitumor efficacy of the Pb-IFNα-2b was determined using RPMI1846 hamster melanoma model (Palencia et al, Journal of Experimental Therapeutics and Oncology, 2002).

80 Syrian female Hamsters of 9-11 weeks of age were inoculated subcutaneously into the right lower flank (near the dorsal thigh region) with a single cell suspension of 95% viable tumor cells in 0.1 mL of serum-free McCoy's 5a medium. The total number of cells implanted in the right side was 10 mln cells per hamster. After formation of palpable tumors, hamsters were weighed and assigned to treatment groups using a randomization procedure. Since tumor volume can influence the effectiveness of any given treatment, the hamsters with tumors ranging between 200-350 mm3 were enrolled in the study and randomized into groups based on tumor volume. Animals (N=10 per group) were dosed with Pb-IFN-a2b 5, 10, or 20 mg/kg dose i.p. twice weekly for total of 8 administrations. Tumors were measured twice a week in two dimensions using a caliper, and the volume was expressed in mm3 using the formula: V = 0.5 (a x b x c) where a, b, and c are the length, width, and height of the tumor, respectively.

Anti-tumor efficacy was evaluated by tumor growth. Animals treated with 20 mg/kg of Pb-IFN-a2b significantly delayed tumor growth compared to control animals (Fig. 50). Additionally, median survival in the group treated with 20 mg/kg dose level was significantly longer compared to the control group (as analyzed by Kaplan-Meier survival curve and Log-rank test). Also, median survival in the treatment group was significantly longer compared to the 5 and 10 mg/kg treatment groups. Therefore, dose

level of 20 mg/kg of Pb-IFN-a2b was associated with anti-tumor efficacy, whereas dose levels of 5 and 10 mg/kg do not demonstrate anti-tumor efficacy.

These results should be taken in the context of equal efficacy of umasked and masked INF-a2b molecules demonstrated in the example 6 and increased tolerability of the masked molecule demonstrated in the Example 22. Altogether the results are in agreement with increased therapeutic interval of the dual masked Pb-IFN-a2b molecule compared to the unmasked benchmark controls.

Table 23. Example sequences

SEQ ID NO.	NAME	SEQUENCE
1	Human Interferon-alpha-2b	CDLPQTHSLGSRRTLMLLAQMRRISLFSCLKDRHDFGF PQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAW DETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKE DSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSF SLSTNLQESLRSKE
2	Linker	GGGS
3	Human IgG4, S228P truncated Fc Region	CPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISK AKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLSLS
4	Human IgG4 Fc region, with S228P mutation and full hinge	ESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREE QFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSS IEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SRLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS
5	CM	LSGRSDNH
6	CM	TGRGPSWV
7	CM	PLTGRSGG
8	CM	TARGPSFK
9	CM	NTLSGRSENHSG
10	CM	NTLSGRSGNHGS
11	CM	TSTSGRSANPRG

12	CM	TSGRSANP
13	CM	VHMPLGFLGP
14	CM	AVGLLAPP
15	CM	AQNLLGMV
16	CM	QNQALRMA
17	CM	LAAPLGLL
18	CM	STFPFGMF
19	CM	ISSGLLSS
20	CM	PAGLWLDP
21	CM	VAGRSMRP
22	CM	VVPEGRRS
23	CM	ILPRSPAF
24	CM	MVLGRSLL
25	CM	QGRAITFI
26	CM	SPRSIMLA
27	CM	SMLRSMPL
28	CM	ISSGLLSGRSDNH
29	CM	AVGLLAPPGGLSGRSDNH
30	CM	ISSGLLSSGGSGGSLSGRSDNH
31	CM	LSGRSGNH
32	CM	SGRSANPRG
33	CM	LSGRSDDH
34	CM	LSGRSDIH
35	CM	LSGRSDQH
36	CM	LSGRSDTH
37	CM	LSGRSDYH
38	CM	LSGRSDNP
39	CM	LSGRSANP
40	CM	LSGRSANI
41	CM	LSGRSDNI

42	CM	MIAPVAYR
43	CM	RPSPMWAY
44	CM	WATPRPMR
45	CM	FRLLDWQW
46	CM	ISSGL
47	CM	ISSGLLS
48	CM	ISSGLL
49	CM	ISSGLLSGRSANPRG
50	CM	AVGLLAPPTSGRSANPRG
51	CM	AVGLLAPPSGRSANPRG
52	CM	ISSGLLSGRSDDH
53	CM	ISSGLLSGRSDIH
54	CM	ISSGLLSGRSDQH
55	CM	ISSGLLSGRSDTH
56	CM	ISSGLLSGRSDYH
57	CM	ISSGLLSGRSDNP
58	CM	ISSGLLSGRSANP
59	CM	ISSGLLSGRSANI
60	CM	AVGLLAPPGGLSGRSDDH
61	CM	AVGLLAPPGGLSGRSDIH
62	CM	AVGLLAPPGGLSGRSDQH
63	CM	AVGLLAPPGGLSGRSDTH
64	CM	AVGLLAPPGGLSGRSDYH
65	CM	AVGLLAPPGGLSGRSDNP
66	CM	AVGLLAPPGGLSGRSANP
67	CM	AVGLLAPPGGLSGRSANI
68	CM	ISSGLLSGRSDNI
69	CM	AVGLLAPPGGLSGRSDNI
70	CM	GLSGRSDNHGGAVGLLAPP
71	CM	GLSGRSDNHGGVHMPLGFLGP

72	CM	LSGRSDNHGGVHMPLGFLGP
73	CM	ISSGLSS
74	CM	PVGYTSSL
75	CM	DWLYWPGI
76	CM	LKAAPRWA
77	CM	GPSHLVLT
78	CM	LPGGLSPW
79	CM	MGLFSEAG
80	CM	SPLPLRVP
81	CM	RMHLRSLG
82	CM	LLAPSHRA
83	CM	GPRSFGL
84	CM	GPRSFG
85	CM	SARGPSRW
86	CM	GGWHTGRN
87	CM	HTGRSGAL
88	CM	AARGPAIH
89	CM	RGPAFNPM
90	CM	SSRGPAYL
91	CM	RGPATPIM
92	CM	RGPA
93	CM	GGQPSGMWGW
94	CM	FPRPLGITGL
95	CM	SPLTGRSG
96	CM	SAGFSLPA
97	CM	LAPLGLQRR
98	CM	SGGPLGVR
99	CM	PLGL
100	CM	SGRSDNI

101	Human Interferon alpha-2a	CDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGF PQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWD ETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKEDS ILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSFSLS TNLQESLRSKE
102	Rat Interferon alpha-2	CDLPHTHNLRNKRAFTLLAQMRRLSPVSCLKDRKDFG FPLEKVDGQQIQKAQAIPVLHELTQQILSLFTSKESSTA WDASLLDSFCNDLQQQLSGLQACLMQQVGVQESPLTQ EDSLLAVREYFHRITVYLREKKHSPCAWEVVRAEVWR ALSSSANLLGRLREERNES
103	Mouse Interferon alpha-2	CDLPHTYNLRNKRALKVLAQMRRLPFLSCLKDRQDFG FPLEKVDNQQIQKAQAIPVLRDLTQQTLNLFTSKASSA AWNATLLDSFCN DLHQQLNDLQ TCLMQQVGVQ EPPLTQEDAL LAVRKYFHRITVYLREKKHS PCAWEVVRAE VWRALSSSVN LLPRLSEEKE
104	Human Interferon Alpha-2b	CDLPQTHSLGSRRTLMLLAQMRRISLFSCLKDRHDFGF PQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWD ETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKEDS ILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSFSLS TNLQESLRSKE
105	Human Interferon Alpha-n3	CDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGF PQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWD ETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKEDS ILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSFSLS TNLQESLRSKECDLPQTHSLGSRRTLMLLAQMRRISLFS CLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLF STKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVG VTETPLMNEDSILAVRKYFQRITLYLKEKKYSPCAWEV VRAEIMRSFSLSTNLQESLRSKECDLPQTHSLGSRRTLM LLAQMRRISLFSCLKDRRDFGFPQEEFGNQFQKAETIPV LHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLN

		DLEACVIQGVGVTETPLMNEDSILAVRKYFQRITLYLKE KKYSPCAWEVVRAEIMRSFSLSTNLQESLRSKE
106	Human Interferon beta-1a	MSYNLLGFLQRSSNFQCQKLLWQLNGRLEYCLKDRM NFDIPEEIKQLQQFQKEDAALTIYEMLQNIFAIFRQDSSS TGWNETIVENLLANVYHQINHLKTVLEEKLEKEDFTR GKLMSSLHLKRYYGRILHYLKAKEYSHCAWTIVRVEIL RNFYFINRLTGYLRN
107	Human Interferon beta-1b	SYNLLGFLQRSSNFQSQKLLWQLNGRLEYCLKDRMNF DIPEEIKQLQQFQKEDAALTIYEMLQNIFAIFRQDSSSTG WNETIVENLLANVYHQINHLKTVLEEKLEKEDFTRGK LMSSLHLKRYYGRILHYLKAKEYSHCAWTIVRVEILRN FYFINRLTGYLRN
108	Mouse Interferon-Beta	MNNRWILHAAFLLCFSTTALSINYKQLQLQERTNIRKC QELLEQLNGKINLTYRADFKIPMEMTEKMQKSYTAFAI QEMLQNVFLVFRNNFSSTGWNETIVVRLLDELHQQTV FLKTVLEEKQEERLTWEMSSTALHLKSYYWRVQRYLK LMKYNSYAWMVVRAEIFRNFLIIRRLTRNFQN
109	Rat Interferon-Beta	MANRWTLHIAFLLCFSTTALSIDYKQLQFRQSTSIRTCQ KLLRQLNGRLNLSYRTDFKIPMEVMHPSQMEKSYTAF AIQVMLQNVFLVFRSNFSSTGWNETIVESLLDELHQQT ELLEIILKEKQEERLTWVTSTTTLGLKSYYWRVQRYLK DKKYNSYAWMVVRAEVFRNFSIILRLNRNFQN
110	Human Interferon Omega	MCDLPQNHGLLSRNTLVLLHQMRRISPFLCLKDRRDFR FPQEMVKGSQLQKAHVMSVLHEMLQQIFSLFHTERSS AAWNMTLLDQLHTGLHQQLQHLETCLLQVVGEGESA GAISSPALTLRRYFQGIRVYLKEKKYSDCAWEVVRMEI MKSLFLSTNMQERLRSKDRDLGSS
111	Human IL-1 alpha	MAKVPDMFEDLKNCYSENEEDSSSIDHLSLNQKSFYH VSYGPLHEGCMDQSVSLSISETSKTSKLTFKESMVVVA TNGKVLKKRRLSLSQSITDDDLEAIANDSEEEIIKPRSAP

		FSFLSNVKYNFMRIIKYEFILNDALNQSIIRANDQYLTA AALHNLDEAVKFDMGAYKSSKDDAKITVILRISKTQLY VTAQDEDQPVLLKEMPEIPKTITGSETNLLFFWETHGT KNYFTSVAHPNLFIATKQDYWVCLAGGPPSITDFQILE NQA
112	Mouse IL-1 alpha	MAKVPDLFEDLKNCYSENEDYSSAIDHLSLNQKSFYD ASYGSLHETCTDQFVSLRTSETSKMSNFTFKESRVTVS ATSSNGKILKKRRLSFSETFTEDDLQSITHDLEETIQPRS APYTYQSDLRYKLMKLVRQKFVMNDSLNQTIYQDVD KHYLSTTWLNDLQQEVKFDMYAYSSGGDDSKYPVTL KISDSQLFVSAQGEDQPVLLKELPETPKLITGSETDLIFF WKSINSKNYFTSAAYPELFIATKEQSRVHLARGLPSMT DFQIS
113	Human IL-1 beta	MAEVPELASEMMAYYSGNEDDLFFEADGPKQMKCSF QDLDLCPLDGGIQLRISDHHYSKGFRQAASVVVAMDK LRKMLVPCPQTFQENDLSTFFPFIFEEEPIFFDTWDNEA YVHDAPVRSLNCTLRDSQQKSLVMSGPYELKALHLQG QDMEQQVVFSMSFVQGEESNDKIPVALGLKEKNLYLS CVLKDDKPTLQLESVDPKNYPKKKMEKRFVFNKIEINN KLEFESAQFPNWYISTSQAENMPVFLGGTKGGQDITDF TMQFVSS
114	Mouse IL-1 beta	MATVPELNCEMPPFDSDENDLFFEVDGPQKMKGCFQT FDLGCPDESIQLQISQQHINKSFRQAVSLIVAVEKLWQL PVSFPWTFQDEDMSTFFSFIFEEEPILCDSWDDDDNLLV CDVPIRQLHYRLRDEQQKSLVLSDPYELKALHLNGQNI NQQVIFSMSFVQGEPSNDKIPVALGLKGKNLYLSCVM KDGTPTLQLESVDPKQYPKKKMEKRFVFNKIEVKSKV EFESAEFPNWYISTSQAEHKPVFLGNNSGQDIIDFTMES VSS
115	Human IL-1RA	MEICRGLRSHLITLLLFLFHSETICRPSGRKSSKMQAFRI WDVNQKTFYLRNNQLVAGYLQGPNVNLEEKIDVVPIE

		PHALFLGIHGGKMCLSCVKSGDETRLQLEAVNITDLSE NRKQDKRFAFIRSDSGPTTSFESAACPGWFLCTAMEAD QPVSLTNMPDEGVMVTKFYFQEDE
116	Mouse IL-1RA	MEICWGPYSHLISLLLILLFHSEAACRPSGKRPCKMQAF RIWDTNQKTFYLRNNQLIAGYLQGPNIKLEEKIDMVPI DLHSVFLGIHGGKLCLSCAKSGDDIKLQLEEVNITDLSK NKEEDKRFTFIRSEKGPTTSFESAACPGWFLCTTLEADR PVSLTNTPEEPLIVTKFYFQEDQ
117	Human IL-18	MAAEPVEDNCINFVAMKFIDNTLYFIAEDDENLESDYF GKLESKLSVIRNLNDQVLFIDQGNRPLFEDMTDSDCRD NAPRTIFIISMYKDSQPRGMAVTISVKCEKISTLSCENKI ISFKEMNPPDNIKDTKSDIIFFQRSVPGHDNKMQFESSS YEGYFLACEKERDLFKLILKKEDELGDRSIMFTVQNED
118	Mouse IL-18	MAAMSEDSCVNFKEMMFIDNTLYFIPEENGDLESDNF GRLHCTTAVIRNINDQVLFVDKRQPVFEDMTDIDQSAS EPQTRLIIYMYKDSEVRGLAVTLSVKDSKMSTLSCKNK IISFEEMDPPENIDDIQSDLIFFQKRVPGHNKMEFESSLY EGHFLACQKEDDAFKLILKKKDENGDKSVMFTLTNLH QS
119	Human IL-2	MYRMQLLSCIALSLALVTNSAPTSSSTKKTQLQLEHLL LDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKH LQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVL ELKGSETTFMCEYADETATIVEFLNRWITFCQSIIS
120	Mouse IL-2	MYSMQLASCVTLTLVLLVNSAPTSSSTSSSTAEAQQQQ QQQQQQQQHLEQLLMDLQELLSRMENYRNLKLPRML TFKFYLPKQATELKDLQCLEDELGPLRHVLDLTQSKSF QLEDAENFISNIRVTVVKLKGSDNTFECQFDDESATVV DFLRRWIAFCQSIISTSPQ
121	Human IL-4	MGLTSQLLPPLFFLLACAGNFVHGHKCDITLQEIIKTLN SLTEQKTLCTELTVTDIFAASKNTTEKETFCRAATVLR

		QFYSHHEKDTRCLGATAQQFHRHKQLIRFLKRLDRNL WGLAGLNSCPVKEANQSTLENFLERLKTIMREKYSKC SS
122	Mouse IL-4	MGLNPQLVVILLFFLECTRSHIHGCDKNHLREIIGILNE VTGEGTPCTEMDVPNVLTATKNTTESELVCRASKVLRI FYLKHGKTPCLKKNSSVLMELQRLFRAFRCLDSSISCT MNESKSTSLKDFLESLKSIMQMDYS
123	Human IL-7	MFHVSFRYIFGLPPLILVLLPVASSDCDIEGKDGKQYES VLMVSIDQLLDSMKEIGSNCLNNEFNFFKRHICDANKE GMFLFRAARKLRQFLKMNSTGDFDLHLLKVSEGTTILL NCTGQVKGRKPAALGEAQPTKSLEENKSLKEQKKLND LCFLKRLLQEIKTCWNKILMGTKEH
124	Mouse IL-7	MFHVSFRYIFGIPPLILVLLPVTSSECHIKDKEGKAYESV LMISIDELDKMTGTDSNCPNNEPNFFRKHVCDDTKEAA FLNRAARKLKQFLKMNISEEFNVHLLTVSQGTQTLVN CTSKEEKNVKEQKKNDACFLKRLLREIKTCWNKILKG SI
125	Human IL-9	MLLAMVLTSALLLCSVAGQGCPTLAGILDINFLINKMQ EDPASKCHCSANVTSCLCLGIPSDNCTRPCFSERLSQMT NTTMQTRYPLIFSRVKKSVEVLKNNKCPYFSCEQPCNQ TTAGNALTFLKSLLEIFQKEKMRGMRGKI
126	Mouse IL-9	MLVTYILASVLLFSSVLGQRCSTTWGIRDTNYLIENLK DDPPSKCSCSGNVTSCLCLSVPTDDCTTPCYREGLLQL TNATQKSRLLPVFHRVKRIVEVLKNITCPSFSCEKPCNQ TMAGNTLSFLKSLLGTFQKTEMQRQKSRP
127	Human IL-13	MHPLLNPLLLALGLMALLLTTVIALTCLGGFASPGPVP PSTALRELIEELVNITQNQKAPLCNGSMVWSINLTAGM YCAALESLINVSGCSAIEKTQRMLSGFCPHKVSAGQFS SLHVRDTKIEVAQFVKDLLLHLKKLFREGRFN

128	Mouse IL-13	MALWVTAVLALACLGGLAAPGPVPRSVSLPLTLKELIE ELSNITQDQTPLCNGSMVWSVDLAAGGFCVALDSLTNI SNCNAIYRTQRILHGLCNRKAPTTVSSLPDTKIEVAHFI TKLLSYTKQLFRHGPF
129	Human IL-15	MRISKPHLRSISIQCYLCLLLNSHFLTEAGIHVFILGCFS AGLPKTEANWVNVISDLKKIEDLIQSMHIDATLYTESD VHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIIL ANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQ MFINTS
130	Mouse IL-15	MKILKPYMRNTSISCYLCFLLNSHFLTEAGIHVFILGCV SVGLPKTEANWIDVRYDLEKIESLIQSIHIDTTLYTDSDF HPSCKVTAMNCFLLELQVILHEYSNMTLNETVRNVLY LANSTLSSNKNVAESGCKECEELEEKTFTEFLQSFIRIV QMFINTS
131	Human IL-3	MSRLPVLLLLQLLVRPGLQAPMTQTTPLKTSWVNCSN MIDEIITHLKQPPLPLLDFNNLNGEDQDILMENNLRRPN LEAFNRAVKSLQNASAIESILKNLLPCLPLATAAPTRHP IHIKDGDWNEFRRKLTFYLKTLENAQAQQTTLSLAIF
132	Mouse IL-3	MVLASSTTSIHTMLLLLLMLFHLGLQASISGRDTHRLT RTLNCSSIVKEIIGKLPEPELKTDDEGPSLRNKSFRRVNL SKFVESQGEVDPEDRYVIKSNLQKLNCCLPTSANDSAL PGVFIRDLDDFRKKLRFYMVHLNDLETVLTSRPPQPAS GSVSPNRGTVEC
133	Human IL-5	MRMLLHLSLLALGAAYVYAIPTEIPTSALVKETLALLS THRTLLIANETLRIPVPVHKNHQLCTEEIFQGIGTLESQT VQGGTVERLFKNLSLIKKYIDGQKKKCGEERRRVNQF LDYLQEFLGVMNTEWIIES
134	Mouse IL-5	MRRMLLHLSVLTLSCVWATAMEIPMSTVVKETLTQLS AHRALLTSNETMRLPVPTHKNHQLCIGEIFQGLDILKN

		QTVRGGTVEMLFQNLSLIKKYIDRQKEKCGEERRRTR QFLDYLQEFLGVMSTEWAMEG
135	Human GM-CSF	MWLQSLLLLGTVACSISAPARSPSPSTQPWEHVNAIQE ARRLLNLSRDTAAEMNETVEVISEMFDLQEPTCLQTRL ELYKQGLRGSLTKLKGPLTMMASHYKQHCPPTPETSC ATQIITFESFKENLKDFLLVIPFDCWEPVQE
136	Mouse GM-CSF	MWLQNLLFLGIVVYSLSAPTRSPITVTRPWKHVEAIKE ALNLLDDMPVTLNEEVEVVSNEFSFKKLTCVQTRLKIF EQGLRGNFTKLKGALNMTASYYQTYCPPTPETDCETQ VTTYADFIDSLKTFLTDIPFECKKPGQK
137	Human IL-6	MNSFSTSAFGPVAFSLGLLLVLPAAFPAPVPPGEDSKD VAAPHRQPLTSSERIDKQIRYILDGISALRKETCNKSNM CESSKEALAENNLNLPKMAEKDGCFQSGFNEETCLVKI ITGLLEFEVYLEYLQNRFESSEEQARAVQMSTKVLIQFL QKKAKNLDAITTPDPTTNASLLTKLQAQNQWLQDMTT HLILRSFKEFLQSSLRALRQM
138	Mouse IL-6	MKFLSARDFHPVAFLGLMLVTTTAFPTSQVRRGDFTE DTTPNRPVYTTSQVGGLITHVLWEIVEMRKELCNGNS DCMNNDDALAENNLKLPEIQRNDGCYQTGYNQEICLL KISSGLLEYHSYLEYMKNNLKDNKKDKARVLQRDTET LIHIFNQEVKDLHKIVLPTPISNALLTDKLESQKEWLRT KTIQFILKSLEEFLKVTLRSTRQT
139	Human IL-11	MNCVCRLVLVVLSLWPDTAVAPGPPPGPPRVSPDPRA ELDSTVLLTRSLLADTRQLAAQLRDKFPADGDHNLDS LPTLAMSAGALGALQLPGVLTRLRADLLSYLRHVQWL RRAGGSSLKTLEPELGTLQARLDRLLRRLQLLMSRLAL PQPPPDPPAPPLAPPSSAWGGIRAAHAILGGLHLTLDW AVRGLLLLKTRL
140	Mouse IL-11	MNCVCRLVLVVLSLWPDRVVAPGPPAGSPRVSSDPRA DLDSAVLLTRSLLADTRQLAAQMRDKFPADGDHSLDS

		LPTLAMSAGTLGSLQLPGVLTRLRVDLMSYLRHVQWL RRAGGPSLKTLEPELGALQARLERLLRRLQLLMSRLAL PQAAPDQPVIPLGPPASAWGSIRAAHAILGGLHLTLDW AVRGLLLLKTRL
141	Human G-CSF	MAGPATQSPMKLMALQLLLWHSALWTVQEATPLGPA SSLPQSFLLKCLEQVRKIQGDGAALQEKLVSECATYKL CHPEELVLLGHSLGIPWAPLSSCPSQALQLAGCLSQLHS GLFLYQGLLQALEGISPELGPTLDTLQLDVADFATTIW QQMEELGMAPALQPTQGAMPAFASAFQRRAGGVLVA SHLQSFLEVSYRVLRHLAQP
142	Mouse G-CSF	MAQLSAQRRMKLMALQLLLWQSALWSGREAVPLVT VSALPPSLPLPRSFLLKSLEQVRKIQASGSVLLEQLCAT YKLCHPEELVLLGHSLGIPKASLSGCSSQALQQTQCLS QLHSGLCLYQGLLQALSGISPALAPTLDLLQLDVANFA TTIWQQMENLGVAPTVQPTQSAMPAFTSAFQRRAGGV LAISYLQGFLETARLALHHLA
143	Human IL-12 alpha	MCPARSLLLVATLVLLDHLSLARNLPVATPDPGMFPCL HHSQNLLRAVSNMLQKARQTLEFYPCTSEEIDHEDITK DKTSTVEACLPLELTKNESCLNSRETSFITNGSCLASRK TSFMMALCLSSIYEDLKMYQVEFKTMNAKLLMDPKR QIFLDQNMLAVIDELMQALNFNSETVPQKSSLEEPDFY KTKIKLCILLHAFRIRAVTIDRVMSYLNAS
144	Human IL-12 beta	MCHQQLVISWFSLVFLASPLVAIWELKKDVYVVELDW YPDAPGEMVVLTCDTPEEDGITWTLDQSSEVLGSGKTL TIQVKEFGDAGQYTCHKGGEVLSHSLLLLHKKEDGIW STDILKDQKEPKNKTFLRCEAKNYSGRFTCWWLTTIST DLTFSVKSSRGSSDPQGVTCGAATLSAERVRGDNKEY EYSVECQEDSACPAAEESLPIEVMVDAVHKLKYENYT SSFFIRDIIKPDPPKNLQLKPLKNSRQVEVSWEYPDTWS TPHSYFSLTFCVQVQGKSKREKKDRVFTDKTSATVICR KNASISVRAQDRYYSSSWSEWASVPCS

145	Mouse IL-12 beta	MCPQKLTISWFAIVLLVSPLMAMWELEKDVYVVEVD WTPDAPGETVNLTCDTPEEDDITWTSDQRHGVIGSGKT LTITVKEFLDAGQYTCHKGGETLSHSHLLLHKKENGIW STEILKNFKNKTFLKCEAPNYSGRFTCSWLVQRNMDL KFNIKSSSSSPDSRAVTCGMASLSAEKVTLDQRDYEKY SVSCQEDVTCPTAEETLPIELALEARQQNKYENYSTSFF IRDIIKPDPPKNLQMKPLKNSQVEVSWEYPDSWSTPHS YFSLKFFVRIQRKKEKMKETEEGCNQKGAFLVEKTSTE VQCKGGNVCVQAQDRYYNSSCSKWACVPCRVRS
146	Mouse IL-12 alpha	MCQSRYLLFLATLALLNHLSLARVIPVSGPARCLSQSR NLLKTTDDMVKTAREKLKHYSCTAEDIDHEDITRDQT STLKTCLPLELHKNESCLATRETSSTTRGSCLPPQKTSL MMTLCLGSIYEDLKMYQTEFQAINAALQNHNHQQIIL DKGMLVAIDELMQSLNHNGETLRQKPPVGEADPYRV KMKLCILLHAFSTRVVTINRVMGYLSSA
147	Human LIF	MKVLAAGVVPLLLVLHWKHGAGSPLPITPVNATCAIR HPCHNNLMNQIRSQLAQLNGSANALFILYYTAQGEPFP NNLDKLCGPNVTDFPPFHANGTEKAKLVELYRIVVYL GTSLGNITRDQKILNPSALSLHSKLNATADILRGLLSNV LCRLCSKYHVGHVDVTYGPDTSGKDVFQKKKLGCQL LGKYKQIIAVLAQAF
148	Mouse LIF	MKVLAAGIVPLLLLVLHWKHGAGSPLPITPVNATCAIR HPCHGNLMNQIKNQLAQLNGSANALFISYYTAQGEPFP NNVEKLCAPNMTDFPSFHGNGTEKTKLVELYRMVAY LSASLTNITRDQKVLNPTAVSLQVKLNATIDVMRGLLS NVLCRLCNKYRVGHVDVPPVPDHSDKEAFQRKKLGC QLLGTYKQVISVVVQAF
149	Human OSM	MGVLLTQRTLLSLVLALLFPSMASMAAIGSCSKEYRVL LGQLQKQTDLMQDTSRLLDPYIRIQGLDVPKLREHCRE RPGAFPSEETLRGLGRRGFLQTLNATLGCVLHRLADLE QRLPKAQDLERSGLNIEDLEKLQMARPNILGLRNNIYC

		MAQLLDNSDTAEPTKAGRGASQPPTPTPASDAFQRKL EGCRFLHGYHRFMHSVGRVFSKWGESPNRSRRHSPHQ ALRKGVRRTRPSRKGKRLMTRGQLPR
150	Mouse OSM	MQTRLLRTLLSLTLSLLILSMALANRGCSNSSSQLLSQL QNQANLTGNTESLLEPYIRLQNLNTPDLRAACTQHSVA FPSEDTLRQLSKPHFLSTVYTTLDRVLYQLDALRQKFL KTPAFPKLDSARHNILGIRNNVFCMARLLNHSLEIPEPT QTDSGASRSTTTPDVFNTKIGSCGFLWGYHRFMGSVG RVFREWDDGSTRSRRQSPLRARRKGTRRIRVRHKGTR RIRVRRKGTRRIWVRRKGSRKIRPSRSTQSPTTRA
151	Human IL-10	MHSSALLCCLVLLTGVRASPGQGTQSENSCTHFPGNLP NMLRDLRDAFSRVKTFFQMKDQLDNLLLKESLLEDFK GYLGCQALSEMIQFYLEEVMPQAENQDPDIKAHVNSL GENLKTLRLRLRRCHRFLPCENKSKAVEQVKNAFNKL QEKGIYKAMSEFDIFINYIEAYMTMKIRN
152	Mouse IL-10	MPGSALLCCLLLLTGMRISRGQYSREDNNCTHFPVGQS HMLLELRTAFSQVKTFFQTKDQLDNILLTDSLMQDFK GYLGCQALSEMIQFYLVEVMPQAEKHGPEIKEHLNSL GEKLKTLRMRLRRCHRFLPCENKSKAVEQVKSDFNKL QDQGVYKAMNEFDIFINCIEAYMMIKMKS
153	Human IL-20	MKASSLAFSLLSAAFYLLWTPSTGLKTLNLGSCVIATN LQEIRNGFSEIRGSVQAKDGNIDIRILRRTESLQDTKPAN RCCLLRHLLRLYLDRVFKNYQTPDHYTLRKISSLANSF LTIKKDLRLCHAHMTCHCGEEAMKKYSQILSHFEKLEP QAAVVKALGELDILLQWMEETE
154	Mouse IL-20	MKGFGLAFGLFSAVGFLLWTPLTGLKTLHLGSCVITAN LQAIQKEFSEIRDSVQAEDTNIDIRILRTTESLKDIKSLD RCCFLRHLVRFYLDRVFKVYQTPDHHTLRKISSLANSF LIIKKDLSVCHSHMACHCGEEAMEKYNQILSHFIELEL QAAVVKALGELGILLRWMEEML

155	Human IL-14	MKNQDKKNGAAKQSNPKSSPGQPEAGPEGAQERPSQ AAPAVEAEGPGSSQAPRKPEGAQARTAQSGALRDVSE ELSRQLEDILSTYCVDNNQGGPGEDGAQGEPAEPEDAE KSRTYVARNGEPEPTPVVNGEKEPSKGDPNTEEIRQSD EVGDRDHRRPQEKKKAKGLGKEITLLMQTLNTLSTPE EKLAALCKKYAELLEEHRNSQKQMKLLQKKQSQLVQ EKDHLRGEHSKAVLARSKLESLCRELQRHNRSLKEEG VQRAREEEEKRKEVTSHFQVTLNDIQLQMEQHNERNS KLRQENMELAERLKKLIEQYELREEHIDKVFKHKDLQ QQLVDAKLQQAQEMLKEAEERHQREKDFLLKEAVES QRMCELMKQQETHLKQQLALYTEKFEEFQNTLSKSSE VFTTFKQEMEKMTKKIKKLEKETTMYRSRWESSNKAL LEMAEEKTVRDKELEGLQVKIQRLEKLCRALQTERND LNKRVQDLSAGGQGSLTDSGPERRPEGPGAQAPSSPRV TEAPCYPGAPSTEASGQTGPQEPTSARA
156	Mouse IL-14	MKNQDKKNGPAKHSNSKGSPGQREAGPEGAHGRPRQ TAPGAEAEGSTSQAPGKTEGARAKAAQPGALCDVSEE LSRQLEDILSTYCVDNNQGGPAEEGAQGEPTEPEDTEK SRTYAARNGEPEPGIPVVNGEKETSKGEPGTEEIRASDE VGDRDHRRPQEKKKAKGLGKEITLLMQTLNTLSTPEE KLAALCKKYAELLEEHRNSQKQMKLLQKKQSQLVQE KDHLRGEHSKAVLARSKLESLCRELQRHNRSLKEEGV QRAREEEEKRKEVTSHFQVTLNDIQLQMEQHNERNSK LRQENMELAERLKKLIEQYELREEHIDKVFKHKDLQQ QLVDAKLQQAQEMLKEAEERHQREKEFLLKEAVESQR MCELMKQQETHLKQQLALYTEKFEEFQNTLSKSSEVF TTFKQEMEKMTKKIKKLEKETTMYRSRWESSNKALLE MAEEKTVRDKELEGLQVKIQRLEKLCRALQTERNDLN KRVQDLTAGGITDIGSERRPEATTASKEQGVESPGAQP ASSPRATDAPCCSGAPSTGTAGQTGPGEPTPATA

157	Human IL-16	MESHSRAGKSRKSAKFRSISRSLMLCNAKTSDDGSSPD EKYPDPFEISLAQGKEGIFHSSVQLADTSEAGPSSVPDL ALASEAAQLQAAGNDRGKTCRRIFFMKESSTASSREKP GKLEAQSSNFLFPKACHQRARSNSTSVNPYCTREIDFP MTKKSAAPTDRQPYSLCSNRKSLSQQLDCPAGKAAGT SRPTRSLSTAQLVQPSGGLQASVISNIVLMKGQAKGLG FSIVGGKDSIYGPIGIYVKTIFAGGAAAADGRLQEGDEI LELNGESMAGLTHQDALQKFKQAKKGLLTLTVRTRLT APPSLCSHLSPPLCRSLSSSTCITKDSSSFALESPSAPIST AKPNYRIMVEVSLQKEAGVGLGIGLCSVPYFQCISGIFV HTLSPGSVAHLDGRLRCGDEIVEISDSPVHCLTLNEVYT ILSHCDPGPVPIIVSRHPDPQVSEQQLKEAVAQAVENTK FGKERHQWSLEGVKRLESSWHGRPTLEKEREKNSAPP HRRAQKVMIRSSSDSSYMSGSPGGSPGSGSAEKPSSDV DISTHSPSLPLAREPVVLSIASSRLPQESPPLPESRDSHPP LRLKKSFEIVRKPMSSKPKPPPRKYFKSDSDPQKSLEER ENSSCSSGHTPPTCGQEARELLPLLLPQEDTAGRSPSAS AGCPGPGIGPQTKSSTEGEPGWRRASPVTQTSPIKHPLL KRQARMDYSFDTTAEDPWVRISDCIKNLFSPIMSENHG HMPLQPNASLNEEEGTQGHPDGTPPKLDTANGTPKVY KSADSSTVKKGPPVAPKPAWFRQSLKGLRNRASDPRG LPDPALSTQPAPASREHLGSHIRASSSSSSIRQRISSFETF GSSQLPDKGAQRLSLQPSSGEAAKPLGKHEEGRFSGLL GRGAAPTLVPQQPEQVLSSGSPAASEARDPGVSESPPP GRQPNQKTLPPGPDPLLRLLSTQAEESQGPVLKMPSQR ARSFPLTRSQSCETKLLDEKTSKLYSISSQVSSAVMKSL LCLPSSISCAQTPCIPKEGASPTSSSNEDSAANGSAETSA LDTGFSLNLSELREYTEGLTEAKEDDDGDHSSLQSGQS VISLLSSEELKKLIEEVKVLDEATLKQLDGIHVTILHKEE GAGLGFSLAGGADLENKVITVHRVFPNGLASQEGTIQK GNEVLSINGKSLKGTTHHDALAILRQAREPRQAVIVTR

		KLTPEAMPDLNSSTDSAASASAASDVSVESTAEATVCT VTLEKMSAGLGFSLEGGKGSLHGDKPLTINRIFKGAAS EQSETVQPGDEILQLGGTAMQGLTRFEAWNIIKALPDG PVTIVIRRKSLQSKETTAAGDS
158	Mouse IL-16	MEPHGHSGKSRKSTKFRSISRSLILCNAKTSDDGSSPDE KYPDPFETSLCQGKEGFFHSSMQLADTFEAGLSNIPDL ALASDSAQLAAAGSDRGKHCRKMFFMKESSSTSSKEK SGKPEAQSSSFLFPKACHQRTRSNSTSVNPYSAGEIDFP MTKKSAAPTDRQPYSLCSNRKSLSQQLDYPILGTARPT RSLSTAQLGQLSGGLQASVISNIVLMKGQAKGLGFSIV GGKDSIYGPIGIYVKSIFAGGAAAADGRLQEGDEILELN GESMAGLTHQDALQKFKQAKKGLLTLTVRTRLTTPPS LCSHLSPPLCRSLSSSTCGAQDSSPFSLESPASPASTAKP NYRIMVEVSLKKEAGVGLGIGLCSIPYFQCISGIFVHTL SPGSVAHLDGRLRCGDEIVEINDSPVHCLTLNEVYTILS HCDPGPVPIIVSRHPDPQVSEQQLKEAVAQAVEGVKFG KDRHQWSLEGVKRLESSWHGRPTLEKEREKHSAPPHR RAQKIMVRSSSDSSYMSGSPGGSPCSAGAEPQPSEREG STHSPSLSPGEEQEPCPGVPSRPQQESPPLPESLERESHP PLRLKKSFEILVRKPTSSKPKPPPRKYFKNDSEPQKKLE EKEKVTDPSGHTLPTCSQETRELLPLLLQEDTAGRAPC TAACCPGPAASTQTSSSTEGESRRSASPETPASPGKHPL LKRQARMDYSFDITAEDPWVRISDCIKNLFSPIMSENHS HTPLQPNTSLGEEDGTQGCPEGGLSKMDAANGAPRVY KSADGSTVKKGPPVAPKPAWFRQSLKGLRNRAPDPRR PPEVASAIQPTPVSRDPPGPQPQASSSIRQRISSFENFGSS QLPDRGVQRLSLQPSSGETTKFPGKQDGGRFSGLLGQG ATVTAKHRQTEVESMSTTFPNSSEVRDPGLPESPPPGQ RPSTKALSPDPLLRLLTTQSEDTQGPGLKMPSQRARSFP LTRTQSCETKLLDEKASKLYSISSQLSSAVMKSLLCLPS SVSCGQITCIPKERVSPKSPCNNSSAAEGFGEAMASDTG

		FSLNLSELREYSEGLTEPGETEDRNHCSSQAGQSVISLL SAEELEKLIEEVRVLDEATLKQLDSIHVTILHKEEGAGL GFSLAGGADLENKVITVHRVFPNGLASQEGTIQKGNEV LSINGKSLKGATHNDALAILRQARDPRQAVIVTRRTTV EATHDLNSSTDSAASASAASDISVESKEATVCTVTLEK TSAGLGFSLEGGKGSLHGDKPLTINRIFKGTEQGEMVQ PGDEILQLAGTAVQGLTRFEAWNVIKALPDGPVTIVIR RTSLQCKQTTASADS
159	Human IL-17	MTPGKTSLVSLLLLLSLEAIVKAGITIPRNPGCPNSEDK NFPRTVMVNLNIHNRNTNTNPKRSSDYYNRSTSPWNL HRNEDPERYPSVIWEAKCRHLGCINADGNVDYHMNSV PIQQEILVLRREPPHCPNSFRLEKILVSVGCTCVTPIVHH VA
160	Mouse IL-17	MSPGRASSVSLMLLLLLSLAATVKAAAIIPQSSACPNTE AKDFLQNVKVNLKVFNSLGAKVSSRRPSDYLNRSTSP WTLHRNEDPDRYPSVIWEAQCRHQRCVNAEGKLDHH MNSVLIQQEILVLKREPESCPFTFRVEKMLVGVGCTCV ASIVRQAA
161	Human CD154	MIETYNQTSPRSAATGLPISMKIFMYLLTVFLITQMIGS ALFAVYLHRRLDKIEDERNLHEDFVFMKTIQRCNTGER SLSLLNCEEIKSQFEGFVKDIMLNKEETKKENSFEMQK GDQNPQIAAHVISEASSKTTSVLQWAEKGYYTMSNNL VTLENGKQLTVKRQGLYYIYAQVTFCSNREASSQAPFI ASLCLKSPGRFERILLRAANTHSSAKPCGQQSIHLGGVF ELQPGASVFVNVTDPSQVSHGTGFTSFGLLKL
162	Mouse CD154	MIETYSQPSPRSVATGLPASMKIFMYLLTVFLITQMIGS VLFAVYLHRRLDKVEEEVNLHEDFVFIKKLKRCNKGE GSLSLLNCEEMRRQFEDLVKDITLNKEEKKENSFEMQR GDEDPQIAAHVVSEANSNAASVLQWAKKGYYTMKSN LVMLENGKQLTVKREGLYYVYTQVTFCSNREPSSQRP

		FIVGLWLKPSSGSERILLKAANTHSSSQLCEQQSVHLG GVFELQAGASVFVNVTEASQVIHRVGFSSFGLLKL
163	Human LT-beta	MGALGLEGRGGRLQGRGSLLLAVAGATSLVTLLLAVP ITVLAVLALVPQDQGGLVTETADPGAQAQQGLGFQKL PEEEPETDLSPGLPAAHLIGAPLKGQGLGWETTKEQAF LTSGTQFSDAEGLALPQDGLYYLYCLVGYRGRAPPGG GDPQGRSVTLRSSLYRAGGAYGPGTPELLLEGAETVTP VLDPARRQGYGPLWYTSVGFGGLVQLRRGERVYVNIS HPDMVDFARGKTFFGAVMVG
164	Mouse LT-beta	MGTRGLQGLGGRPQGRGCLLLAVAGATSLVTLLLAVP ITVLAVLALVPQDQGRRVEKIIGSGAQAQKRLDDSKPS CILPSPSSLSETPDPRLHPQRSNASRNLASTSQGPVAQSS REASAWMTILSPAADSTPDPGVQQLPKGEPETDLNPEL PAAHLIGAWMSGQGLSWEASQEEAFLRSGAQFSPTHG LALPQDGVYYLYCHVGYRGRTPPAGRSRARSLTLRSA LYRAGGAYGRGSPELLLEGAETVTPVVDPIGYGSLWY TSVGFGGLAQLRSGERVYVNISHPDMVDYRRGKTFFG AVMVG
165	Human TNF-alpha	STESMIRDVELAEEALPKKTGGPQGSRRCLFLSLFSFLI VAGATTLFCLLHFGVIGPQREEFPRDLSLISPLAQAVRS SSRTPSDKPVAHVVANPQAEGQLQWLNRRANALLAN GVELRDNQLVVPSEGLYLIYSQVLFKGQGCPSTHVLLT HTISRIAVSYQTKVNLLSAIKSPCQRETPEGAEAKPWYE PIYLGGVFQLEKGDRLSAEINRPDYLDFAESGQVYFGII AL
166	Mouse TNF-alpha	NHQVEEQLEWLSQRANALLANGMDLKDNQLVVPAD GLYLVYSQVLFKGQGCPDYVLLTHTVSRFAISYQEKV NLLSAVKSPCPKDTPEGAELKPWYEPIYLGGVFQLEKG DQLSAEVNLPKYLDFAESGQVYFGVIAL
167	Human TNF-beta	MTPPERLFLPRVCGTTLHLLLLGLLLVLLPGAQGLPGV GLTPSAAQTARQHPKMHLAHSTLKPAAHLIGDPSKQN

		SLLWRANTDRAFLQDGFSLSNNSLLVPTSGIYFVYSQV VFSGKAYSPKATSSPLYLAHEVQLFSSQYPFHVPLLSSQ KMVYPGLQEPWLHSMYHGAAFQLTQGDQLSTHTDGI PHLVLSPSTVFFGAFAL
168	Human 4-1BBL	MEYASDASLDPEAPWPPAPRARACRVLPWALVAGLLL LLLLAAACAVFLACPWAVSGARASPGSAASPRLREGP ELSPDDPAGLLDLRQGMFAQLVAQNVLLIDGPLSWYS DPGLAGVSLTGGLSYKEDTKELVVAKAGVYYVFFQLE LRRVVAGEGSGSVSLALHLQPLRSAAGAAALALTVDL PPASSEARNSAFGFQGRLLHLSAGQRLGVHLHTEARAR HAWQLTQGATVLGLFRVTPEIPAGLPSPRSE
169	Mouse 4-1BBL	MDQHTLDVEDTADARHPAGTSCPSDAALLRDTGLLAD AALLSDTVRPTNAALPTDAAYPAVNVRDREAAWPPAL NFCSRHPKLYGLVALVLLLLIAACVPIFTRTEPRPALTIT TSPNLGTRENNADQVTPVSHIGCPNTTQQGSPVFAKLL AKNQASLCNTTLNWHSQDGAGSSYLSQGLRYEEDKK ELVVDSPGLYYVFLELKLSPTFTNTGHKVQGWVSLVL QAKPQVDDFDNLALTVELFPCSMENKLVDRSWSQLLL LKAGHRLSVGLRAYLHGAQDAYRDWELSYPNTTSFGL FLVKPDNPWE
170	Human APRIL	AVLTQKQKKQHSVLHLVPINATSKDDSDVTEVMWQP ALRRGRGLQAQGYGVRIQDAGVYLLYSQVLFQDVTFT MGQVVSREGQGRQETLFRCIRSMPSHPDRAYNSCYSA GVFHLHQGDILSVIIPRARAKLNLSPHGTFLGFVKL
171	Mouse APRIL	MPASSPGHMGGSVREPALSVALWLSWGAVLGAVTCA VALLIQQTELQSLRREVSRLQRSGGPSQKQGERPWQSL WEQSPDVLEAWKDGAKSRRRRAVLTQKHKKKHSVLH LVPVNITSKADSDVTEVMWQPVLRRGRGLEAQGDIVR VWDTGIYLLYSQVLFHDVTFTMGQVVSREGQGRRETL FRCIRSMPSDPDRAYNSCYSAGVFHLHQGDIITVKIPRA NAKLSLSPHGTFLGFVKL

172	Human CD70	MPEEGSGCSVRRRPYGCVLRAALVPLVAGLVICLVVCI QRFAQAQQQLPLESLGWDVAELQLNHTGPQQDPRLY WQGGPALGRSFLHGPELDKGQLRIHRDGIYMVHIQVT LAICSSTTASRHHPTTLAVGICSPASRSISLLRLSFHQGC TIASQRLTPLARGDTLCTNLTGTLLPSRNTDETFFGVQ WVRP
173	Mouse CD70	MPEEGRPCPWVRWSGTAFQRQWPWLLLVVFITVFCC WFHCSGLLSKQQQRLLEHPEPHTAELQLNLTVPRKDPT LRWGAGPALGRSFTHGPELEEGHLRIHQDGLYRLHIQV TLANCSSPGSTLQHRATLAVGICSPAAHGISLLRGRFGQ DCTVALQRLTYLVHGDVLCTNLTLPLLPSRNADETFFG VQWICP
174	Human CD153	MDPGLQQALNGMAPPGDTAMHVPAGSVASHLGTTSR SYFYLTTATLALCLVFTVATIMVLVVQRTDSIPNSPDN VPLKGGNCSEDLLCILKRAPFKKSWAYLQVAKHLNKT KLSWNKDGILHGVRYQDGNLVIQFPGLYFIICQLQFLV QCPNNSVDLKLELLINKHIKKQALVTVCESGMQTKHV YQNLSQFLLDYLQVNTTISVNVDTFQYIDTSTFPLENVL SIFLYSNSD
175	Mouse CD153	MEPGLQQAGSCGAPSPDPAMQVQPGSVASPWRSTRP WRSTSRSYFYLSTTALVCLVVAVAIILVLVVQKKDSTP NTTEKAPLKGGNCSEDLFCTLKSTPSKKSWAYLQVSK HLNNTKLSWNEDGTIHGLIYQDGNLIVQFPGLYFIVCQ LQFLVQCSNHSVDLTLQLLINSKIKKQTLVTVCESGVQ SKNIYQNLSQFLLHYLQVNSTISVRVDNFQYVDTNTFP LDNVLSVFLYSSSD
176	Human CD178	MQQPFNYPYPQIYWVDSSASSPWAPPGTVLPCPTSVPR RPGQRRPPPPPPPPLPPPPPPPLPPLPLPPLKKRGNHST GLCLLVMFFMVLVALVGLGLGMFQLFHLQKELAELRE STSQMHTASSLEKQIGHPSPPPEKKELRKVAHLTGKSN SRSMPLEWEDTYGIVLLSGVKYKKGGLVINETGLYFV

		YSKVYFRGQSCNNLPLSHKVYMRNSKYPQDLVMMEG KMMSYCTTGQMWARSSYLGAVFNLTSADHLYVNVSE LSLVNFEESQTFFGLYKL
177	Mouse CD178	MQQPMNYPCPQIFWVDSSATSSWAPPGSVFPCPSCGPR GPDQRRPPPPPPPVSPLPPPSQPLPLPPLTPLKKKDHNTN LWLPVVFFMVLVALVGMGLGMYQLFHLQKELAELRE FTNQSLKVSSFEKQIANPSTPSEKKEPRSVAHLTGNPHS RSIPLEWEDTYGTALISGVKYKKGGLVINETGLYFVYS KVYFRGQSCNNQPLNHKVYMRNSKYPEDLVLMEEKR LNYCTTGQIWAHSSYLGAVFNLTSADHLYVNISQLSLI NFEESKTFFGLYKL
178	Human GITRL	MTLHPSPITCEFLFSTALISPKMCLSHLENMPLSHSRTQ GAQRSSWKLWLFCSIVMLLFLCSFSWLIFIFLQLETAKE PCMAKFGPLPSKWQMASSEPPCVNKVSDWKLEILQNG LYLIYGQVAPNANYNDVAPFEVRLYKNKDMIQTLTNK SKIQNVGGTYELHVGDTIDLIFNSEHQVLKNNTYWGIIL LANPQFIS
179	Mouse GITRL	MEEMPLRESSPQRAERCKKSWLLCIVALLLMLLCSLGT LIYTSLKPTAIESCMVKFELSSSKWHMTSPKPHCVNTTS DGKLKILQSGTYLIYGQVIPVDKKYIKDNAPFVVQIYK KNDVLQTLMNDFQILPIGGVYELHAGDNIYLKFNSKD HIQKTNTYWGIILMPDLPFIS
180	Human LIGHT	MEESVVRPSVFVVDGQTDIPFTRLGRSHRRQSCSVARV GLGLLLLLMGAGLAVQGWFLLQLHWRLGEMVTRLPD GPAGSWEQLIQERRSHEVNPAAHLTGANSSLTGSGGPL LWETQLGLAFLRGLSYHDGALVVTKAGYYYIYSKVQL GGVGCPLGLASTITHGLYKRTPRYPEELELLVSQQSPC GRATSSSRVWWDSSFLGGVVHLEAGEKVVVRVLDER LVRLRDGTRSYFGAFMV
181	Mouse LIGHT	MESVVQPSVFVVDGQTDIPFRRLEQNHRRRRCGTVQV SLALVLLLGAGLATQGWFLLRLHQRLGDIVAHLPDGG

		KGSWEKLIQDQRSHQANPAAHLTGANASLIGIGGPLL WETRLGLAFLRGLTYHDGALVTMEPGYYYVYSKVQL SGVGCPQGLANGLPITHGLYKRTSRYPKELELLVSRRS PCGRANSSRVWWDSSFLGGVVHLEAGEEVVVRVPGN RLVRPRDGTRSYFGAFMV
182	Human OX40L	MERVQPLEENVGNAARPRFERNKLLLVASVIQGLGLL LCFTYICLHFSALQVSHRYPRIQSIKVQFTEYKKEKGFIL TSQKEDEIMKVQNNSVIINCDGFYLISLKGYFSQEVNIS LHYQKDEEPLFQLKKVRSVNSLMVASLTYKDKVYLN VTTDNTSLDDFHVNGGELILIHQNPGEFCVL
183	Mouse OX40L	MEGEGVQPLDENLENGSRPRFKWKKTLRLVVSGIKGA GMLLCFIYVCLQLSSSPAKDPPIQRLRGAVTRCEDGQL FISSYKNEYQTMEVQNNSVVIKCDGLYIIYLKGSFFQEV KIDLHFREDHNPISIPMLNDGRRIVFTVVASLAFKDKVY LTVNAPDTLCEHLQINDGELIVVQLTPGYCAPEGSYHS TVNQVP
184	Human TALL-1	MDDSTEREQSRLTSCLKKREEMKLKECVSILPRKESPS VRSSKDGKLLAATLLLALLSCCLTVVSFYQVAALQGD LASLRAELQGHHAEKLPAGAGAPKAGLEEAPAVTAGL KIFEPPAPGEGNSSQNSRNKRAVQGPEETVTQDCLQLI ADSETPTIQKGSYTFVPWLLSFKRGSALEEKENKILVKE TGYFFIYGQVLYTDKTYAMGHLIQRKKVHVFGDELSL VTLFRCIQNMPETLPNNSCYSAGIAKLEEGDELQLAIPR ENAQISLDGDVTFFGALKLL
185	Mouse TALL-1	MAMAFCPKDQYWDSSRKSCVSCALTCSQRSQRTCTDF CKFINCRKEQGRYYDHLLGACVSCDSTCTQHPQQCAH FCEKRPRSQANLQPELGRPQAGEVEVRSDNSGRHQGS EHGPGLRLSSDQLTLYCTLGVCLCAIFCCFLVALASFLR RRGEPLPSQPAGPRGSQANSPHAHRPVTEACDEVTASP

		QPVETCSFCFPERSSPTQESAPRSLGIHGFAGTAAPQPC MRATVGGLGVLRASTGDARPAT
186	Human TRAIL	MAMMEVQGGPSLGQTCVLIVIFTVLLQSLCVAVTYVY FTNELKQMQDKYSKSGIACFLKEDDSYWDPNDEESMN SPCWQVKWQLRQLVRKMILRTSEETISTVQEKQQNISP LVRERGPQRVAAHITGTRGRSNTLSSPNSKNEKALGRK INSWESSRSGHSFLSNLHLRNGELVIHEKGFYYIYSQTY FRFQEEIKENTKNDKQMVQYIYKYTSYPDPILLMKSAR NSCWSKDAEYGLYSIYQGGIFELKENDRIFVSVTNEHLI DMDHEASFFGAFLVG
187	Mouse TRAIL	MPSSGALKDLSFSQHFRMMVICIVLLQVLLQAVSVAVT YMYFTNEMKQLQDNYSKIGLACFSKTDEDFWDSTDGE ILNRPCLQVKRQLYQLIEEVTLRTFQDTISTVPEKQLSTP PLPRGGRPQKVAAHITGITRRSNSALIPISKDGKTLGQKI ESWESSRKGHSFLNHVLFRNGELVIEQEGLYYIYSQTY FRFQEAEDASKMVSKDKVRTKQLVQYIYKYTSYPDPI VLMKSARNSCWSRDAEYGLYSIYQGGLFELKKNDRIF VSVTNEHLMDLDQEASFFGAFLIN
188	Human TWEAK	MAARRSQRRRGRRGEPGTALLVPLALGLGLALACLGL LLAVVSLGSRASLSAQEPAQEELVAEEDQDPSELNPQT EESQDPAPFLNRLVRPRRSAPKGRKTRARRAIAAHYEV HPRPGQDGAQAGVDGTVSGWEEARINSSSPLRYNRQI GEFIVTRAGLYYLYCQVHFDEGKAVYLKLDLLVDGVL ALRCLEEFSATAASSLGPQLRLCQVSGLLALRPGSSLRI RTLPWAHLKAAPFLTYFGLFQVH
189	Mouse TWEAK	MASAWPRSLPQILVLGFGLVLMRAAAGEQAPGTSPCS SGSSWSADLDKCMDCASCPARPHSDFCLGCAAAPPAH FRLLWPILGGALSLVLVLALVSSFLVWRRCRRREKFTT PIEETGGEGCPGVALIQ
190	Human TRANCE	MRRASRDYTKYLRGSEEMGGGPGAPHEGPLHAPPPPA PHQPPAASRSMFVALLGLGLGQVVCSVALFFYFRAQM

		DPNRISEDGTHCIYRILRLHENADFQDTTLESQDTKLIP DSCRRIKQAFQGAVQKELQHIVGSQHIRAEKAMVDGS WLDLAKRSKLEAQPFAHLTINATDIPSGSHKVSLSSWY HDRGWAKISNMTFSNGKLIVNQDGFYYLYANICFRHH ETSGDLATEYLQLMVYVTKTSIKIPSSHTLMKGGSTKY WSGNSEFHFYSINVGGFFKLRSGEEISIEVSNPSLLDPDQ DATYFGAFKVRDID
191	Mouse TRANCE	MRRASRDYGKYLRSSEEMGSGPGVPHEGPLHPAPSAP APAPPPAASRSMFLALLGLGLGQVVCSIALFLYFRAQM DPNRISEDSTHCFYRILRLHENADLQDSTLESEDTLPDS CRRMKQAFQGAVQKELQHIVGPQRFSGAPAMMEGSW LDVAQRGKPEAQPFAHLTINAASIPSGSHKVTLSSWYH DRGWAKISNMTLSNGKLRVNQDGFYYLYANICFRHHE TSGSVPTDYLQLMVYVVKTSIKIPSSHNLMKGGSTKN WSGNSEFHFYSINVGGFFKLRAGEEISIQVSNPSLLDPD QDATYFGAFKVQDID
192	Human TGF-beta1	MPPSGLRLLLLLLPLLWLLVLTPGRPAAGLSTCKTIDM ELVKRKRIEAIRGQILSKLRLASPPSQGEVPPGPLPEAVL ALYNSTRDRVAGESAEPEPEPEADYYAKEVTRVLMVE THNEIYDKFKQSTHSIYMFFNTSELREAVPEPVLLSRAE LRLLRLKLKVEQHVELYQKYSNNSWRYLSNRLLAPSD SPEWLSFDVTGVVRQWLSRGGEIEGFRLSAHCSCDSRD NTLQVDINGFTTGRRGDLATIHGMNRPFLLLMATPLER AQHLQSSRHRRALDTNYCFSSTEKNCCVRQLYIDFRKD LGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVLAL YNQHNPGASAAPCCVPQALEPLPIVYYVGRKPKVEQL SNMIVRSCKCS
193	Mouse TGF-beta1	MPPSGLRLLPLLLPLPWLLVLTPGRPAAGLSTCKTIDM ELVKRKRIEAIRGQILSKLRLASPPSQGEVPPGPLPEAVL ALYNSTRDRVAGESADPEPEPEADYYAKEVTRVLMVD RNNAIYEKTKDISHSIYMFFNTSDIREAVPEPPLLSRAEL

		RLQRLKSSVEQHVELYQKYSNNSWRYLGNRLLTPTDT PEWLSFDVTGVVRQWLNQGDGIQGFRFSAHCSCDSKD NKLHVEINGISPKRRGDLGTIHDMNRPFLLLMATPLER AQHLHSSRHRRALDTNYCFSSTEKNCCVRQLYIDFRKD LGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVLAL YNQHNPGASASPCCVPQALEPLPIVYYVGRKPKVEQLS NMIVRSCKCS
194	Human TGF-beta2	MHYCVLSAFLILHLVTVALSLSTCSTLDMDQFMRKRIE AIRGQILSKLKLTSPPEDYPEPEEVPPEVISIYNSTRDLLQ EKASRRAAACERERSDEEYYAKEVYKIDMPPFFPSENA IPPTFYRPYFRIVRFDVSAMEKNASNLVKAEFRVFRLQ NPKARVPEQRIELYQILKSKDLTSPTQRYIDSKVVKTRA EGEWLSFDVTDAVHEWLHHKDRNLGFKISLHCPCCTF VPSNNYIIPNKSEELEARFAGIDGTSTYTSGDQKTIKSTR KKNSGKTPHLLLMLLPSYRLESQQTNRRKKRALDAAY CFRNVQDNCCLRPLYIDFKRDLGWKWIHEPKGYNANF CAGACPYLWSSDTQHSRVLSLYNTINPEASASPCCVSQ DLEPLTILYYIGKTPKIEQLSNMIVKSCKCS
195	Mouse TGF-beta2	MHYCVLSTFLLLHLVPVALSLSTCSTLDMDQFMRKRIE AIRGQILSKLKLTSPPEDYPEPDEVPPEVISIYNSTRDLL QEKASRRAAACERERSDEEYYAKEVYKIDMPSHLPSE NAIPPTFYRPYFRIVRFDVSTMEKNASNLVKAEFRVFRL QNPKARVAEQRIELYQILKSKDLTSPTQRYIDSKVVKT RAEGEWLSFDVTDAVQEWLHHKDRNLGFKISLHCPCC TFVPSNNYIIPNKSEELEARFAGIDGTSTYASGDQKTIKS TRKKTSGKTPHLLLMLLPSYRLESQQSSRRKKRALDAA YCFRNVQDNCCLRPLYIDFKRDLGWKWIHEPKGYNAN FCAGACPYLWSSDTQHTKVLSLYNTINPEASASPCCVS QDLEPLTILYYIGNTPKIEQLSNMIVKSCKCS
196	Human TGF-beta3	MKMHLQRALVVLALLNFATVSLSLSTCTTLDFGHIKK KRVEAIRGQILSKLRLTSPPEPTVMTHVPYQVLALYNS

		TRELLEEMHGEREEGCTQENTESEYYAKEIHKFDMIQG LAEHNELAVCPKGITSKVFRFNVSSVEKNRTNLFRAEF RVLRVPNPSSKRNEQRIELFQILRPDEHIAKQRYIGGKN LPTRGTAEWLSFDVTDTVREWLLRRESNLGLEISIHCPC HTFQPNGDILENIHEVMEIKFKGVDNEDDHGRGDLGRL KKQKDHHNPHLILMMIPPHRLDNPGQGGQRKKRALDT NYCFRNLEENCCVRPLYIDFRQDLGWKWVHEPKGYY ANFCSGPCPYLRSADTTHSTVLGLYNTLNPEASASPCC VPQDLEPLTILYYVGRTPKVEQLSNMVVKSCKCS
197	Mouse TGF-beta3	MHLQRALVVLALLNLATISLSLSTCTTLDFGHIKKKRV EAIRGQILSKLRLTSPPEPSVMTHVPYQVLALYNSTREL LEEMHGEREEGCTQETSESEYYAKEIHKFDMIQGLAEH NELAVCPKGITSKVFRFNVSSVEKNGTNLFRAEFRVLR VPNPSSKRTEQRIELFQILRPDEHIAKQRYIGGKNLPTR GTAEWLSFDVTDTVREWLLRRESNLGLEISIHCPCHTF QPNGDILENVHEVMEIKFKGVDNEDDHGRGDLGRLKK QKDHHNPHLILMMIPPHRLDSPGQGSQRKKRALDTNY CFRNLEENCCVRPLYIDFRQDLGWKWVHEPKGYYANF CSGPCPYLRSADTTHSTVLGLYNTLNPEASASPCCVPQ DLEPLTILYYVGRTPKVEQLSNMVVKSCKCS
198	Human EPO	MGVHECPAWLWLLLSLLSLPLGLPVLGAPPRLICDSRV LERYLLEAKEAENITTGCAEHCSLNENITVPDTKVNFY AWKRMEVGQQAVEVWQGLALLSEAVLRGQALLVNS SQPWEPLQLHVDKAVSGLRSLTTLLRALGAQKEAISPP DAASAAPLRTITADTFRKLFRVYSNFLRGKLKLYTGEA CRTGDR
199	Mouse EPO	MGVPERPTLLLLLSLLLIPLGLPVLCAPPRLICDSRVLER YILEAKEAENVTMGCAEGPRLSENITVPDTKVNFYAW KRMEVEEQAIEVWQGLSLLSEAILQAQALLANSSQPPE TLQLHIDKAISGLRSLTSLLRVLGAQKELMSPPDTTPPA

		PLRTLTVDTFCKLFRVYANFLRGKLKLYTGEVCRRGD R
200	Human TPO	MELTELLLVVMLLLTARLTLSSPAPPACDLRVLSKLLR DSHVLHSRLSQCPEVHPLPTPVLLPAVDFSLGEWKTQM EETKAQDILGAVTLLLEGVMAARGQLGPTCLSSLLGQL SGQVRLLLGALQSLLGTQLPPQGRTTAHKDPNAIFLSF QHLLRGKVRFLMLVGGSTLCVRRAPPTTAVPSRTSLVL TLNELPNRTSGLLETNFTASARTTGSGLLKWQQGFRAK IPGLLNQTSRSLDQIPGYLNRIHELLNGTRGLFPGPSRRT LGAPDISSGTSDTGSLPPNLQPGYSPSPTHPPTGQYTLFP LPPTLPTPVVQLHPLLPDPSAPTPTPTSPLLNTSYTHSQN LSQEG
201	Mouse TPO	MELTDLLLAAMLLAVARLTLSSPVAPACDPRLLNKLL RDSHLLHSRLSQCPDVDPLSIPVLLPAVDFSLGEWKTQ TEQSKAQDILGAVSLLLEGVMAARGQLEPSCLSSLLGQ LSGQVRLLLGALQGLLGTQLPLQGRTTAHKDPNALFLS LQQLLRGKVRFLLLVEGPTLCVRRTLPTTAVPSSTSQLL TLNKFPNRTSGLLETNFSVTARTAGPGLLSRLQGFRVKI TPGQLNQTSRSPVQISGYLNRTHGPVNGTHGLFAGTSL QTLEASDISPGAFNKGSLAFNLQGGLPPSPSLAPDGHTP FPPSPALPTTHGSPPQLHPLFPDPSTTMPNSTAPHPVTM YPHPRNLSQET
202	Human FLT-3L	MTVLAPAWSPTTYLLLLLLLSSGLSGTQDCSFQHSPISS DFAVKIRELSDYLLQDYPVTVASNLQDEELCGGLWRL VLAQRWMERLKTVAGSKMQGLLERVNTEIHFVTKCA FQPPPSCLRFVQTNISRLLQETSEQLVALKPWITRQNFS RCLELQCQPDSSTLPPPWSPRPLEATAPTAPQPPLLLLL LLPVGLLLLAAAWCLHWQRTRRRTPRPGEQVPPVPSP QDLLLVEH
203	Mouse FLT-3L	MTVLAPAWSPNSSLLLLLLLLSPCLRGTPDCYFSHSPIS SNFKVKFRELTDHLLKDYPVTVAVNLQDEKHCKALW

		SLFLAQRWIEQLKTVAGSKMQTLLEDVNTEIHFVTSCT FQPLPECLRFVQTNISHLLKDTCTQLLALKPCIGKACQN FSRCLEVQCQPDSSTLLPPRSPIALEATELPEPRPRQLLL LLLLLLPLTLVLLAAAWGLRWQRARRRGELHPGVPLP SHP
204	Human SCF	MKKTQTWILTCIYLQLLLFNPLVKTEGICRNRVTNNVK DVTKLVANLPKDYMITLKYVPGMDVLPSHCWISEMV VQLSDSLTDLLDKFSNISEGLSNYSIIDKLVNIVDDLVE CVKENSSKDLKKSFKSPEPRLFTPEEFFRIFNRSIDAFKD FVVASETSDCVVSSTLSPEKDSRVSVTKPFMLPPVAASS LRNDSSSSNRKAKNPPGDSSLHWAAMALPALFSLIIGF AFGALYWKKRQPSLTRAVENIQINEEDNEISMLQEKER EFQEV
205	Mouse SCF	MKKTQTWIITCIYLQLLLFNPLVKTKEICGNPVTDNVK DITKLVANLPNDYMITLNYVAGMDVLPSHCWLRDMVI QLSLSLTTLLDKFSNISEGLSNYSIIDKLGKIVDDLVLCM EENAPKNIKESPKRPETRSFTPEEFFSIFNRSIDAFKDFM VASDTSDCVLSSTLGPEKDSRVSVTKPFMLPPVAASSL RNDSSSSNRKAAKAPEDSGLQWTAMALPALISLVIGFA FGALYWKKKQSSLTRAVENIQINEEDNEISMLQQKERE FQEV
206	Human M-CSF	MTAPGAAGRCPPTTWLGSLLLLVCLLASRSITEEVSEY CSHMIGSGHLQSLQRLIDSQMETSCQITFEFVDQEQLK DPVCYLKKAFLLVQDIMEDTMRFRDNTPNAIAIVQLQE LSLRLKSCFTKDYEEHDKACVRTFYETPLQLLEKVKNV FNETKNLLDKDWNIFSKNCNNSFAECSSQDVVTKPDC NCLYPKAIPSSDPASVSPHQPLAPSMAPVAGLTWEDSE GTEGSSLLPGEQPLHTVDPGSAKQRPPRSTCQSFEPPET PVVKDSTIGGSPQPRPSVGAFNPGMEDILDSAMGTNW VPEEASGEASEIPVPQGTELSPSRPGGGSMQTEPARPSN FLSASSPLPASAKGQQPADVTGTALPRVGPVRPTGQD

		WNHTPQKTDHPSALLRDPPEPGSPRISSLRPQGLSNPST LSAQPQLSRSHSSGSVLPLGELEGRRSTRDRRSPAEPEG GPASEGAARPLPRFNSVPLTDTGHERQSEGSFSPQLQES VFHLLVPSVILVLLAVGGLLFYRWRRRSHQEPQRADSP LEQPEGSPLTQDDRQVELPV
207	Mouse M-CSF	MTARGAAGRCPSSTWLGSRLLLVCLLMSRSIAKEVSE HCSHMIGNGHLKVLQQLIDSQMETSCQIAFEFVDQEQL DDPVCYLKKAFFLVQDIIDETMRFKDNTPNANATERLQ ELSNNLNSCFTKDYEEQNKACVRTFHETPLQLLEKIKN FFNETKNLLEKDWNIFTKNCNNSFAKCSSRDVVTKPDC NCLYPKATPSSDPASASPHQPPAPSMAPLAGLAWDDS QRTEGSSLLPSELPLRIEDPGSAKQRPPRSTCQTLESTEQ PNHGDRLTEDSQPHPSAGGPVPGVEDILESSLGTNWVL EEASGEASEGFLTQEAKFSPSTPVGGSIQAETDRPRALS ASPFPKSTEDQKPVDITDRPLTEVNPMRPIGQTQNNTPE KTDGTSTLREDHQEPGSPHIATPNPQRVSNSATPVAQL LLPKSHSWGIVLPLGELEGKRSTRDRRSPAELEGGSASE GAARPVARFNSIPLTDTGHVEQHEGSSDPQIPESVFHLL VPGIILVLLTVGGLLFYKWKWRSHRDPQTLDSSVGRPE DSSLTQDEDRQVELPV
208	Human MSP	MGWLPLLLLLTQCLGVPGQRSPLNDFQVLRGTELQHL LHAVVPGPWQEDVADAEECAGRCGPLMDCRAFHYNV SSHGCQLLPWTQHSPHTRLRRSGRCDLFQKKDYVRTCI MNNGVGYRGTMATTVGGLPCQAWSHKFPNDHKYTPT LRNGLEENFCRNPDGDPGGPWCYTTDPAVRFQSCGIKS CREAACVWCNGEEYRGAVDRTESGRECQRWDLQHPH QHPFEPGKFLDQGLDDNYCRNPDGSERPWCYTTDPQIE REFCDLPRCGSEAQPRQEATTVSCFRGKGEGYRGTAN TTTAGVPCQRWDAQIPHQHRFTPEKYACKDLRENFCR NPDGSEAPWCFTLRPGMRAAFCYQIRRCTDDVRPQDC YHGAGEQYRGTVSKTRKGVQCQRWSAETPHKPQFTFT

		SEPHAQLEENFCRNPDGDSHGPWCYTMDPRTPFDYCA LRRCADDQPPSILDPPDQVQFEKCGKRVDRLDQRRSKL RVVGGHPGNSPWTVSLRNRQGQHFCGGSLVKEQWILT ARQCFSSCHMPLTGYEVWLGTLFQNPQHGEPSLQRVP VAKMVCGPSGSQLVLLKLERSVTLNQRVALICLPPEW YVVPPGTKCEIAGWGETKGTGNDTVLNVALLNVISNQ ECNIKHRGRVRESEMCTEGLLAPVGACEGDYGGPLAC FTHNCWVLEGIIIPNRVCARSRWPAVFTRVSVFVDWIH KVMRLG
209	Mouse MSP	MGLPLPLLQSSLLLMLLLRLSAASTNLNWQCPRIPYAA SRDFSVKYVVPSFSAGGRVQATAAYEDSTNSAVFVAT RNHLHVLGPDLQFIENLTTGPIGNPGCQTCASCGPGPH GPPKDTDTLVLVMEPGLPALVSCGSTLQGRCFLHELEP RGKALHLAAPACLFSANNNKPEACTDCVASPLGTRVT VVEQGHASYFYVASSLDPELAASFSPRSVSIRRLKSDTS GFQPGFPSLSVLPKYLASYLIKYVYSFHSGDFVYFLTVQ PISVTSPPSALHTRLVRLNAVEPEIGDYRELVLDCHFAP KRRRRGAPEGTQPYPVLQAAHSAPVDAKLAVELSISEG QEVLFGVFVTVKDGGSGMGPNSVVCAFPIYHLNILIEE GVEYCCHSSNSSSLLSRGLDFFQTPSFCPNPPGGEASGP SSRCHYFPLMVHASFTRVDLFNGLLGSVKVTALHVTR LGNVTVAHMGTVDGRVLQVEIARSLNYLLYVSNFSLG SSGQPVHRDVSRLGNDLLFASGDQVFKVPIQGPGCRHF LTCWRCLRAQRFMGCGWCGDRCDRQKECPGSWQQD HCPPEISEFYPHSGPLRGTTRLTLCGSNFYLRPDDVVPE GTHQITVGQSPCRLLPKDSSSPRPGSLKEFIQELECELEP LVTQAVGTTNISLVITNMPAGKHFRVEGISVQEGFSFVE PVLTSIKPDFGPRAGGTYLTLEGQSLSVGTSRAVLVNG TQCRLEQVNEEQILCVTPPGAGTARVPLHLQIGGAEVP GSWTFHYKEDPIVLDISPKCGYSGSHIMIHGQHLTSAW HFTLSFHDGQSTVESRCAGQFVEQQQRRCRLPEYVVR

		NPQGWATGNLSVWGDGAAGFTLPGFRFLPPPSPLRAG LVELKPEEHSVKVEYVGLGAVADCVTVNMTVGGEVC QHELRGDVVICPLPPSLQLGKDGVPLQVCVDGGCHILS QVVRSSPGRASQRILLIALLVLILLVAVLAVALIFNSRR RKKQLGAHSLSPTTLSDINDTASGAPNHEESSESRDGTS VPLLRTESIRLQDLDRMLLAEVKDVLIPHEQVVIHTDQ VIGKGHFGVVYHGEYTDGAQNQTHCAIKSLSRITEVQE VEAFLREGLLMRGLHHPNILALIGIMLPPEGLPRVLLPY MRHGDLLHFIRSPQRNPTVKDLVSFGLQVACGMEYLA EQKFVHRDLAARNCMLDESFTVKVADFGLARGVLDK EYYSVRQHRHARLPVKWMALESLQTYRFTTKSDVWS FGVLLWELLTRGAPPYPHIDPFDLSHFLAQGRRLPQPE YCPDSLYHVMLRCWEADPAARPTFRALVLEVKQVVA SLLGDHYVQLTAAYVNVGPRAVDDGSVPPEQVQPSPQ HCRSTSKPRPLSEPPLPT
210	Linker	GSSGGSGGSGG
211	Linker	GGGSGGGS
212	Linker	GGGSGGGSGGGS
213	Linker	GGGGSGGGGSGGGGS
214	Linker	GGGGSGGGGSGGGGSGGGGSGGGGS
215	Linker	GGGGSGGGGS
216	Linker	(GGGGS)n
217	Linker	GGGGSGS
218	Linker	GGGGSGGGGSGGGGSGS
219	Linker	GGSLDPKGGGGS
220	Linker	PKSCDKTHTCPPCPAPELLG
221	Linker	SKYGPPCPPCPAPEFLG
222	Linker	GKSSGSGSESKS
223	Linker	GSTSGSGKSSEGKG
224	Linker	GSTSGSGKSSEGSGSTKG

225	Linker	GSTSGSGKPGSGEGSTKG
226	Linker	GSTSGSGKPGSSEGST
227	Linker	(GSGGS)n
228	Linker	(GGGS)n
229	Linker	GGSG
230	Linker	GGSGG
231	Linker	GSGSG
232	Linker	GSGGG
233	Linker	GGGSG
234	Linker	GSSSG
235	Linker	GPQGTAGQ
236	Linker	YGAGLGW
237	CM	AQNLLGMY
238	CM	LSGRSDNHGGAVGLLAPP
239	CM	VHMPLGFLGPGGLSGRSDNH
240	CM	LSGRSDNHGGVHMPLGFLGP
241	CM	LSGRSDNHGGSGGSISSGLLSS
242	CM	ISSGLLSSGGSGGSLSGRSGNH
243	CM	LSGRSDNHGGSGGSQNQALRMA
244	CM	QNQALRMAGGSGGSLSGRSDNH
245	CM	LSGRSGNHGGSGGSQNQALRMA
246	CM	QNQALRMAGGSGGSLSGRSGNH
247	CM	ISSGLLSGRSGNH
248	CM	AVGLLAPPGGTSTSGRSANPRG
249	CM	TSTSGRSANPRGGGAVGLLAPP
250	CM	VHMPLGFLGPGGTSTSGRSANPRG
251	CM	TSTSGRSANPRGGGVHMPLGFLGP

252	CM	LSGRSGNHGGSGGSISSGLLSS
253	Cleavable Sequence	PRFKIIGG
254	Cleavable Sequence	PRFRIIGG
255	Cleavable Sequence	SSRHRRALD
256	Cleavable Sequence	RKSSIIIRMRDVVL
257	Cleavable Sequence	SSSFDKGKYKKGDDA
258	Cleavable Sequence	SSSFDKGKYKRGDDA
259	Cleavable Sequence	IEGR
260	Cleavable Sequence	IDGR
261	Cleavable Sequence	GGSIDGR
262	Cleavable Sequence	PLGLWA
263	Cleavable Sequence	GPQGIAGQ
264	Cleavable Sequence	GPQGLLGA
265	Cleavable Sequence	GIAGQ
266	Cleavable Sequence	GPLGIAGI
267	Cleavable Sequence	GPEGLRVG
268	Cleavable Sequence	YGAGLGVV
269	Cleavable Sequence	AGLGVVER
270	Cleavable Sequence	AGLGISST
271	Cleavable Sequence	EPQALAMS
272	Cleavable Sequence	QALAMSAI
273	Cleavable Sequence	AAYHLVSQ
274	Cleavable Sequence	MDAFLESS
275	Cleavable Sequence	ESLPVVAV
276	Cleavable Sequence	SAPAVESE
277	Cleavable Sequence	DVAQFVLT
278	Cleavable Sequence	VAQFVLT
279	Cleavable Sequence	VAQFVLTE
280	Cleavable Sequence	AQFVLTEG
281	Cleavable Sequence	PVQPIGPQ

282	IFN-α2b-1204dL-hIgG4, with signal sequence	*METDTLLLWVLLLWVPGSTG*CDLPQTHSLGSRRTLMLL AQMRRISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVL HEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLND LEACVIQGVGVTETPLMKEDSILAVRKYFQRITLYLKE KKYSPCAWEVVRAEIMRSFSLSTNLQESLRSKESGRSD NIGGGSESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTL MISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNA KTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS DGSFFLYSRLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLS
283	IFN-α-1204dL-hIgG4 (polynucleotide)	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGCTT TTGTGGGTGCCAGGATCCACAGGCTGTGATCTGCCT CAAACGCATTCATTGGGGTCCAGGCGCACGCTTATG TTGCTTGCACAGATGAGGAGAATATCACTTTTCTCTT GCTTGAAGGACCGCCACGATTTTGGCTTTCCGCAGG AAGAGTTCGGTAACCAGTTCCAAAAGGCAGAGACA ATCCCCGTTTTGCATGAGATGATCCAACAGATCTTTA ACCTGTTTTCAACCAAGGATAGCAGCGCAGCGTGGG ATGAGACACTGCTTGACAAGTTTTACACCGAGCTCT ATCAGCAACTTAATGATCTCGAAGCCTGCGTAATTC AAGGAGTAGGCGTTACAGAGACACCTTTGATGAAGG AGGATTCCATCCTTGCAGTAAGAAAATACTTCCAGA GGATCACCCTCTACCTCAAAGAAAAGAAATACTCCC CATGCGCGTGGGAAGTAGTGCGAGCTGAAATAATGC GGAGCTTTTCTTTGTCAACTAATCTCCAAGAATCTCT GAGAAGCAAGGAGTCAGGTAGGTCTGATAATATCG GGGGAGGTTCTGAATCTAAGTACGGCCCTCCTTGTC CTCCATGTCCTGCTCCAGAGTTTCTCGGAGGCCCCTC CGTGTTCCTGTTTCCTCCAAAGCCTAAGGACACCCTG

		ATGATCAGCAGAACCCCTGAAGTGACCTGCGTGGTG GTCGACGTTTCACAAGAGGACCCCGAGGTGCAGTTC AATTGGTACGTGGACGGCGTGGAAGTGCACAACGCC AAGACCAAGCCTAGAGAGGAACAGTTCAACAGCAC CTACAGAGTGGTGTCCGTGCTGACCGTGCTGCACCA GGATTGGCTGAACGGCAAAGAGTACAAGTGCAAGG TGTCCAACAAGGGCCTGCCTAGCAGCATCGAGAAAA CCATCAGCAAGGCCAAGGGCCAGCCAAGGGAACCC CAGGTTTACACACTGCCACCTAGCCAAGAGGAAATG ACCAAGAACCAGGTGTCCCTGACCTGCCTGGTCAAG GGCTTTTACCCCTCCGATATCGCCGTGGAATGGGAG AGCAATGGCCAGCCTGAGAACAACTACAAGACCAC ACCTCCTGTGCTGGACAGCGACGGCTCATTCTTCCTG TACAGCAGACTGACCGTGGACAAGAGCAGATGGCA GCAGGGCAACGTGTTCAGCTGCAGCGTGATGCACGA GGCCCTGCACAACCACTACACCCAGAAGTCTCTGAG CCTGAGCTGA
284	IFN-α2b-1490DNI-hIgG4, with signal sequence	*METDTLLLWVLLLWVPGSTG*CDLPQTHSLGSRRTLMLL AQMRRISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVL HEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLND LEACVIQGVGVTETPLMKEDSILAVRKYFQRITLYLKE KKYSPCAWEVVRAEIMRSFSLSTNLQESLRSKEISSGLL SGRSDNIGGGSESKYGPPCPPCPAPEFLGGPSVFLFPPKP KDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEV HNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLYSRLTVDKSRWQQGNVFSCSVMHEALH NHYTQKSLSLS
285	IFN-α2b-1490DNI-hIgG4	ATGGAAACCGACACACTGCTGCTGTGGGTGCTGCTT TTGTGGGTGCCAGGATCCACAGGCTGTGATCTGCCT

	(polynucleotide)	CAAACGCATTCATTGGGGTCCAGGCGCACGCTTATG TTGCTTGCACAGATGAGGAGAATATCACTTTTCTCTT GCTTGAAGGACCGCCACGATTTTGGCTTTCCGCAGG AAGAGTTCGGTAACCAGTTCCAAAAGGCAGAGACA ATCCCCGTTTTGCATGAGATGATCCAACAGATCTTTA ACCTGTTTTCAACCAAGGATAGCAGCGCAGCGTGGG ATGAGACACTGCTTGACAAGTTTTACACCGAGCTCT ATCAGCAACTTAATGATCTCGAAGCCTGCGTAATTC AAGGAGTAGGCGTTACAGAGACACCTTTGATGAAGG AGGATTCCATCCTTGCAGTAAGAAAATACTTCCAGA GGATCACCCTCTACCTCAAAGAAAAGAAATACTCCC CATGCGCGTGGGAAGTAGTGCGAGCTGAAATAATGC GGAGCTTTTCTTTGTCAACTAATCTCCAAGAATCTCT GAGAAGCAAGGAGATTAGTTCTGGCCTGCTGTCAGG TAGGTCTGATAATATCGGGGGAGGTTCTGAATCTAA GTACGGCCCTCCTTGTCCTCCATGTCCTGCTCCAGAG TTTCTCGGAGGCCCCTCCGTGTTCCTGTTTCCTCCAA AGCCTAAGGACACCCTGATGATCAGCAGAACCCCTG AAGTGACCTGCGTGGTGGTCGACGTTTCACAAGAGG ACCCCGAGGTGCAGTTCAATTGGTACGTGGACGGCG TGGAAGTGCACAACGCCAAGACCAAGCCTAGAGAG GAACAGTTCAACAGCACCTACAGAGTGGTGTCCGTG CTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAA GAGTACAAGTGCAAGGTGTCCAACAAGGGCCTGCCT AGCAGCATCGAGAAAACCATCAGCAAGGCCAAGGG CCAGCCAAGGGAACCCCAGGTTTACACACTGCCACC TAGCCAAGAGGAAATGACCAAGAACCAGGTGTCCCT GACCTGCCTGGTCAAGGGCTTTTACCCCTCCGATATC GCCGTGGAATGGGAGAGCAATGGCCAGCCTGAGAA CAACTACAAGACCACACCTCCTGTGCTGGACAGCGA CGGCTCATTCTTCCTGTACAGCAGACTGACCGTGGA

		CAAGAGCAGATGGCAGCAGGGCAACGTGTTCAGCT GCAGCGTGATGCACGAGGCCCTGCACAACCACTACA CCCAGAAGTCTCTGAGCCTGAGCTGA
286	ProC440	CDLPQTHSLGSRRTLMLLAQMRRISLFSCLKDRHDFGF PQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAW DETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKE DSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSF SLSTNLQESLRSKESGRSDNICPPCPAPEFLGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSRLTVDKSRWQQGNVFSCSVMHE ALHNHYTQKSLSLS
287	human IgG Fc with a knob mutation	CPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISK AKGQPREPQVYTLPPCQEEMTKNQVSLWCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVD KSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG
288	human IgG Fc with a hole mutation	CPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISK AKGQPREPQVCTLPPSQEEMTKNQVSLSCAVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSRLTVD KSRWQEGNVFSCSVMHEALHNRFTQKSLSLSLG
289	stub moiety	SDNI
290	ProC732	QSGQTDVDYYREWSWTQVSGSSGGSLSGRSDNIGSGG SCDLPQTHSLGSRRTLMLLAQMRRISLFSCLKDRHDFG FPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAW DETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKE

		DSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSF SLSTNLQESLRSKELSGRSDNICPPCPAPEFLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVD GVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQ EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSRLTVDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLS
291	ProC733	QSGQTDVDYYREWSWTQVSGSSGGSLSGRSDNIGSGG SCDLPQTHSLGSRRTLMLLAQMRRISLFSCLKDRHDFG FPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAW DETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKE DSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSF SLSTNLQESLRSKEESKYGPPCPPCPAPEFLGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLYSRLTVDKSRWQQGNVFSCSVMHE ALHNHYTQKSLSLS
292	IFNa-2b masking peptide	TDVDYYREWSWTQVS
293	Linker	GSSGGS
294	Linker	ESKY
295	ProC286	ESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREE QFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSS IEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SRLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS SGGGGSGRSDNIGGGSCDLPQTHSLGSRRTLMLLAQM

		RRISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMI QQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEAC VIQGVGVTETPLMKEDSILAVRKYFQRITLYLKEKKYS PCAWEVVRAEIMRSFSLSTNLQESLRSKE
296	Linker	SGGG
297	Truncated IFNa-2b (amino acid 1-150)	CDLPQTHSLGSRRTLMLLAQMRRISLFSCLKDRHDFGF PQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAW DETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKE DSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRS
298	IFNa-2b L130P mutant	CDLPQTHSLGSRRTLMLLAQMRRISLFSCLKDRHDFGF PQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAW DETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKE DSILAVRKYFQRITLYPKEKKYSPCAWEVVRAEIMRSF SLSTNLQESLRSKE
299 to 446	PM sequences	(See Table 24 below for sequences)
447	ProC859 sequence	CDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGF PQEEFGNQFQKAETIPVLHEMIQQIFNLFTTKDSSAAW DEDLLDKFCTELYQQLNDLEACVMQEERVGETPLMN VDSILAVKKYFRRITLYLTEKKYSPCAWEVVRAEIMRS LSLSTNLQERLRRKELSGRSDNICPPCPAPEFLGGPSVFL FPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPS QEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSRLTVDKSRWQQGNVFSCSVM HEALHNHYTQKSLSLS
448	Universal IFN-alpha A/D sequence	CDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFGF PQEEFGNQFQKAETIPVLHEMIQQIFNLFTTKDSSAAW DEDLLDKFCTELYQQLNDLEACVMQEERVGETPLMN

		VDSILAVKKYFRRITLYLTEKKYSPCAWEVVRAEIMRS LSLSTNLQERLRRKE
449	Interferon beta, Chain A, human (1AU1)	MSYNLLGFLQRSSNFQCQKLLWQLNGRLEYCLKDRM NFDIPEEIKQLQQFQKEDAALTIYEMLQNIFAIF RQDSSSTGWNETIVENLLANVYHQINHLKTVLEEKLEK EDFTRGKLMSSLHLKRYYGRILHYLKAKEYSH CAWTIVRVEILRNFYFINRLTGYLRN
450	IFNB_CHICK Q90873.1	MTANHQSPGMHSILLLLLLPALTTTFSCNHLRHQDANF SWKSLQLLQNTAPPPQPCPQQDVTFPFPETL LKSKDKKQAAITTLRILQHLFNMLSSPHTPKHWIDRTR HSLLNQIQHYIHHLEQCFVNQGTRSQRRGPRN AHLSINKYFRSIHNFLQHNNYSACTWDHVRLQARDCF RHVDTLIQWMKSRAPLTASSKRLNTQ
451	IFNA3_CANLF O97945.1	MALPCSFSVALVLLSCHSLCCLACHLPDTHSLRNWRV LTLLGQMRRLSASSCDHYTTDFAFPKELFDGQR LQEAQALSVVHVMTQKVFHLFCTNTSSAPWNMTLLEE LCSGLSEQLDDLDACPLQEAGLAETPLMHEDST LRTYFQRISLYLQDRNHSPCAWEMVRAEIGRSFFSLTIL QERVRRRK
452	IFN_ANAPL P51526.1	MPGPSAPPPPAIYSALALLLLLTPPANAFSCSPLRLHDS AFAWDSLQLLRNMAPSPTQPCPQQHAPCSFP DTLLDTNDTQQAAHTALHLLQHLFDTLSSPSTPAHWL HTARHDLLNQLQHHIHHLERCFPADAARLHRRG PRNLHLSINKYFGCIQHFLQNHTYSPCAWDHVRLEAH ACFQRIHRLTRTMR
453	IFNAH_BOVIN P49878.1	MAPAWSFLLALLLLSCNAICSLGCHLPHTHSLPNRRVL TLLRQLRRVSPSSCLQDRNDFAFPQEALGGSQ LQKAQAISVLHEVTQHTFQLFSTEGSAAAWDESLLDKL RAALDQQLTDLQACLRQEEGLRGAPLLKEDAS LAVRKYFHRLTLYLREKRHNPCAWEVVRAEVMRAFS SSTNLQERFRRKD

454	IFNA1_CHICK P42165.1	MAVPASPQHPRGYGILLLTLLLKALATTASACNHLRPQ DATFSHDSLQLLRDMAPTLPQLCPQHNASCSF NDTILDTSNTRQADKTTHDILQHLFKILSSPSTPAHWND SQRQSLLNRIHRYTQHLEQCLDSSDTRSRTR WPRNLHLTIKKHFSCLHTFLQDNDYSACAWEHVRLQA RAWFLHIHNLTGNTRT
455	IFNA_FELCA P35849.1	MALPSSFLVALVALGCNSVCSLGCDLPQTHGLLNRRA LTLLGQMRRLPASSCQKDRNDFAFPQDVFGGDQ SHKAQALSVVHVTNQKIFHFFCTEASSSAAWNTTLLEE FCTGLDRQLTRLEACVLQEVEEGEAPLTNEDI HPEDSILRNYFQRLSLYLQEKKYSPCAWEIVRAEIMRSL YYSSTALQKRLRSEK
456	interferon-beta-1 [Sus scrofa] AAA31056.1	MANKCILQIALLMCFSTTALSMSYDVLRYQQRSSNLA CQKLLGQLPGTPQYCLEDRMNFEVPEEIMQPPQ FQKEDAVLIIHEMLQQIFGILRRNFSSTGWNETVIKTILV ELDGQMDDLETILEEIMEEENFPRGDMTIL HLKKYYLSILQYLKSKEYRSCAWTVVQVEILRNFSFLN RLTDYLRN
457	IFNB2_BOVIN P01576.1	MTHRCLLQMVLLLCFSTTALSRSYSLLRFQQRRSLALC QKLLRQLPSTPQHCLEARMDFQMPEEMKQAQQ FQKEDAILVIYEMLQQIFNILTRDFSSTGWSETIIEDLLE ELYEQMNHLEPIQKEIMQKQNSTMGDTTVL HLRKYYFNLVQYLKSKEYNRCAWTVVRVQILRNFSFL TRLTGYLRE
458	A Chain A, INTERFERON-ALPHA 2B 1RH2	CDLPQTHSLGSRRTLMLLAQMRRISLFSCLKDRHDFGF PQEEFGNQFQKAETIPVLHEMIQQIFNLFSTK DSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVTE TPLMNEDSILAVRKYFQRITLYLKEKKYSPCAW EVVRAEIMRSFSLSTNLQESLRSKE
459	Linker	SGGGG

460	ProC288	CDLPQTHSLGSRRTLMLLAQMRRISLFSCLKDRHDFGF PQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAWD ETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKEDS ILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSFSLS TNLQESLRSKESGGGGSGRSDNI**CPPC**PAPEFLGGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPS QEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSRLTVDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLS
461	ProC289	CDLPQTHSLGSRRTLMLLAQMRRISLFSCLKDRHDFGF PQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAW DETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKE DSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSF SLSTNLQESLRSKESGGGGSGRSDNIGPP**CPPC**PAPEFL GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEV QFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQ VYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLS
462	ProC290	CDLPQTHSLGSRRTLMLLAQMRRISLFSCLKDRHDFGF PQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAW DETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKE DSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSF SLSTNLQESLRSKESGGGGSGRSDNIESKYGPP**CPPC**PA PEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQED PEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPR EPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWE

		SNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLS
463	ProC291	CDLPQTHSLGSRRTLMLLAQMRRISLFSCLKDRHDFGF PQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAW DETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKE DSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSF SLSTNLQESLRSKESGGGGSGRSDNIGGGSESKYGPPCP PCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDV SQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAK GQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLS
464	ProC441	CDLPQTHSLGSRRTLMLLAQMRRISLFSCLKDRHDFGF PQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAW DETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKE DSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSF SLSTNLQESLRSKESGRSDNIGPPCPPCPAPEFLGGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV DGVEVHNA
465	ProC442	CDLPQTHSLGSRRTLMLLAQMRRISLFSCLKDRHDFGF PQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAW DETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKE DSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSF SLSTNLQESLRSKESGRSDNIESKYGPPCPPCPAPEFLGG PSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFN WYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYT LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYSRLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLS

466	ProC443	CDLPQTHSLGSRRTLMLLAQMRRISLFSCLKDRHDFGF PQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAW DETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKE DSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSF SLSTNLQESLRSKESGRSDNIGGGSESKYGPPCPPCPAP EFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDP EVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPR EPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLS
467	CM	GLSGRSDNHG
468	Signal sequence	MRAWIFFLLCLAGRALA
469	Signal sequence	MALTFALLVALLVLSCKSSCSVG
470	Signal sequence	METDTLLLWVLLLWVPGSTG
471	spacer	QGQSGS
472	spacer	GQSGS
473	spacer	QSGS
474	spacer	QGQSGQG
475	spacer	GQSGQG
476	spacer	QSGQG
477	spacer	SGQG
478	spacer	QGQSGQ
479	spacer	GQSGQ
480	spacer	QSGQ
481	spacer	QGQSG
482	spacer	QGQS
493	ProC1023	QSGQTDVDYYREWSWTQVSGSSGGSLSGRSDNIGSGG SCDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDFG FPQEEFGNQFQKAETIPVLHEMIQQIFNLFTTKDSSAAW

		DEDLLDKFCTELYQQLNDLEACVMQEERVGETPLMNV DSILAVKKYFRRITLYLTEKKYSPCAWEVVRAEIMRSLS LSTNLQERLRRKELSGRSDNICPPCPAPEFLGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSRLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLS
494	ProC1549	QSGQTDVDYYREWSWTQVSGSSGGSGGGSGGGSGSG GSCDLPQTHSLGSRRTLMLLAQMRKISLFSCLKDRHDF GFPQEEFGNQFQKAETIPVLHEMIQQIFNLFTTKDSSAA WDEDLLDKFCTELYQQLNDLEACVMQEERVGETPLM NVDSILAVKKYFRRITLYLTEKKYSPCAWEVVRAEIMR SLSLSTNLQERRRKEGGSGGGGSCPPCPAPEFLGGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPS QEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSRLTVDKSRWQQGNVFSCSVM HEALHNHYTQKSLSLS
495	Non cleavable linker	GGSGGGGS
507	ProC659 (non-cleavable steric masked IFN-a2b)	CDLPQTHSLGSRRTLMLLAQMRRISLFSCLKDRHDFGF PQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSSAAW DETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKE DSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSF SLSTNLQESLRSKEGGGSGGSCPPCPAPEFLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVD GVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQ

		EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSRLTVDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLS
504	CX-171-HC = C5H9-mIgG2a	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWV RQAPGKGLEWVSSIWRNGIVTVYADSVKGRFTISRDNS KNTLYLQMNSLRAEDTAVYYCAKWSAAFDYWGQGT LVTVSSAKTTAPSVYPLAPVCGDTTGSSVTLGCLVKGY FPEPVTLTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVT SSTWPSQSITCNVAHPASSTKVDKKIEPRGPTIKPCPPC KCPAPNLLGGPSVFIFPPKIKDVLMISLSPIVTCVVVDVS EDDPDVQISWFVNNVEVHTAQTQTHREDYNSTLRVVS ALPIQHQDWMSGKEFKCKVNNKDLPAPIERTISKPKGS VRAPQVYVLPPPEEEMTKKQVTLTCMVTDFMPEDIYV EWTNNGKTELNYKNTEPVLDSDGSYFMYSKLRVEKK NWVERNSYSCSVVHEGLHNHHTTKSFSRTPGK
505	CX-171-HC = C5H9-mIgG2a (without C-terminal lysine)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWV RQAPGKGLEWVSSIWRNGIVTVYADSVKGRFTISRDNS KNTLYLQMNSLRAEDTAVYYCAKWSAAFDYWGQGT LVTVSSAKTTAPSVYPLAPVCGDTTGSSVTLGCLVKGY FPEPVTLTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVT SSTWPSQSITCNVAHPASSTKVDKKIEPRGPTIKPCPPC KCPAPNLLGGPSVFIFPPKIKDVLMISLSPIVTCVVVDVS EDDPDVQISWFVNNVEVHTAQTQTHREDYNSTLRVVS ALPIQHQDWMSGKEFKCKVNNKDLPAPIERTISKPKGS VRAPQVYVLPPPEEEMTKKQVTLTCMVTDFMPEDIYV EWTNNGKTELNYKNTEPVLDSDGSYFMYSKLRVEKK NWVERNSYSCSVVHEGLHNHHTTKSFSRTPG
506	CX-171-LC = C5H9v2-mCk	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQ KPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSL QPEDFATYYCQQDNGYPSTFGGGTKVEIKRADAAPTV SIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWKIDGSE

		RQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNS YTCEATHKTSTSPIVKSFNRNEC

Table 24. Examples of Masking Peptides (PMs) Correlated with Appropriate Cytokines

Cytokine that may be coupled with the PM	PM Sequence	SEQ ID NO.
IFN	IAYLEYYEHLHMAYG	299
IFN	TDVDYYREWCWTQVS	300
IFN	FPLNTFDLVHELLSR	301
IFN	FLNDIHRFLHWTDLM	302
IFN	PYTFVEQVEYWLHAT	303
IFN	ACVIHFLDRISNILE	304
IFN	FCYIAAFSAMQRQSC	305
IFN	PLYLPEIGWMFGLPT	306
IFN	TVLVIPDLHYLYVDR	307
IFN	FINNVETALDTIYNL	308
IFN	SAKHLHPGRLPPMTK	309
IFN	ATMYAYLERLEAILS	310
IFN	IYPLDALLRHLNSLC	311
IFN	CFPTVVWRELYNLYG	312
IFN	NLDFYLNHLYNTLAG	313
IFN	DFINSMRSHLQSSDQ	314
IFN	EPKCSFCSPLIVPSP	315
IFN	PNCIESFLSSIHDSL	316
IFN	TDNALFLETVQHYLY	317
IFN	CYPSISWLFADAPRN	318
IFN	ELTQLLNALVDVRNC	319
IFN	LLSSFVETMSSILTC	320
IFN	YLLRLPSLEELWGPS	321
IFN	ATCYIINHWVERYII	322

IFN	IAYLEYYEHLHMAY	323
IFN	RVTCDDYYYGFGCNKFGRPA	324
IFN	MLAVVGAAALVLVAGAPWVLPSAAGGENLKPPENID VYIIDDNYTLKWSSHGESMGSVTFSAEYRTKDEAKWL KVPECQHTTTTKCEFSLLDTNVYIKTQFRVRAEEGNST SSWNEVDPFIPFYTAHMSPPEVRLEAEDKAILVHISPPG QDGNMWALEKPSFSYTIRIWQKSSSDKKTINSTYYVEK IPELLPETTYCLEVKAIHPSLKKHSNYSTVQCISTTVAN KMPVPGNLQVDAQGKSYVLKWDYIASADVLFRAQW LPGYSKSSSGSRSDKWKPIPTCANVQTTHCVFSQDTVY TGTFFLHVQASEGNHTSFWSEEKFIDSQKHILPPPPVIT VTAMSDTLLVYVNCQDSTCDGLNYEIIFWENTSNTKIS MEKDGPEFTLKNLQPLTVYCVQARVLFRALLNKTSNF SEKLCEKTRPGSFST	325
IFN	MLLSQNAFIFRSLNLVLMVYISLVFGISYDSPDYTDESC TFKISLRNFRSILSWELKNHSIVPTHYTLLYTIMSKPEDL KVVKNCANTTRSFCDLTDEWRSTHEAYVTVLEGFSGN TTLFSCSHNFWLAIDMSFEPPEFEIVGFTNHINVMVKFP SIVEEELQFDLSLVIEEQSEGIVKKHKPEIKGNMSGNFT YIIDKLIPNTNYCVSVYLEHSDEQAVIKSPLKCTLLPPG QESESAESAK	326
IFN	MMVVLLGATTLVLVAVAPWVLSAAAGGKNLKSPQK VEVDIIDDNFILRWNRSDESVGNVTFSFDYQKTGMDN WIKLSGCQNITSTKCNFSSLKLNVYEEIKLRIRAEKENT SSWYEVDSFTPFRKAQIGPPEVHLEAEDKAIVIHISPGT KDSVMWALDGLSFTYSLVIWKNSSGVEERIENIYSRHK IYKLSPETTYCLKVKAALLTSWKIGVYSPVHCIKTTVE NELPPPENIEVSVQNQNYVLKWDYTYANMTFQVQWL HAFLKRNPGNHLYKWKQIPDCENVKTTQCVFPQNVFQ KGIYLLRVQASDGNNTSFWSEEIKFDTEIQAFLLPPVFN IRSLSDSFHIYIGAPKQSGNTPVIQDYPLIYEIIFWENTSN	327

	AERKIIEKKTDVTVPNLKPLTVYCVKARAHTMDEKLN KSSVFSDAVCEKTKPGNTSK	
IFN	MRSRCTVSAVGLLSLCLVVSASLETITPSAFDGYPDEP CTINITIRNSRLILSWELENKSGPPANYTLWYTVMSKDE NLTKVKNCSDTTKSSCDVTDKWLEGMESYVVAIVIVH RGDLTVCRCSDYIVPANAPLEPPEFEIVGFTDHINVTME FPPVTSKIIQEKMKTTPFVIKEQIGDSVRKKHEPKVNNV TGNFTFVLRDLLPKTNYCVSLYFDDDPAIKSPLKCIVL QPGQESGLSESA	328
IFN-α	TDVDYYREWXXXXXXXX (X may be any amino acid)	329
IFN-α and IFN-β	GSGTDVDYYREWSWTQV	330
IFN-α and IFN-β	GSGTDVDYYREWSWTQVS	331
IFN-α and IFN-β	TDVDYYREWSWTQV	332
IFN-α and IFN-β	TDVDYYREWSWTQVS	292
IFN-γ	ALTSTEDPEPPSVPVPTNVLIKSYNLNPVVCWEYQNMS QTPIFTVQVKVYSGSWTDSCTNISDHCCNIYEQIMYPD VSAWARVKAKVGQKESDYARSKEFLMCLKGKVGPPG LEIRRKKEEQLSVLVFHPEVVVNGESQGTMFGDGSTC YTFDYTVYVEHNRSGEILHTKHTVEKEECNETLCELNI SVSTLDSRYCLSVDGISSFWQVRTEKSKDVCIPPFHDD RKDS	333

IFN-γ	ASSPDSFSQLAAPLNPRLHLYNDEQILTWEPSPSSNDPR PVVYQVEYSFIDGSWHRLLEPNCTDITETKCDLTGGGR LKLFPHPFTVFLRVRAKRGNLTSKWVGLEPFQHYENV TVGPPKNISVTPGKGSLVIHFSPPFDVFHGATFQYLVHY WEKSETQQEQVEGPFKSNSIVLGNLKPYRVYCLQTEA QLILKNKKIRPHGLLSNVSCHETTANASARLQQVILIPL GIFALLLGLTGACFTLFLKYQSRVKYWFQAPPNIPEQIE EYLKDPDQFILEVLDKDGSPKEDSWDSVSIISSPEKERD DVLQTP	334
IFN-γ	EMGTADLGPSSVPTPTNVTIESYNMNPIVYWEYQIMPQ VPVFTVEVKNYGVKNSEWIDACINISHHYCNISDHVGD PSNSLWVRVKARVGQKESAYAKSEEFAVCRDGKIGPP KLDIRKEEKQIMIDIFHPSVFVNGDEQEVDYDPETTCYI RVYNVYVRMNGSEIQYKILTQKEDDCDEIQCQLAIPVS SLNSQYCVSAEGVLHVWGVTTEKSKEVCITIFNSSIKG	335
IFN-γ	SQLPAPQHPKIRLYNAEQVLSWEPVALSNSTRPVVYQ VQFKYTDSKWFTADIMSIGVNCTQITATECDFTAASPS AGFPMDFNVTLRLRAELGALHSAWVTMPWFQHYRNV TVGPPENIEVTPGEGSLIIRFSSPFDIADTSTAFFCYYVH YWEKGGIQQVKGPFRSNSISLDNLKPSRVYCLQVQAQ LLWNKSNIFRVGHLSNISCYETMADASTELQQ	336
IL-12	CRTSECCFQDPPYPDADSGSASGPRDLRCYRISSDRYE CSWQYEGPTAGVSHFLRCCLSSGRCCYFAAGSATRLQ FSDQAGVSVLYTVTLWVESWARNQTEKSPEVTLQLY NSVKYEPPLGDIKVSKLAGQLRMEWETPDNQVGAEV QFRHRTPSSPWKLGDCGPQDDDTESCLCPLEMNVAQE FQLRRRQLGSQGSSWSKWSSPVCVPPENPPQPQVRFSV EQLGQDGRRRLTLKEQPTQLELPEGCQGLAPGTEVTY RLQLHMLSCPCKAKATRTLHLGKMPYLSGAAYNVAV ISSNQFGPGLNQTWHIPADTHTEPVALNISVGTNGTTM YWPARAQSMTYCIEWQPVGQDGGLATCSLTAPQDPD	337

	PAGMATYSWSRESGAMGQEKCYYITIFASAHPEKLTL WSTVLSTYHFGGNASAAGTPHHVSVKNHSLDSVSVD WAPSLLSTCPGVLKEYVVRCRDEDSKQVSEHPVQPTE TQVTLSGLRAGVAYTVQVRADTAWLRGVWSQPQRFS IEVQVSDWLIFFASLGSFLSILLVGVLGYLGLNRAARHL CPPLPTPC AS S AIEFPGGKETW QWINP VDF QEEASLQEAL VVEMS WDKGERTEPLEKTELPEGAP ELALDTELSLEDGDRCKAKM	
IL-12	KIDACKRGDVTVKPSHVILLGSTVNITCSLKPRQGCFH YSRRNKLILYKFDRRINFHHGHSLNSQVTGLPLGTTLF VCKLACINSDEIQICGAEIFVGVAPEQPQNLSCIQKGEQ GTVACTWERGRDTHLYTEYTLQLSGPKNLTWQKQCK DIYCDYLDFGINLTPESPESNFTAKVTAVNSLGSSSSLP STFTFLDIVRPLPPWDIRIKFQKASVSRCTLYWRDEGLV LLNRLRYRPSNSRLWNMVNVTKAKGRHDLLDLKPFT EYEFQISSKLHLYKGSWSDWSESLRAQTPEEEPTGMLD VWYMKRHIDYSRQQISLFWKNLSVSEARGKILHYQVT LQELTGGKAMTQNITGHTSWTTVIPRTGNWAVAVSAA NSKGSSLPTRINIMNLCEAGLLAPRQVSANSEGMDNIL VTWQPPRKDPSAVQEYVVEWRELHPGGDTQVPLNWL RSRPYNVSALISENIKSYICYEIRVYALSGDQGGCSSILG NSKHKAPLSGPHINAITEEKGSILISWNSIPVQEQMGCL LHYRIYWKERDSNSQPQLCEIPYRVSQNSHPINSLQPR VTYVLWMTALTAAGESSHGNEREFCLQGKANWMAF VAPSICIAIIMVGIFSTHYFQQKVFVLLAALRPQWCSREI PDPANSTCAKKYPIAEEKTQLPLDRLLIDWPTPEDPEPL VISEVLHQVTPVFRHPPCSNWPQREKGIQGHQASEKD MMHSASSPPPPRALQAESRQLVDLYKVLESRGSDPKPE NPACPWTVLPAGDLPTHDGYLPSNIDDLPSHEAPLADS	338

	LEELEPQHISLSVFPSSSLHPLTFSCGDKLTLDQLKMRC DSLML	
IL-12	NIDVCKLGTVTVQPAPVIPLGSAANISCSLNPKQGCSH YPSSNELILLKFVNDVLVENLHGKKVHDHTGHSSTFQ VTNLSLGMTLFVCKLNCSNSQKKPPVPVCGVEISVGV APEPPQNISCVQEGENGTVACSWNSGKVTYLKTNYTL QLSGPNNLTCQKQCFSDNRQNCNRLDLGINLSPDLAES RFIVRVTAINDLGNSSSLPHTFTFLDIVIPLPPWDIRINFL NASGSRGTLQWEDEGQVVLNQLRYQPLNSTSWNMVN ATNAKGKYDLRDLRPFTEYEFQISSKLHLSGGSWSNW SESLRTRTPEEEPVGILDIWYMKQDIDYDRQQISLFWK SLNPSEARGKILHYQVTLQEVTKKTTLQNTTRHTSWTR VIPRTGAWTASVSAANSKGASAPTHINIVDLCGTGLLA PHQVSAKSENMDNILVTWQPPKKADSAVREYIVEWR ALQPGSITKFPPHWLRIPPDNMSALISENIKPYICYEIRV HALSESQGGCSSIRGDSKHKAPVSGPHITAITEKKERLF ISWTHIPFPEQRGCILHYRIYWKERDSTAQPELCEIQYR RSQNSHPISSLQPRVTYVLWMTAVTAAGESPQGNERE FCPQGKANWKAFVISSICIAIITVGTFSIRYFRQKAFTLL STLKPQWYSRTIPDPANSTWVKKYPILEEKIQLPTDNLL MAWPTPEEPEPLIIHEVLYHMIPVVRQPYYFKRGQGFQ GYSTSKQDAMYIANPQATGTLTAETRQLVNLYKVLES RDPDSKLANLTSPLTVTPVNYLPSHEGYLPSNIEDLSPH EADPTDSFDLEHQHISLSIFASSSLRPLIFGGERLTLDRL KMGYDSLMSNEA	339

IL-12	QLGASGPGDGCCVEKTSFPEGASGSPLGPRNLSCYRVS KTDYECSWQYDGPEDNVSHVLWCCFVPPNHTHTGQE RCRYFSSGPDRTVQFWEQDGIPVLSKVNFWVESRLGN RTMKSQKISQYLYNWTKTTPPLGHIKVSQSHRQLRMD WNVSEEAGAEVQFRRRMPTTNWTLGDCGPQVNSGSG VLGDIRGSMSESCLCPSENMAQEIQIRRRRRLSSGAPG GPWSDWSMPVCVPPEVLPQALVPRGS	340
IL-12	QLGASGPGDGCCVEKTSFPEGASGSPLGPRNLSCYRVS KTDYECSWQYDGPEDNVSHVLWCCFVPPNHTHTGQE RCRYFSSGPDRTVQFWEQDGIPVLSKVNFWVESRLGN RTMKSQKISQYLYNWTKTTPPLGHIKVSQSHRQLRMD WNVSEEAGAEVQFRRRMPTTNWTLGDCGPQVNSGSG VLGDIRGSMSESCLCPSENMAQEIQIRRRRRLSSGAPG GPWSDWSMPVCVPPEVLPQAKIKFLVEPLNQGGRRRL TMQGQSPQLAVPEGCRGRPGAQVKKHLVLVRMLSCR CQAQTSKTVPLGKKLNLSGATYDLNVLAKTRFGRSTI QKWHLPAQELTETRALNVSVGGNMTSMQWAAQAPG TTYCLEWQPWFQHRNHTHCTLIVPEEEDPAKMVTHS WSSKPTLEQEECYRITVFASKNPKNPMLWATVLSSYY FGGNASRAGTPRHVSVRNQTGDSVSVEWTASQLSTCP GVLTQYVVRCEAEDGAWESEWLVPPTKTQVTLDGLR SRVMYKVQVRADTARLPGAWSHPQRFSFEVQISRLSII FASLGSFASVLLVGSLGYIGLNRAAWHLCPPLPTPCGS TAVEFPGSQGKQAWQWCNPEDFPEVLYPRDALVVEM PGDRGDGTESPQAAPECALDTRRPLETQRQRQVQALS EARRLGLAREDCPRGDLAHVTLPLLLGGVTQGASVLD DLWRTHKTAEPGPPTLGQEA	341
IL-15	AVNGTSQFTCFYNSRANISCVWSQDGALQDTSCQVHA WPDRRRWNQTCELLPVSQASWACNLILGAP**D**SQKLTT VDIVTLRVLCREGVRWRVMAIQDFKPFENLRLMAPISL QVVHVETHRCNISWEISQASHYFERHLEFEARTLSPGH	342

	TWEEAPLLTLKQKQEWICLETLTPDTQYEFQVRVKPL QGEFTTWSPWSQPLAFRTKPAALGKDT	
IL-15	ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAG TSSLTECVLNKATNVAHWTTPSLKCIRDPALVHQRPAP P	343
IL-15	ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAG TSSLTECVLNKATNVAHWTTPSLKCIRDP	344
IL-15	ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAG TSSLTECVLNKATNVAHWTTPSLKCIR	345
IL-15	ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAG TSSLTECVLNKATNVAHWTTPSLKCIRDPALVHQRPAP PSTVTTAGVTPQPESLSPSGKEPAASSPSSNNTAATTAA IVPGSQLMPSKSPSTGTTEISSHESSHGTPSQTTAKNWE LTASASHQPPGVYPQGHSDTT	346
IL-15	ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAG TSSLTECVLNKATNVAHWTTPSLKCIRDPALVHQRPAP PSTVTTAGVTPQPESLSPSGKEPAAS	347
IL-15	ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAG TSSLTECVLNKATNVAHWTTPSLKCIRDPALVHQRPAP PS	348
IL-15	MAPRRARGCRTLGLPALLLLLLLRPPATRGITCPPPMS VEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECV LNKATNVAHWTTPSLKCIRDPALVHQRPAPPSTVTTA GVTPQPESLSPSGKEPAASSPSSNNTAATTAAIVPGSQL MPSKSPSTGTTEISSHESSHGTPSQTTAKNWELTASASH QPPGVYPQGHSDTTVAISTSTVLLCGLSAVSLLACYLK SRQTPPLASVEMEAMEALPVTWGTSSRDEDLENCSHH L	349

IL-2	AVKNCSHLECFYNSRANVSCMWSHEEALNVTTCHVH AKSNLRHWNKTCELTLVRQASWACNLILGSFPESQSL TSVDLLDINVVCWEEKGWRRVKTCDFHPFDNLRLVAP HSLQVLHIDTQRCNISWKVSQVSHYIEPYLEFEARRRL LGHSWEDASVLSLKQRQQWLFLEMLIPSTSYEVQVRV KAQRNNTGTW SPW SQPLTFRTRPADPMKE	350
IL-2	AVNGTSQFTCFYNSRANISCVWSQDGALQDTSCQVHA WPDRRRWNQTCELLPVSQASWACNLILGAPDSQKLTT VDIVTLRVLCREGVRWRVMAIQDFKPFENLRLMAPISL QVVHVETHRCNISWEISQASHYFERHLEFEARTLSPGH TWEEAPLLTLKQKQEWICL ETLTPDTQYEFQVRVKPLQGEFTTWSPWSQPLAFRTKP AALGKDT	351
IL-2	AVNGTSQFTCFYNSRANISCVWSQDGALQDTSCQVHA WPDRRRWNQTCELLPVSQASWACNLILGAPDSQKLTT VDIVTLRVLCREGVRWRVMAIQDFKPFENLRLMAPISL QVVHVETHRCNISWEISQASHYFERHLEFEARTLSPGH TWEEAPLLTLKQKQEWICLETLTPDTQYEF QVRVKPLQ	352
IL-2	AVNGTSQFTCFYNSRANISCVWSQDGALQDTSCQVHA WPDRRRWNQTCELLPVSQASWACNLILGAPDSQKLTT VDIVTLRVLCREGVRWRVMAIQDF	353
IL-2	AVNGTSQFTCFYNSRANISCVWSQDGALQDTSCQVHA WPDRRRWNQTCELLPVSQASWACNLILGAPDSQKLTT VDIVTLRVLCREGVRWRVMAIQDFKPFENLRLMAPISL QVVHVETHRCNISWEISQASHYFERHLEFEARTLSPGH TWEEAPLLTLKQKQEWICLETLTPDTQYEFQVRVKPL QGEFTTWSPWSQPLAFRTKPAALGKD	354

IL-2	AVNGTSQFTCFYNSRANISCVWSQDGALQDTSCQVHA WPDRRRWNQTCELLPVSQASWACNLILGAPDSQKLTT VDIVTLRVLCREGVRWRVMAIQDFKPFENLRLMAPISL QVVHVETHRSNISWEISQASHYFERHLEFEARTLSPGH TWEEAPLLTLKQKQEWISLETLTPDTQYEFQVRVKPLQ GEFTTWSPWSQPLAFRTKPAALGKD	355
IL-2	AVNGTSQFTCFYNSRANISCVWSQDGALQDTSCQVHA WPDRRRWNQTCELLPVSQASWACNLILGAPDSQKLTT VDIVTLRVLCREGVRWRVMAIQDFKPFENLRLMAPISL QVVHVETHRSNISWEISQASHYFEDHLEFEARTLSPGH TWEEAPLLTLKWKQEWISLATLTPDTQYEFQVRVKPL QGEFTTWSPWSQPLAFRTKPAALGKD	356
IL-2	CGGHQYERRGGC	357
IL-2	CGGHYFERHGGC	358
IL-2	CQKLTTVDIC	359
IL-2	CSFHQYERHEGC	360
IL-2	CSGHQYERREGC	361
IL-2	CSGHYFERHEGC	362
IL-2	CSHYFERC	363
IL-2	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLD WYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFT LKLISRVEAEDVGVYYCMQALQTPLTFGGGTKVEIKR	364
IL-2	DIVMTQTPLSSPVTLGQPASISCRSSQSLVHSDGNTYLS WLQQRPGQPPRLLIYKISNRFSGVPDRFSGSGAGTDFT LKISRVEAEDVGVYYCMQATQFPTFGQGTKVEIKR	365
IL-2	DIVMTQTPLSSPVTLGQPASISCRSSQSLVHSDGNTYLS WLQQRPGQPPRLLIYKISNRFSGVPDRFSGSGAGTDFT LKISRVEAEDVGVYYCMQTSQFPTFGQGTKVEIKR	366

IL-2	DIVMTQTPLSSPVTLGQPASISCRSSQSLVHSDGNTYLS WLQQRPGQPPRLLIYKISNRFSGVPDRFSGSGAGTDFT LKISRVEAEDVGVYYCMQTTQFPTFGQGTKVEIKR	367
IL-2	DIVMTQTPLSSPVTLGQPASISCRSSQSLVHSDGNTYLS WLQQRPGQPPRLLIYKISNRFSGVPDRFSGSGAGTDFT LKISRVEAEDVGVYYCMQVTQFPTFGQGTKVEIKR	368
IL-2	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQ QKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTIS RLEPEDFAVYYCQQYGSSPLTFGGGTKVEIKR	369
IL-2	ELCDDDPPEIPHATFKAMAYKEGTILNCECKRGFRRIK SGSLYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTP QPEEQKERKTTEMQSPMQPVDQASLPGHCREPPPWEN EATERIYHFVVGQMVYYQCVQGYRALHRGPAESVCK MTHGKTRWTQPQLICTGEMETSQFPGEEKPQASPEGR PESETSCLVTTTDFQIQTEMAATMETSIFTTEYQ	370
IL-2	ELCDDDPPEIPHATFKAMAYKEGTILNCECKRGFRRIK SGSLYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTP QPEEQKERKTTEMQSPMQPVDQASLPGHCREPPPWEN EATERIYHFVVGQMVYYQCVQGYRALHRGPAESVCK MTHGKTRWTQPQLICTGEMETSQFPGEEKPQASPEGR PESETSC	371
IL-2	ELCDDDPPEIPHATFKAMAYKEGTILNCECKRGFRRIK SGSLYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTP QPEEQKERKTTEMQSPMQPVDQASLPGHCREPPPWEN EATERIYHFVVGQMVYYQCVQGYRALHRGPAESVCK MTHGKTRWTQPQLICTGEMETSQFPGEEKP	372
IL-2	ELCDDDPPEIPHATFKAMAYKEGTILNCECKRGFRRIK SGSVYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTP QPEEQKERKTTEMQSPMQPVDQASLPGHCREPPPWEN EATERIYHFVVGQMVYYQCVQGYRALHRGPAESVCK	373

	MTHGKTRWTQPQLICTGEMETSQFPGEEKPQASPEGR PESETSCLVTTTDFQIQTEMAATMETSIFTTEYQ	
IL-2	ELCDDDPPEIPHATFKAMAYKEGTILNCECKRGFRRIK SGSVYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTP QPEEQKERKTTEMQSPMQPVDQASLPGHCREPPPWEN EATERIYHFVVGQMVYYQCVQGYRALHRGPAESVCK MTHGKTRWTQPQLICTGEMETSQFPGEEKPQASPEGR PESETSC	374
IL-2	ELCDDDPPEIPHATFKAMAYKEGTILNCECKRGFRRIK SGSVYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTP QPEEQKERKTTEMQSPMQPVDQASLPGHCREPPPWEN EATERIYHFVVGQMVYYQCVQGYRALHRGPAESVCK MTHGKTRWTQPQLICTGEMETSQFPGEEKP	375
IL-2	ELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRI KELVYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTP QPEEQKERKTTEMQSPMQPVDQASLPGHCREPPPWEN EATERIYHFVVGQMVYYQCVQGYRALHRGPAESVCK MTHGKTRWTQPQLICTGEMETSQFPGEEKPQASPEGR PESETSCLVTTTDFQIQTEMAATMETSIFTTEYQ	376
IL-2	ELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRI KELVYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTP QPEEQKERKTTEMQSPMQPVDQASLPGHCREPPPWEN EATERIYHFVVGQMVYYQCVQGYRALHRGPAESVCK MTHGKTRWTQPQLICTGEMETSQFPGEEKPQASPEGR PESETSC	377
IL-2	ELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRI KELVYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTP QPEEQKERKTTEMQSPMQPVDQASLPGHCREPPPWEN	378

	EATERIYHFVVGQMVYYQCVQGYRALHRGPAESVCK MTHGKTRWTQPQLICTGEMETSQFPGEEKP	
IL-2	ELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRI KSGSLYMLCTGNSSHSSWDNQCQCTS	379
IL-2	ELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRI KSGSLYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVT PQPEEQKERKTTEMQSPMQPVDQASLPGHCREPPPWE NEATERIYHFVVGQMVYYQCVQGYRALHRGPAESVC KMTHGKTRWTQPQLICTGE	380
IL-2	ELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRI KSGSLYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVT PQPEEQKERKTTEMQSPMQPVDQASLPGHCREPPPWE NEATERIYHFVVGQMVYYQCVQGYRALHRGPAESVC KMTHGKTRWTQPQLICTGEMETSQFPGEEKPQASPEG RPESETSCLVTTTDFQIQTEMAATMETSIFTTEYQ	381
IL-2	ELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRI KSGSLYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVT PQPEEQKERKTTEMQSPMQPVDQASLPGHCREPPPWE NEATERIYHFVVGQMVYYQCVQGYRALHRGPAESVC KMTHGKTRWTQPQLICTGEMETSQFPGEEKPQASPEG RPESETSC	382
IL-2	ELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRI KSGSLYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVT PQPEEQKERKTTEMQSPMQPVDQASLPGHCREPPPWE NEATERIYHFVVGQMVYYQCVQGYRALHRGPAESVC KMTHGKTRWTQPQLICTGEMETSQFPGEEKP	383
IL-2	ELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRI KSGSLYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVT PQPEEQKERKTTEMQSPMQPVDQASLPGHCREPPPWE NEATERIYHFVVGQMVYYQCVQGYRALHRGPAESVC	384

	KMTHGKTRWTQPQLICTGEMETSQFPGEEKPQASPEG RPESETSCLVTTTDFQIQTEMAATMETSIFTTEYQ	
IL-2	ELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRI KSGSLYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVT PQPEEQKERKTTEMQSPMQPVDQASLPGHCREPPPWE NEATERIYHFVVGQMVYYQCVQGYRALHRGPAESVC KMTHGKTRWTQPQLICTG	385
IL-2	ELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRI KSGSLYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVT PQPEEQKERKTTEMQSPMQPVDQASLPGHCREPPPWE NEATERIYHFVVGQMVYYQCVQGYRALHRGPAESVC KMTHGKTRWTQPQLICT	386
IL-2	ELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRI KSGSLYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVT PQPEEQKERKTTEMQSPMQPVDQASLPGHCREPPPWE NEATERIYHFVVGQMVYYQCVQGYRALHRGPAESVC KMTHGKTRWTQPQLICTGEMETSQFPGEEKPQASPEG RPESETSCLVTTTDFQIQTEMAATMETS	387
IL-2	ELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRI KSGSLYMLCTGSSSHSSWDNQCQCTSSATRSTTKQVT PQPEEQKERKTTEMQSPMQPVDQASLPGHCREPPPWE NEATERIYHFVVGQMVYYQCVQGYRALHRGPAESVC KMTHGKTRWTQPQLICTGE	388
IL-2	ELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRI KSGSVYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVT PQPEEQKERKTTEMQSPMQPVDQASLPGHCREPPPWE NEATERIYHFVVGQMVYYQCVQGYRALHRGPAESVC KMTHGKTRWTQPQLICTGEMETSQFPGEEKPQASPEG RPESETSCLVTTTDFQIQTEMAATMETSIFTTEYQ	389

IL-2	ELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRI KSGSVYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVT PQPEEQKERKTTEMQSPMQPVDQASLPGHCREPPPWE NEATERIYHFVVGQMVYYQCVQGYRALHRGPAESVC KMTHGKTRWTQPQLICTGEMETSQFPGEEKPQASPEG RPESETSC	390
IL-2	ELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRI KSGSVYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVT PQPEEQKERKTTEMQSPMQPVDQASLPGHCREPPPWE NEATERIYHFVVGQMVYYQCVQGYRALHRGPAESVC KMTHGKTRWTQPQLICTGEMETSQFPGEEKP	391
IL-2	ELCLYDPPEIPHATFKAMAYKEGTILNCECKRGFRRIKS GSLYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQ PEEQKERKTTEMQSPMQPVDQASLPGHCREPPPWENE ATERIYHFVVGQMVYYQCVQGYRALHRGPAESVCKM THGKTRWTQPQLICTGEMETSQFPGEEKPQASPEGRPE SETSCLVTTTDFQIQTEMAATMETSIFTTEYQ	392
IL-2	ELCLYDPPEIPHATFKAMAYKEGTILNCECKRGFRRIKS GSLYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQ PEEQKERKTTEMQSPMQPVDQASLPGHCREPPPWENE ATERIYHFVVGQMVYYQCVQGYRALHRGPAESVCKM THGKTRWTQPQLICTGEMETSQFPGEEKPQASPEGRPE SETSC	393
IL-2	ELCLYDPPEIPHATFKAMAYKEGTILNCECKRGFRRIKS GSVYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQ PEEQKERKTTEMQSPMQPVDQASLPGHCREPPPWENE ATERIYHFVVGQMVYYQCVQGYRALHRGPAESVCKM THGKTRWTQPQLICTGEMETSQFPGEEKPQASPEGRPE SETSCLVTTTDFQIQTEMAATMETSIFTTEYQ	394

IL-2	ELCLYDPPEIPHATFKAMAYKEGTILNCECKRGFRRIKS GSVYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQ PEEQKERKTTEMQSPMQPVDQASLPGHCREPPPWENE ATERIYHFVVGQMVYYQCVQGYRALHRGPAESVCKM THGKTRWTQPQLICTGEMETSQFPGEEKPQASPEGRPE SETSC	395
IL-2	ELCLYDPPEIPHATFKAMAYKEGTILNCECKRGFRRIKS GSVYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQ PEEQKERKTTEMQSPMQPVDQASLPGHCREPPPWENE ATERIYHFVVGQMVYYQCVQGYRALHRGPAESVCKM THGKTRWTQPQLICTGEMETSQFPGEEKP	396
IL-2	ELCLYDPPEIPHATFKAMAYKEGTMLNCECKRGFRRIK SGSLYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTP QPEEQKERKTTEMQSPMQPVDQASLPGHCREPPPWEN EATERIYHFVVGQMVYYQCVQGYRALHRGPAESVCK MTHGKTRWTQPQLICTGEMETSQFPGEEKPQASPEGR PESETSCLVTTTDFQIQTEMAATMETSIFTTEYQ	397
IL-2	ELCLYDPPEIPHATFKAMAYKEGTMLNCECKRGFRRIK SGSLYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTP QPEEQKERKTTEMQSPMQPVDQASLPGHCREPPPWEN EATERIYHFVVGQMVYYQCVQGYRALHRGPAESVCK MTHGKTRWTQPQLICTGEMETSQFPGEEKPQASPEGR PESETSC	398
IL-2	ELCLYDPPEIPHATFKAMAYKEGTMLNCECKRGFRRIK SGSLYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTP QPEEQKERKTTEMQSPMQPVDQASLPGHCREPPPWEN EATERIYHFVVGQMVYYQCVQGYRALHRGPAESVCK MTHGKTRWTQPQLICTGEMETSQFPGEEKP	399

IL-2	ELCLYDPPEIPHATFKAMAYKEGTMLNCECKRGFRRIK SGSVYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTP QPEEQKERKTTEMQSPMQPVDQASLPGHCREPPPWEN EATERIYHFVVGQMVYYQCVQGYRALHRGPAESVCK MTHGKTRWTQPQLICTGEMETSQFPGEEKPQASPEGR PESETSCLVTTTDFQIQTEMAATMETSIFTTEYQ	400
IL-2	ELCLYDPPEIPHATFKAMAYKEGTMLNCECKRGFRRIK SGSVYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTP QPEEQKERKTTEMQSPMQPVDQASLPGHCREPPPWEN EATERIYHFVVGQMVYYQCVQGYRALHRGPAESVCK MTHGKTRWTQPQLICTGEMETSQFPGEEKPQASPEGR PESETSC	401
IL-2	ELCLYDPPEIPHATFKAMAYKEGTMLNCECKRGFRRIK SGSVYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTP QPEEQKERKTTEMQSPMQPVDQASLPGHCREPPPWEN EATERIYHFVVGQMVYYQCVQGYRALHRGPAESVCK MTHGKTRWTQPQLICTGEMETSQFPGEEKP	402
IL-2	ELCLYDPPEVPNATFKALSYKNGTILNCECKRGFRRLK ELVYMRCLGNSWSSNCQCTS	403
IL-2	ELCLYDPPEVPNATFKALSYKNGTILNCECKRGFRRLK ELVYMRCLGNSWSSNCQCTSNSHDKSRKQVTAQLEH QKEQQTTTDMQKPTQSMHQENLTGHCREPPPWKHED SKRIYHFVEGQSVHYECIPGYKALQRGPAISICKMKCG KTGWTQPQLTCVDEREHHRFLASEESQGSRNSSPESET SCPITTTDFPQPTETTAMTETFVLTMEYK	404
IL-2	ELCLYDPPEVPNATFKALSYKNGTILNCECKRGFRRLK ELVYMRCLGNSWSSNCQCTSNSHDKSRKQVTAQLEH QKEQQTTTDMQKPTQSMHQENLTGHCREPPPWKHED SKRIYHFVEGQSVHYECIPGYKALQRGPAISICKMKCG KTGWTQPQLTCVDEREHHRFLASEESQGSRNS SPESETSCPITTTDFPQPTETTAMTETFVLTMEYK	405

IL-2	ELCLYDPPEVPNATFKALSYKNGTILNCECKRGFRRLK ELVYMRCLGNSWSSNCQCTSSATRNTTKQVTPQPEEQ KERKTTEMQSPMQPVDQASLPGHCREPPPWENEATER IYHFVVGQMVYYQCVQGYRALHRGPAESVCKMTHG KTRWTQPQLICTGEMETSQFPGEEKPQASPEGRPESET SCLVTTTDFQIQTEMAATMETSIFTTEYQ	406
IL-2	EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWV RQMPGKGLEWMGIIYPGDSDTRYSPSFQGQVTISADKS ISTAYLQWSSLKASDTAMYYCARQQVAGMLDYWGQ GTTVTVSS	407
IL-2	GMLSLAVNGTSQFTCFYNSRANISCVWSQDGALQDTS CQVHAWPDRRRWNQTCELLPVSQASWACNLILGAPD SQKLTTVDIVTLRVLCREGVRWRVMAIQDFKPFENLR LMAPISLQVVHVETHRCNISWEISQASHYFERHLEFEA RTLSPGHTWEEAPLLTLKQKQEWICLETLTPDTQYEFQ VRVKPLQAFRTLTGH	408
IL-2	GMLSLELCDDDPPEIPHATFKAMAYKEGTMLNCECKR GFRRIKSGSLYMLCTGSSSHSSWDNQCQCTSSATRSTT KQVTPQPEEQKERKTTEMQSPMQPVDQASLPGHCREP PPWENEATERIYHFVVGQMVYYQCVQGYRALHRGPA ESVCKMTHGKTRWTQPQLICTGE	409
IL-2	GMLSLELCDDDPPEIPHATFKAMAYKEGTMLNCECKR GFRRIKSGSLYMLCTGSSSHSSWDNQCQCTSSATRSTT KQVTPQPEEQKERKTTEMQSPMQPVDQASLPGHCREP PPWENEATERIYHFVVGQMVYYQCVQGYRALHRGPA ESVCKMTHGKTRWTQPQLICTGEAS	410
IL-2	GMLSLELCDDDPPEIPHATFKAMAYKEGTMLNCECKR GFRRIKSGSLYMLCTGSSSHSSWDNQCQCTSSATRSTT KQVTPQPEEQKERKTTEMQSPMQPVDQASLPGHCREP PPWENEATERIYHFVVGQMVYYQCVQGYRALHRGPA ESVCKMTHGKTRWTQPQLICTGEASGGGGHHHHHH	411

IL-2	GMLSLELCDDDPPEIPHATFKAMAYKEGTMLNCECKR GFRRIKSGSLYMLCTGSSSHSSWDNQCQCTSSATRSTT KQVTPQPEEQKERKTTEMQSPMQPVDQASLPGHCREP PPWENEATERIYHFVVGQMVYYQCVQGYRALHRGPA ESVCKMTHGKTRWTQPQLICTGEAS	412
IL-2	GMLSLELCDDDPPEIPHATFKAMAYKEGTMLNCECKR GFRRIKSGSLYMLCTGSSSHSSWDNQCQCTSSATRSTT KQVTPQPEEQKERKTTEMQSPMQPVDQASLPGHCREP PPWENEATERIYHFVVGQMVYYQCVQGYRALHRGPA ESVCKMTHGKTRWTQPQLICTGEASGGGGHHHHHH	413
IL-2	LNTTILTPNGNEDTTADFFLTTMPTDSLSVSTLPLPEVQ CFVFNVEYMNCTWNSSSEPQPTNLTLHYWYKNSDND KVQKCSHYLFSEEITSGCQLQKKEIHLYQTFVVQLQDP REPRRQATQMLKLQNLVIPWAPENLTLHKLSESQLEL NWNNRFLNHCLEHLVQYRTDWDHSWTEQSVDYRHK FSLPSVDGQKRYTFRVRSRFNPLCGSAQHWSEWSHPIH WGSNTSKENPFLFALEAV	414
IL-2	MDSYLLMWGLLTFIMVPGCQAELCDDDPPEIPHATFK AMAYKEGTMLNCECKRGFRRIKSGSLYMLCTGNSSHS SWDNQCQCTSSATRNTTKQVTPQPEEQKERKTTEMQS PMQPVDQASLPGHCREPPPWENEATERIYHFVVGQMV YYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLIC TGEMETSQFPGEEKPQASPEGRPESETSCLVTTTDFQIQ TEMAATMETSIFTTEYQVAVAGCVFLLISVLLLSGLTW QRRQRKSRRTI	415
IL-2	MLSLELCDDDPPEIPHATFKAMAYKEGTMLNCECKRG FRRIKSGSLYMLCTGSSSHSSWDNQCQCTSSATRSTTK QVTPQPEEQKERKTTEMQSPMQPVDQASLPGHCREPP PWENEATERIYHFVVGQMVYYQCVQGYRALHRGPAE SVCKMTHGKTRWTQPQLICTGE	416

IL-2	QKLTTVDI	417
IL-2	QVQLVESGGGVVQPGRSLRLSCAASGFTFSIYGMHWV RQAPGKGLEWVTVIWYDGSNEYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAREDWLGEADYGM DVWGQGTTVTVSS	418
IL-2	QVQLVESGGGVVQPGRSLRLSCAASGFTFSIYGMHWV RQAPGKGLEWVTVIWYDGSNEYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDGEQWRGFDYW GQGTTVTVSS	419
IL-2	QVQLVESGGGVVQPGRSLRLSCAASGFTFSIYGMHWV RQAPGKGLEWVTVIWYDGSNEYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDQEQWRLAFDY WGQGTTVTVSS	420
IL-2	QVQLVESGGGVVQPGRSLRLSCAASGFTFSIYGMHWV RQAPGKGLEWVTVIWYDGSNEYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARGAVAGTGRDYYY YGMDVWGQGTTVTVSS	421
IL-2	QVQLVESGGGVVQPGRSLRLSCAASGFTFSIYGMHWV RQAPGKGLEWVTVIWYDGSNEYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARGSYYDSSGYYYG EDFDYWGQGTTVTVSS	422
IL-2	QVQLVESGGGVVQPGRSLRLSCAASGFTFSIYGMHWV RQAPGKGLEWVTVIWYDGSNEYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAREEWELEDYGMDV WGQGTTVTVSS	423
IL-2	QVQLVESGGGVVQPGRSLRLSCAASGFTFSIYGMHWV RQAPGKGLEWVTVIWYDGSNEYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDNWGSDAFDIWG QGTTVTVSS	424

IL-2	QVQLVESGGGVVQPGRSLRLSCAASGFTFSIYGMHWV RQAPGKGLEWVTVIWYDGSNEYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDDWFGEADYGM DVWGQGTTVTVSS	425
IL-2	QVQLVESGGGVVQPGRSLRLSCAASGFTFSIYGMHWV RQAPGKGLEWVTVIWYDGSNEYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARRISITPFDYWGQG TTVTVSS	426
IL-2	QVQLVESGGGVVQPGRSLRLSCAASGFTFSIYGMHWV RQAPGKGLEWVTVIWYDGSNEYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDDFWSDYPFDYW GQGTTVTVSS	427
IL-2	QVQLVESGGGVVQPGRSLRLSCAASGFTFSIYGMHWV RQAPGKGLEWVTVIWYDGSNEYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAREEWFGEADYGM DVWGQGTTVTVSS	428
IL-2	QVQLVESGGGVVQPGRSLRLSCAASGFTFSIYGMHWV RQAPGKGLEWVTVIWYDGSNEYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARGSYYDSSGYYFG EDFDYWGQGTTVTVSS	429
IL-2	QVQLVESGGGVVQPGRSLRLSCAASGFTFSIYGMHWV RQAPGKGLEWVTVIWYDGSNEYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARGTVAGTGRDYYY YGMDVWGQGTTVTVSS	430
IL-2	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHW VRQAPGKGLEWVAVIWYDGSNKYYADSVKGRFTISR DNSKNTLYLQMNSLRAEDTAVYYCAREDFDSHYGMD VWGQGTTVTVSS	431
IL-2	SHYFER	432

IL-2	TLPLPEVQCFVFNVEYMNCTWNSSSEPQPTNLTLHYW YKNSDNDKVQKCSHYLFSEEITSGCQLQKKEIHLYQTF VVQLQDPREPRRQATQMLKLQNLVIPWAPENLTLHKL SESQLELNWNNRFLNHCLEHLVQYRTDWDHSWTEQS VDYRHKFSLPSVDGQKRYTFRVRSRFNPLCGSAQHWS EWSHPIHWGSNT	433
IL-2	TLPLPEVQCFVFNVEYMNCTWNSSSEPQPTNLTLHYW YKNSDNDKVQKCSHYLFSEEITSGCQLQKKEIHLYQTF VVQLQDPREPRRQATQMLKLQNLVI	434
IL-2	WSSKVLMSSANEDIKADLILTSTAPEHLSAPTLPLPEVQ CFVFNIEYMNCTWNSSSEPQATNLTLHYRYKVSDNNT FQECSHYLFSKEITSGCQIQKEDIQLYQTFVVQLQDPQK PQRRAVQKLNLQNLVIPRAPENLTLSNLSESQLELRWK SRHIKERCLQYLVQYRSNRDRSWTELIVNHEPRFSLPS VDELKRYTFRVRSRYNPICGSSQQWSKWSQPVHWGS HTVEENPSLFALEA	435
IL-2 and IL-15	AVNGTSQFTCFYNSRANISCVWSQDGALQDTSCQVHA WPDRRRWNQTCELLPVSQASWACNLILGAPDSQKLTT VDIVTLRVLCREGVRWRVMAIQDFKPFENLRLMAPISL QVVHVETHRCNISWEISQASHYFERHLEFEARTLSPGH TWEEAPLLTLKQKQEWICLETLTPDTQYEFQVRVKPL QGEFTTWSPWSQPLAFRTKPAALGKDTGGGGSGGGGS GGGGSISSGLLSSGGSGGSLSGRSDNHGGGGSGGGGSL NTTILTPNGNEDTTADFFLTTMPTDSLSVSTLPLPEVQC FVFNVEYMNCTWNSSSEPQPTNLTLHYWYKNSDNDK VKCSHYLFSEEITSGCQLQKKEIHLYQTFVVQLQDPRE PRRQATQMLKLQNLVIPWAPENLTLHKLSESQLELNW NNRFLNHCLEHLVQYRTDWDHSWTEQSVDYRHKFSL PSVDGQKRYTFRVRSRFNPLCGSAQHWSEWSHPIHWG SNTSKENPFLFALEA	436

IL-2 and IL-15	AVNGTSQFTCFYNSRANISCVWSQDGALQDTSCQVHA WPDRRRWNQTCELLPVSQASWACNLILGAPDSQKLTT VDIVTLRVLCREGVRWRVMAIQDFKPFENLRLMAPISL QVVHVETHRCNISWEISQASHYFERHLEFEARTLSPGH TWEEAPLLTLKQKQEWICLETLTPDTQYEFQVRVKPL QGEFTTWSPWSQPLAFRTKPAALGKDTGGGGSGGGGS GGGGSISSGLLSSGGSGGSLSGRSDNHGGGGSGGGGSA VNGTSQFTCFYNSRANISCVWSQDGALQDTSCQVHA WPDRRRWNQTCELLPVSQASWACNLILGAPDSQKLTT VDIVTLRVLCREGVRWRVMAIQDFKPFENLRLMAPISL QVVHVETHRCNISWEISQASHYFERHLEFEARTLSPGH TWEEAPLLTLKQKQEWICLETLTPDTQYEFQVRVKPL QGEFTTWSPWSQPLAFRTKPAALGKDT	437
IL-2 and IL-15	AVNGTSQFTCFYNSRANISCVWSQDGALQDTSCQVHA WPDRRRWNQTCELLPVSQASWACNLILGAPESQKLTT VDIVTLRVLCREGVRWRVMAIQDFKPFENLRLMAPISL QVVHVETHRCNISWEISQASHYFERHLEFEARTLSPGH TWEEAPLLTLKQKQEWICLETLTPDTQYEFQVRVKPL QGEFTTWSPWSQPLAFRTKPAALGKDT	438
IL-2 and IL-15	AVNGTSQFTCFYNSRANISCVWSQDGALQDTSCQVHA WPDRRRWNQTCELLPVSQASWACNLILGAPDHQKLT TVDIVTLRVLCREGVRWRVMAIQDFKPFENLRLMAPIS LQVVHVETHRCNISWEISQASHYFERHLEFEARTLSPG HTWEEAPLLTLKQKQEWICLETLTPDTQYEFQVRVKP LQGEFTTWSPWSQPLAFRTKPAALGKDT	439
IL-2 and IL-15	AVNGTSQFTCFYNSRANISCVWSQDGALQDTSCQVHA WPDRRRWNQTCELLPVSQASWACNLILGAPDSQKLTT QDIVTLRVLCREGVRWRVMAIQDFKPFENLRLMAPISL QVVHVETHRCNISWEISQASHYFERHLEFEARTLSPGH TWEEAPLLTLKQKQEWICLETLTPDTQYEFQVRVKPL QGEFTTWSPWSQPLAFRTKPAALGKDT	440

IL-2 and IL-15	AVNGTSQFTCFYNSRANISCVWSQDGALQDTSCQVHA WPDRRRWNQTCELLPVSQASWACNLILGAPDSQKLTT FDIVTLRVLCREGVRWRVMAIQDFKPFENLRLMAPISL QVVHVETHRCNISWEISQASHYFERHLEFEARTLSPGH TWEEAPLLTLKQKQEWICLETLTPDTQYEFQVRVKPL QGEFTTWSPWSQPLAFRTKPAALGKDT	441
IL-2 and IL-15	AVNGTSQFTCFYNSRANISCVWSQDGALQDTSCQVHA WPDRRRWNQTCELLPVSQASWACNLILGAPDSQKLTT VDIVTLRVLCREGVRWRVMAIQDFKPFENLRLMAPISL QVVHVETHRCNISWEISQASHYFQRHLEFEARTLSPGH TWEEAPLLTLKQKQEWICLETLTPDTQYEFQVRVKPL QGEFTTWSPWSQPLAFRTKPAALGKDT	442
IL-2 and IL-15	AVNGTSQFTCFYNSRANISCVWSQDGALQDTSCQVHA WPDRRRWNQTCELLPVSQASWACNLILGAPDSQKLTT VDIVTLRVLCREGVRWRVMAIQDFKPFENLRLMAPISL QVVHVETHRCNISWEISQASHYFQRRLEFEARTLSPGH TWEEAPLLTLKQKQEWICLETLTPDTQYEFQVRVKPL QGEFTTWSPWSQPLAFRTKPAALGKDT	443
IL-2 and IL-15	AVNGTSQFTCFYNSYANISCVWSQDGALQDTSCQVHA WPDRRRWNQTCELLPVSQASWACNLILGAPDSQKLTT VDIVTLRVLCREGVRWRVMAIQDFKPFENLRLMAPISL QVVHVETHRCNISWEISQASHYFERHLEFEARTLSPGH TWEEAPLLTLKQKQEWICLETLTPDTQYEFQVRVKPL QGEFTTWSPWSQPLAFRTKPAALGKDT	444
IL-2, IL-15, and IL-21	LNTTILTPNGNEDTTADFFLTTMPTDSLSVSTLPLPEVQ CFVFNVEYMNCTWNSSSEPQPTNLTLHYWYKNSDND KVQKCSHYLFSEEITSGCQLQKKEIHLYQTFVVQLQDP REPRRQATQMLKLQNLVIPWAPENLTLHKLSESQLEL NWNNRFLNHCLEHLVQYRTDWDHSWTEQSVDYRHK FSLPSVDGQKRYTFRVRSRFNPLCGSAQHWSEWSHPIH WGSNTSKENPFLFALEA	445

IL-21	CPDLVCYTDYLQTVICILEMWNLHPSTLTLTWQDQYE ELKDEATSCSLHRSAHNATHATYTCHMDVFHFMADDI FSVNITDQSGNYSQECGSFLLAESIKPAPPFNVTVTFSG QYNISWRSDYEDPAFYMLKGKLQYELQYRNRGDPWA VSPRRKLISVDSRSVSLLPLEFRKDSSYELQVRAGPMP GSSYQGTWSEWSDPVIFQTQSEELKE	446

Table 25. Example PD-1/PD-L1 Pathway Inhibitors

PD-L1 Antibodies (CX-072(activatable) and CX-075 (not activatable))		
Peptide	SEQUENCE	SEQ ID NO.
Heavy Chain (anti-PD-L1)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSW VRQAPGKGLEWVSSIWRNGIVTVYADSVKGRFTISR DNSKNTLYLQMNSLRAEDTAVYYCAKWSAAFDYW GQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVE SKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTP EVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKP REEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK GLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHN HYTQKSLSLSLG	485
Light Chain (CX-072- anti-PD-L1)	QGQSGSGIALCPSHFCQLPQTGGGSSGGSGGSGGISS GLLSGRSDNHGGSDIQMTQSPSSLSASVGDRVTITCR ASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSR FSGSGSGTDFTLTISSLQPEDFATYYCQQDNGYPSTF GGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCL LNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD	496

	STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVT KSFNRGEC	
Light Chain (CX-075, anti-PD-L1-without mask and substrate)	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQ QKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTI SSLQPEDFATYYCQQDNGYPSTFGGGTKVEIKRTVA APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSK ADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	497
PD-1 Antibody (CX-188)		
Peptide	SEQUENCE	SEQ ID NO.
VL CDR1	RASESVDAYGISFMN	490
VL CDR2	AASNQGS	491
VL CDR3	QQSKDVPWT	492
Variable Light Chain	DIQLTQSPSSLSASVGDRVTITCRASESVDAYGISFM NWFQQKPGKAPKLLIYAASNQGSGVPSRFSGSGSGT DFTLTISSMQPEDFATYYCQQSKDVPWTFGQGTKLE IK	484
Masking Moiety (MM)	TSYCSIEHYPCNTHH	486
Cleavable Moiety (CM)	ISSGLLSGRSDNP	57
Spacer	QGQSGQG	474
Full Light Chain: spacer-MM-GGGSSGGS linker-CM-GGGS linker- VL	QGQSGQGTSYCSIEHYPCNTHHGGGSSGGSISSGLLS GRSDNPGGGSDIQLTQSPSSLSASVGDRVTITCRASE SVDAYGISFMNWFQQKPGKAPKLLIYAASNQGSGV PSRFSGSGSGTDFTLTISSMQPEDFATYYCQQSKDVP WTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASV	498

	VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD SKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSS PVTKSFNRGEC	
VH CDR1	GFTFSGYAMS	487
VH CDR2	YISNSGGNAH	488
VH CDR3	EDYGTSPFVY	489
Variable Heavy Chain	EVQLVESGGGLVQPGGSLRLSCAASGFTFSGYAMS WVRQAPGKGLEWVAYISNSGGNAHYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAVYYCTREDYGTSP FVYWGQGTLVTVSS	483
IgG4	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPS SSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPC PAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDV SQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYR VVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIS KAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGF YPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG	499
Full Heavy Chain (VH + IgG4)	EVQLVESGGGLVQPGGSLRLSCAASGFTFSGYAMS WVRQAPGKGLEWVAYISNSGGNAHYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAVYYCTREDYGTSP FVYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVD KRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNA KTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT	500

	KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHE ALHNHYTQKSLSLSLG	
Full Light Chain: (without spacer) MM-GGGSSGGS	TSYCSIEHYPCNTHHGGGSSGGSISSGLLSGRSDNPG GGSDIQLTQSPSSLSASVGDRVTIT CRASESVDAYGISFMNWFQQKPGKAPKLLIYAASNQ GSGVPSRFSGSGSGTDFTLTISSM QPEDFATYYCQQSKDVPWTFGQGTKLEIKRTVAAPS VFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY SLSSTLTLSKADYEKHKVYACEV THQGLSSPVTKSFNRGEC	501
Light Chain with set of version "1.4" CDRs: VL CDR1 [+ same VL CDR2 and VL CDR3 of version 1.5]	QGQSGQGAMSGCSWSAFCPYLAGGGSSGGSISSGLL SGRSDNHGGGSDIQLTQSPSSLSA SVGDRVTITCRASESVDSYGISFMNWFQQKPGKAPK LLIYAASNQGSGVPSRFSGSGSGT DFTLTISSMQPEDFATYYCQQSKDVPWTFGQGTKLE IK	502
Full heavy chain with IgG4 with the same sequence as CX-188 heavy chain (SEQ ID NO:927), but with a C-terminal lysine	EVQLVESGGGLVQPGGSLRLSCAASGFTFSGYAMS WVRQAPGKGLEWVAYISNSGGNAHYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAVYYCTREDYGTSP FVYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVD KRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNA KTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHE ALHNHYTQKSLSLSLGK	503

ProC1301	QSGQTDVDYYREWSWTQVSGSSGGSGGGSGGGSGS GGSCDLPQTHSLGSRRTLMLLAQMRRISLFSCLKDR HDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTK DSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGV TETPLMKEDSILAVRKYFQRITLYLKEKKYSPCAWE VVRAEIMRSFSLSTNLQESRSKEGGSGGGGSCPPCPA PEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQ EDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKA KGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLT VDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS	508
ProC1640	DNIGSGGSCDLPQTHSLGSRRTLMLLAQMRRISLFSC LKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNL FSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQG VGVTETPLMKEDSILAVRKYFQRITLYLKEKKYSPC AWEVVRAEIMRSFSLSTNLQESLRSKELSGRS	509
ProC1823	ISYDSPDYTDESCTFKISLRNFRSILSWELKNHSIVPT HYTLLYTIMSKPEDLKVVKNCANTTRSFCDLTDEW RSTHEAYVTVLEGFSGNTTLFSCSHNFWLAIDMSFEP PEFEIVGFTNHINVMVKFPSIVEEELQFDLSLVIEEQS EGIVKKHKPEIKGNMSGNFTYIIDKLIPNTNYCVSVY LEHSDEQAVIKSPLKCTLLPPGQESESAESAKPKSCD KTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPG	510

ProC1976	DNIGSGGSCDLPQTHSLGSRRTLMLLAQMRRISLFSC LKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFNL FSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQG VGVTETPLMKEDSILAVRKYFQRITLYLKEKKYSPC AWEVVRAEIMRSFSLSTNLQESLRSKELSGRS	511
ProC1718	ISYDSPDYTDESCTFKISLRNFRSILSWELKNHSIVPT HYTLLYTIMSKPEDLKVVKNCANTTRSFCDLTDEW RSTHEAYVTVLEGFSGNTTLFSCSHNFWLAIDMSFEP PEFEIVGFTNHINVMVKFPSIVEEELQFDLSLVIEEQS EGIVKKHKPEIKGNMSGNFTYIIDKLIPNTNYCVSVY LEHSDEQAVIKSPLKCTLLPPGQESESAESAKGGGGS HHHHHHHH	512
ProC1824	KNLKSPQKVEVDVIDDNFILRWNRSEESVGNVTFSF DYQKPEMDNWIKLPGCQNMTSTKCNFSSLKLNIYD EIKLRIRAEKENTSSWCEVDSFTPFRKAQIGPPEVHLE AEDKAIVIYISPPGTEDSVMWALDRSSFTYSLVIWKN SSSVEERIENIYSRHKISKLSPETTYCLKVKAALLTSR KIGVYGPVHCIKTTVENELPPPENIEVIVQNQNYVLK WDYTYANMTFQVQWLHAFLKRKPGNHLYKWKQIP DCENVTTTQCVFPPNTFQKGIYLLRVQASDGNNTSF WSEEIKFDTEIQASLLPPVFNIRSLSDSLHISIGAPKWS ENKPVIQDYPLIYEILFWENTSKAERKIIKKKTDVTIP NLKPLTVYCVKARAHSMDEKLNKSSVFSDVVCEET KSGNTSKPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPG	513

ProC1825	ISHDLPDYTSESCTFKISLRNFRSILSWELKNHSIVAT HYKLLYTIMSKPEDLKIVKNCANTTRSFCDLTDEWR STHEAYVTSLEGFSGNTTLFNCSHNFWLDIDMSFEPP EFEIVGFTNHINVIVKFPSIVEEELQFDLSLVIEEQSEG IVKKHKPTIKGNMSGNFTYIIDKLIPNTNYCVSVYFD HNDEQAVIKSPLKCTLLQPGQESESAESAKPKSCDK THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSL TCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY TQKSLSLSPG	514
ProC1822	KNLKSPQKVEVDIIDDNFILRWNRSDESVGNVTFSFD YQKTGMDNWIKLSGCQNITSTKCNFSSLKLNVYEEI KLRIRAEKENTSSWYEVDSFTPFRKAQIGPPEVHLEA EDKAIVIHISPGTKDSVMWALDGLSFTYSLVIWKNSS GVEERIENIYSRHKIYKLSPETTYCLKVKAALLTSWK IGVYSPVHCIKTTVENELPPPENIEVSVQNQNYVLKW DYTYANMTFQVQWLHAFLKRNPGNHLYKWKQIPD CENVKTTQCVFPQNVFQKGIYLLRVQASDGNNTSF WSEEIKFDTEIQAFLLPPVFNIRSLSDSFHIYIGAPKQS GNTPVIQDYPLIYEIIFWENTSNAERKIIEKKTDVTVP NLKPLTVYCVKARAHTMDEKLNKSSVFSDAVCEKT KPGNTSKPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPG	515

The molecules of the present disclosure may also include an IgG1 heavy chain (SEQ ID NO: 517), an IgG4 heavy chain (SEQ ID NO: 520), an IgG4 S228P heavy chain (SEQ ID NO: 516), a mutated IgG1 N297A heavy chain (SEQ ID NO: 518) or a mutated IgG1 N297Q heavy chain (SEQ ID NO: 519).

IgG4 S228P Heavy Chain (Hc) amino acid sequence:
EVQLVESGGGLVQPGGSLRLSCAASGFTFSGYAMSWVRQAPGKGLEWVAYISN
SGGNAHYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCTREDYGTSPFV
YWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNS
GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRV
ESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ
FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
GLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHY
TQKSLSLSLGK (SEQ ID NO: 516).

IgG1 Heavy Chain (Hc) amino acid sequence:
EVQLVESGGGLVQPGGSLRLSCAASGFTFSGYAMSWVRQAPGKGLEWVAYISN
SGGNAHYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCTREDYGTSPFV
YWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN
SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK
VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHED
PEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK
VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA
VEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA
LHNHYTQKSLSLSPG (SEQ ID NO: 517).

IgG1NA Hc amino acid sequence:
EVQLVESGGGLVQPGGSLRLSCAASGFTFSGYAMSWVRQAPGKGLEWVAYISN
SGGNAHYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCTREDYGTSPFV
YWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN
SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK
VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHED

PEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCK
VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA
VEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA
LHNHYTQKSLSLSPG (SEQ ID NO: 518).

IgG1NQ Hc amino acid sequence:
EVQLVESGGGLVQPGGSLRLSCAASGFTFSGYAMSWVRQAPGKGLEWVAYISN
SGGNAHYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCTREDYGTSPFV
YWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN
SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK
VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHED
PEVKFNWYVDGVEVHNAKTKPREEQYQSTYRVVSVLTVLHQDWLNGKEYKCK
VSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA
VEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA
LHNHYTQKSLSLSPG (SEQ ID NO: 519).

IgG4 Hc amino acid sequence:
EVQLVESGGGLVQPGGSLRLSCAASGFTFSGYAMSWVRQAPGKGLEWVAYISN
SGGNAHYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCTREDYGTSPFV
YWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNS
GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRV
ESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ
FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
GLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHY
TQKSLSLSLG (SEQ ID NO: 520).

Light Chain (Lc) amino acid sequence:
AMSGCSWSAFCPYLA[X1]nLSGRSDNH[X2]nDIQLTQSPSSLSASVGDRVTITCRA
SESVDNYGISFMNWFQQKPGKAPKLLIYAASNQGSGVPSRFSGSGSGTDFTLTISS
MQPEDFATYYCQQSKDVPWTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASV
VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADY
EKHKVYACEVTHQGLSSPVTKSFNRGEC

where each of [X1]n and [X2]n independently can be a linking peptide of between 0 and 20 amino acids (SEQ ID NO: 521).

OTHER EMBODIMENTS

It is to be understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

WHAT IS CLAIMED IS:

1. A method of treating a subject in need thereof comprising administering a combination of an activatable cytokine construct (ACC) and a PD-1/PD-L1 pathway inhibitor to the subject, wherein the ACC includes a first monomer construct and a second monomer construct, wherein:

(a) the first monomer construct comprises a first peptide mask (PM1), a first mature cytokine protein (CP1), a first and a third cleavable moieties (CM1 and CM3), and a first dimerization domain (DD1), wherein the CM1 is positioned between the CP1 and the DD1 and the CM3 is positioned between the PM1 and the CP1; and

(b) the second monomer construct comprises a second mature cytokine protein (CP2), a second cleavable moiety (CM2), and a second dimerization domain (DD2), wherein the CM2 is positioned between the CP2 and the DD2;

wherein the DD1 and the DD2 bind to each other thereby forming a dimer of the first monomer construct and the second monomer construct.

2. The method of claim 1, wherein the second monomer construct further comprises a second peptide mask (PM2) and a fourth cleavable moiety (CM4), wherein the CM4 is positioned between the PM2 and the CP2.

3. The method of claim 1 or 2, wherein the first monomer construct comprises a first polypeptide that comprises the PM1, the CM3, the CP1, the CM1, and the DD1.

4. The method of any one of claims 1-3, wherein the second monomer construct comprises a second polypeptide that comprises the CP2, the CM2, and the DD2.

5. The method of claim 2, wherein the second monomer construct comprises a second polypeptide that comprises the PM2, the CM4, the CP2, the CM2, and the DD2.

6. The method of any one of claims 1-5, wherein the CP1 and/or the CP2 is/are each individually selected from the group consisting of: an interferon, an interleukin, GM-CSF, G-CSF, LIF, OSM, CD154, LT-β, TNF-α, TNF-β, 4-1BBL, APRIL, CD70, CD153, CD178, GITRL, LIGHT, OX40L, TALL-1, TRAIL, TWEAK, TRANCE, TGF-β1, TGF-β1, TGF-β3, Epo, Tpo, Flt-3L, SCF, M-CSF, and MSP, optionally wherein the CP1 and/or the CP2 is independently selected from IL-2, IL-7, IL-8, IL-10, IL-12, IL-15, IL-21, an IFN-alpha, an IFN beta, an IFN gamma, GM-CSF, TGF-beta, LIGHT, GITR-L, CD40L, CD27L, 4-1BB-L, OX40, and OX40L.

7. The method of any one of claims 1-6, wherein:
the PM1 comprises a sequence selected from SEQ ID NOs: 297, 298, 292, and 299-336, and the CP1 is an interferon;
the PM1 comprises a sequence selected from SEQ ID NOs: 297, 298, 292, and 299-332, and the CP1 is an interferon alpha;
the PM1 comprises a sequence selected from SEQ ID NOs: 299-328, and 330-332, and the CP1 is an interferon beta;
the PM1 comprises a sequence selected from SEQ ID NOs: 299-328, and 333-336, and the CP1 is an interferon gamma;
the PM1 comprises a sequence selected from SEQ ID NOs: 337-341, and the CP1 is an IL-12;
the PM1 comprises a sequence selected from SEQ ID NOs: 342-349, 436-444, 478, and the CP1 is an IL-15;
the PM1 comprises a sequence selected from SEQ ID NOs: 350-435, 436-445, and the CP1 is an IL-2; or
the PM1 comprises a sequence selected from SEQ ID NOs: 445 and 446, and the CP1 is an IL-21.

8. The method of any one of claims 2-7, wherein:
the PM2 comprises a sequence selected from SEQ ID NOs: 297, 298, 292, and 299-336, and the CP2 is an interferon;

the PM2 comprises a sequence selected from SEQ ID NOs: 297, 298, 292, and 299-332, and the CP2 is an interferon alpha;
the PM2 comprises a sequence selected from SEQ ID NOs: 299-328, and 330-332, and the CP2 is an interferon beta;
the PM2 comprises a sequence selected from SEQ ID NOs: 299-328, and 333-336, and the CP2 is an interferon gamma;
the PM2 comprises a sequence selected from SEQ ID NOs: 337-341, and the CP2 is an IL-12;
the PM2 comprises a sequence selected from SEQ ID NOs: 342-349, 436-444, 478, and the CP2 is an IL-15;
the PM2 comprises a sequence selected from SEQ ID NOs: 350-435, 436-445, and the CP2 is an IL-2; or
the PM2 comprises a sequence selected from SEQ ID NOs: 445 and 446, and the CP2 is an IL-21.

9. The method of any one of claims 1 to 8, wherein the DD1 and the DD2 are a pair selected from the group consisting of: a pair of Fc domains; a sushi domain from an alpha chain of human IL-15 receptor (IL15Rα) and a soluble IL-15; barnase and barnstar; a PKA and an AKAP; adapter/docking tag modules based on mutated RNase I fragments; an epitope and sdAb; an epitope and scFv; and SNARE modules based on interactions of the proteins syntaxin, synaptotagmin, synaptobrevin, and SNAP25; an antigen-binding domain and an epitope.

10. The method of claim 9, wherein the DD1 and the DD2 are a pair of Fc domains.

11. The method of claim 10, wherein the pair of Fc domains is a pair of human Fc domains.

12. The method of claim 11, wherein the human Fc domains are human IgG1 Fc domains, human IgG2 Fc domains, human IgG3 Fc domains, or human IgG4 Fc domains.

13. The method of claim 12, wherein the human Fc domains are human IgG4 Fc domains.

14. The method of claim 11, wherein the human Fc domains comprise a sequence that is at least 80% identical to SEQ ID NO: 3.

15. The method of claim 14, wherein the human Fc domains comprise a sequence that is at least 90% identical to SEQ ID NO: 3.

16. The method of claim 15, wherein the human Fc domains comprise SEQ ID NO: 3.

17. The method of claim 9, wherein the DD1 and the DD2 comprise SEQ ID NOs: 287 and 288, respectively.

18. The method of any one of claims 1-16, wherein the DD1 and the DD2 are the same.

19. The method of claim 9, wherein the DD1 comprises an antigen-binding domain and DD2 comprises a corresponding epitope.

20. The method of claim 19, wherein the antigen-binding domain is an anti-His tag antigen-binding domain and wherein the DD2 comprises a His tag.

21. The method of claim 19, wherein the antigen-binding domain is a single chain variable fragment (scFv).

22. The method of claim 19, wherein the antigen-binding domain is a single domain antibody (sdAb).

23. The method of claim 9, wherein at least one of the DD1 and the DD2 comprises a dimerization domain substituent selected from the group consisting of a non-polypeptide polymer and a small molecule.

24. The method of claim 23, wherein the DD1 and the DD2 comprise non-polypeptide polymers covalently bound to each other.

25. The method of claim 24, wherein the non-polypeptide polymer is a sulfur-containing polyethylene glycol, and wherein the DD1 and the DD2 are covalently bound to each other via one or more disulfide bonds.

26. The method of claim 23, wherein at least one of the DD1 and the DD2 comprises a small molecule.

27. The method of claim 26, wherein the small molecule is biotin.

28. The method of claim 27, wherein DD1 comprises biotin and DD2 comprises an avidin.

29. The method of any one of claims 1-28, wherein the CP1 and the CP2 are mature cytokines.

30. The method of any one of claims 1-28, wherein the CP1 and the CP2 comprise a signal peptide.

31. The method of any one of claims 1-30, wherein the CP1 and the CP2 are the same.

32. The method of any one of claims 1-30 wherein the CP1 and the CP2 are different.

33. The method of any one of claims 1-30, wherein the CP1 and/or the CP2 is/are an interferon.

34. The method of claim 33, wherein the CP1 and the CP2 are an interferon.

35. The method of claim 33, wherein the CP1 and the CP2 are different interferons.

36. The method of claim 33, wherein the CP1 and the CP2 are the same interferon.

37. The method of any one of claims 33-36, wherein the interferon(s) is/are a human wildtype mature interferon.

38. The method of any one of claims 33-37, wherein the interferon(s) is/are selected from the group consisting of: interferon-alpha, interferon-beta, interferon-omega, and interferon-tau.

39. The method of claim 38, wherein the interferons is/are an interferon-alpha.

40. The method of claim 39, wherein the interferon(s) is/are selected from the group consisting of: interferon alpha-2a, interferon alpha-2b, and interferon alpha-n3.

41. The method of claim 40, wherein the interferon(s) is/are interferon alpha-2b.

42. The method of claim 41, wherein the CP1 and/or the CP2 comprises a sequence that is at least 80% identical to SEQ ID NO: 1.

43. The method of claim 42, wherein the CP1 and/or the CP2 comprises a sequence that is at least 90% identical to SEQ ID NO: 1.

44. The method of claim 43, wherein the CP1 and/or the CP2 comprises the sequence of SEQ ID NO: 1.

45. The method of claim 38, wherein the interferon is an interferon beta.

46. The method of claim 45, wherein the interferon beta is selected from the group consisting of interferon beta-1a, and interferon beta-1b.

47. The method of any one of claims 1-46, wherein the CP1 and/or the CP2 comprises an IFab domain.

48. The method of any one of claims 1-33, wherein the CP1 and/or the CP2 comprises an interleukin.

49. The method of claim 48, wherein the interleukin is selected from the group consisting of IL-1α, IL-1β, IL-1RA, IL-18, IL-2, IL-4, IL-7, IL-9, IL-13, IL-15, IL-3, IL-5, IL-6, IL-11, IL-12, IL-10, IL-20, IL-21, IL-14, IL-16, and IL-17.

50. The method of any one of claims 1-49, wherein each of the CM1 and the CM2 comprises a total of about 3 amino acids to about 15 amino acids.

51. The method of any one of claims 1-50, wherein one or more of the CM1, the CM2, the CM3, and the CM4 comprise substrates for different proteases.

52. The method of any one of claims 1-51, wherein the CM1, the CM2, and the CM3 comprise substrates for the same protease.

53. The method of any one of claims 1-52, wherein the protease(s) is/are selected from the group consisting of: ADAM8, ADAM9, ADAM10, ADAM12, ADAM15, ADAM17/TACE, ADAMDEC1, ADAMTS1, ADAMTS4, ADAMTS5, BACE, Renin, Cathepsin D, Cathepsin E, Caspase 1, Caspase 2, Caspase 3, Caspase 4, Caspase 5, Caspase 6, Caspase 7, Caspase 8, Caspase 9, Caspase 10, Caspase 14, Cathepsin B, Cathepsin C, Cathepsin K, Cathespin L, Cathepsin S, Cathepsin V/L2, Cathepsin X/Z/P, Cruzipain, Legumain, Otubain-2, KLK4, KLK5, KLK6, KLK7, KLK8, KLK10, KLK11, KLK13, KLK14, Meprin, Neprilysin, PSMA, BMP-1, MMP-1, MMP-2, MMP-3, MMP-7, MMP-9, MMP-10, MMP-11, MMP-12, MMP-13, MMP-14, MMP-15, MMP-16, MMP-17, MMP-19, MMP-20, MMP-23, MMP-24, MMP-26, MMP-27, activated protein C, cathepsin A, cathepsin G, Chymase, FVIIa, FIXa, FXa, FXIa, FXIIa, Elastase, Granzyme B, Guanidinobenzoatase, HtrA1, human neutrophil lyase, lactoferrin,

marapsin, NS3/4A, PACE4, Plasmin, PSA, tPA, thrombin, tryptase, uPA, DESC1, DPP-4, FAP, Hepsin, Matriptase-2, MT-SP1/Matripase, TMPRSS2, TMPRSS3, and TMPRSS4.

54. The method of claim 53, wherein the protease(s) is/are selected from the group consisting of: uPA, legumain, MT-SP1, ADAM17, BMP-1, TMPRSS3, TMPRSS4, MMP-2, MMP-9, MMP-12, MMP-13, and MMP-14.

55. The method of any one of claim 1-52, wherein the CM1, CM2, CM3, and/or the CM4 comprise a sequence selected from the group consisting of: LSGRSDNH (SEQ ID NO: 5), TGRGPSWV (SEQ ID NO: 6), PLTGRSGG (SEQ ID NO: 7), TARGPSFK (SEQ ID NO: 8), NTLSGRSENHSG (SEQ ID NO: 9), NTLSGRSGNHGS (SEQ ID NO: 10), TSTSGRSANPRG (SEQ ID NO: 11), TSGRSANP (SEQ ID NO: 12), VHMPLGFLGP (SEQ ID NO: 13), AVGLLAPP (SEQ ID NO: 14), AQNLLGMV (SEQ ID NO: 15), QNQALRMA (SEQ ID NO: 16), LAAPLGLL (SEQ ID NO: 17), STFPFGMF (SEQ ID NO: 18), ISSGLLSS (SEQ ID NO: 19), PAGLWLDP (SEQ ID NO: 20), VAGRSMRP (SEQ ID NO: 21), VVPEGRRS (SEQ ID NO: 22), ILPRSPAF (SEQ ID NO: 23), MVLGRSLL (SEQ ID NO: 24), QGRAITFI (SEQ ID NO: 25), SPRSIMLA (SEQ ID NO: 26), SMLRSMPL (SEQ ID NO: 27), ISSGLLSGRSDNH (SEQ ID NO: 28), AVGLLAPPGGLSGRSDNH (SEQ ID NO: 29), ISSGLLSSGGSGGSLSGRSDNH (SEQ ID NO: 30), LSGRSGNH (SEQ ID NO: 31), SGRSANPRG (SEQ ID NO: 32), LSGRSDDH (SEQ ID NO: 33), LSGRSDIH (SEQ ID NO: 34), LSGRSDQH (SEQ ID NO: 35), LSGRSDTH (SEQ ID NO: 36), LSGRSDYH (SEQ ID NO: 37), LSGRSDNP (SEQ ID NO: 38), LSGRSANP (SEQ ID NO: 39), LSGRSANI (SEQ ID NO: 40), LSGRSDNI (SEQ ID NO: 41), MIAPVAYR (SEQ ID NO: 42), RPSPMWAY (SEQ ID NO: 43), WATPRPMR (SEQ ID NO: 44), FRLLDWQW (SEQ ID NO: 45), ISSGL (SEQ ID NO: 46), ISSGLLS (SEQ ID NO: 47), ISSGLL (SEQ ID NO: 48), ISSGLLSGRSANPRG (SEQ ID NO: 49), AVGLLAPPTSGRSANPRG (SEQ ID NO: 50), AVGLLAPPSGRSANPRG (SEQ ID NO: 51), ISSGLLSGRSDDH (SEQ ID NO: 52), ISSGLLSGRSDIH (SEQ ID NO: 53), ISSGLLSGRSDQH (SEQ ID NO: 54), ISSGLLSGRSDTH (SEQ ID NO: 55), ISSGLLSGRSDYH (SEQ ID NO: 56),

ISSGLLSGRSDNP (SEQ ID NO: 57), ISSGLLSGRSANP (SEQ ID NO: 58), ISSGLLSGRSANI (SEQ ID NO: 59), AVGLLAPPGGLSGRSDDH (SEQ ID NO: 60), AVGLLAPPGGLSGRSDIH (SEQ ID NO: 61), AVGLLAPPGGLSGRSDQH (SEQ ID NO: 62), AVGLLAPPGGLSGRSDTH (SEQ ID NO: 63), AVGLLAPPGGLSGRSDYH (SEQ ID NO: 64), AVGLLAPPGGLSGRSDNP (SEQ ID NO: 65), AVGLLAPPGGLSGRSANP (SEQ ID NO: 66), AVGLLAPPGGLSGRSANI (SEQ ID NO: 67), ISSGLLSGRSDNI (SEQ ID NO: 68), AVGLLAPPGGLSGRSDNI (SEQ ID NO: 69), GLSGRSDNHGGAVGLLAPP (SEQ ID NO: 70), GLSGRSDNHGGVHMPLGFLGP (SEQ ID NO: 71), LSGRSDNHGGVHMPLGFLGP (SEQ ID NO: 72), ISSGLSS (SEQ ID NO: 73), PVGYTSSL (SEQ ID NO: 74), DWLYWPGI (SEQ ID NO: 75), LKAAPRWA (SEQ ID NO: 76), GPSHLVLT (SEQ ID NO: 77), LPGGLSPW (SEQ ID NO: 78), MGLFSEAG (SEQ ID NO: 79), SPLPLRVP (SEQ ID NO: 80), RMHLRSLG (SEQ ID NO: 81), LLAPSHRA (SEQ ID NO: 82), GPRSFGL (SEQ ID NO: 83), GPRSFG (SEQ ID NO: 84), SARGPSRW (SEQ ID NO: 85), GGWHTGRN (SEQ ID NO: 86), HTGRSGAL (SEQ ID NO: 87), AARGPAIH (SEQ ID NO: 88), RGPAFNPM (SEQ ID NO: 89), SSRGPAYL (SEQ ID NO: 90), RGPATPIM (SEQ ID NO: 91), RGPA (SEQ ID NO: 92), GGQPSGMWGW (SEQ ID NO: 93), FPRPLGITGL (SEQ ID NO: 94), SPLTGRSG (SEQ ID NO: 95), SAGFSLPA (SEQ ID NO: 96), LAPLGLQRR (SEQ ID NO: 97), SGGPLGVR (SEQ ID NO: 98), PLGL (SEQ ID NO: 99), and SGRSDNI (SEQ ID NO: 100).

56. The method of claim 55, wherein the CM1, the CM2, the CM3 and/or the CM4 comprises a sequence selected from the group consisting of: ISSGLLSGRSDNH (SEQ ID NO: 28), LSGRSDDH (SEQ ID NO: 33), ISSGLLSGRSDQH (SEQ ID NO: 54), SGRSDNI (SEQ ID NO: 100), and ISSGLLSGRSDNI (SEQ ID NO: 68).

57. The method of any one of claims 1-56, wherein the protease(s) is/are produced by a tumor in a subject.

58. The method of claim 57, wherein the subject has been diagnosed or identified as having a cancer.

59. The method of any one of claims 1-58, wherein the CP1 and the CM1 directly abut each other in the first monomer construct.

60. The method of any one of claims 1-59, wherein the CM1 and the DD1 directly abut each other in the first monomer construct.

61. The method of any one of claims 1-60, wherein the CP2 and the CM2 directly abut each other in the second monomer construct.

62. The method of any one of claims 1-61, wherein the CM2 and the DD2 directly abut each other in the second monomer construct.

63. The method of any one of claims 1-58, wherein the first monomer construct comprises at least one linker.

64. The method of claim 63, wherein the at least one linker is a linker L1 disposed between the PM1 and the CM3 and/or a linker L2 disposed between the CM3 and the CP1.

65. The method of claim 63, wherein the second monomer construct comprises at least one linker.

66. The method of claim 65, wherein the at least one linker is a linker L3 disposed between the PM2 and the CM4 and/or a linker L4 disposed between the CM4 and the CP2.

67. The method of claim 66, wherein the first monomer construct comprises a linker L1 and the second monomer construct comprises a linker L3.

68. The method of claim 67, wherein L1 and L3 are the same.

69. The method of claim 66, wherein the first monomer construct comprises a linker L2 and the second monomer construct comprises a linker L4.

70. The method of claim 69, wherein L2 and L4 are the same.

71. The method of any one of claims 63-70, wherein each linker has a total length of 1 amino acid to about 15 amino acids.

72. The method of claim 71, wherein each linker has a total length of at least 5 amino acids.

73. The method of claim 63, wherein the first monomer construct comprises at least one linker, wherein each linker is independently selected from the group consisting of GSSGGSGGSGG (SEQ ID NO: 210); GGGS (SEQ ID NO: 2); GGGSGGGS (SEQ ID NO: 211); GGGSGGGSGGGS (SEQ ID NO: 212); GGGGSGGGGSGGGGS (SEQ ID NO: 213); GGGGSGGGGSGGGGSGGGGSGGGGS (SEQ ID NO: 214); GGGGSGGGGS (SEQ ID NO: 215); GGGGS (SEQ ID NO: 216); GS; GGGGSGS (SEQ ID NO: 217); GGGGSGGGGSGGGGSGS (SEQ ID NO: 218); GGSLDPKGGGGS (SEQ ID NO: 219); PKSCDKTHTCPPCPAPELLG (SEQ ID NO: 220); SKYGPPCPPCPAPEFLG (SEQ ID NO: 221); GKSSGSGSESKS (SEQ ID NO: 222); GSTSGSGKSSEGKG (SEQ ID NO: 223); GSTSGSGKSSEGSGSTKG (SEQ ID NO: 224); GSTSGSGKPGSGEGSTKG (SEQ ID NO: 225); GSTSGSGKPGSSEGST (SEQ ID NO: 226); (GS)n, (GGS)n, (GSGGS)n (SEQ ID NO: 227), (GGGS)n (SEQ ID NO: 228), (GGGGS)n (SEQ ID NO: 216), wherein each n is an integer of at least one; GGSG (SEQ ID NO: 229); GGSGG (SEQ ID NO: 230); GSGSG (SEQ ID NO: 231; GSGGG (SEQ ID NO: 232); GGGSG (SEQ ID NO: 233); GSSSG (SEQ ID NO: 234); GGGGSGGGGSGGGGS (SEQ ID NO: 213); GGGGSGGGGSGGGGSGGGGS (SEQ ID NO: 214); GSTSGSGKPGSSEGST (SEQ ID NO: 226); SGGG (SEQ ID NO: 296); and SGGGG (SEQ ID NO: 459).

74. The method of claim 73, wherein the linker comprises a sequence of GGGS (SEQ ID NO: 2).

75. The method of any one of claims 1-74, wherein the first monomer construct comprises in a N- to C- terminal direction, the PM1, the CM3, the CP1, the CM1, and the DD1.

76. The method of any one of claims 1-74, wherein the first polypeptide comprises in a C- to N-terminal direction, the PM1, the CM3, the CP1, the CM1, and the DD1.

77. The method of any one of claims 1-76, wherein the second polypeptide comprises in a N- to C-terminal direction, the CP2, CM2, and the DD2.

78. The method of any one of claims 1-77, wherein the second polypeptide comprises in a C- to N-terminal direction, the CP2, CM2, and the DD2.

79. The method of any one of claims 1-31, 33, 34, or 36-78, wherein the first monomer construct and the second monomer construct are the same.

80. The method of any one of claims 1-74, wherein the first monomer construct comprises in a N- to C- terminal direction, the PM1, an optional linker, the CM3, an optional linker, the CP1, the CM1, and the DD1, wherein the CP1 and the CM1 directly abut each other, wherein the CM1 and the DD1 directly abut each other, wherein the CM1 is a peptide of not more than 10 amino acids, wherein the second monomer construct is the same as the first monomer construct, and wherein the first and second monomer constructs are covalently bound to each other via at least two disulfide bonds.

81. The method of claim 80, wherein the DD1 and the DD2 are each a human Fc domain having an N-terminus at Cysteine 216, as numbered according to EU numbering.

82. The method of claim 80 or 81, wherein the CM1 is a peptide of not more than 7 amino acids.

83. The method of any one of claim 80-82, wherein the CP1 and the CP2 comprise an amino acid sequence that is at least 90% identical to SEQ ID NO: 1.

84. The method of any one of claims 1-83, wherein the ACC is characterized by having a reduced level of at least one CP1 and/or CP2 activity as compared to a control level of at least one CP1 and/or CP2 activity.

85. The method of claim 84, wherein the at least one of the CP1 and the CP2 activity is a level of proliferation of lymphoma cells.

86. The method of claim 84, wherein the at least one of the CP1and the CP2 activity is the level of JAK/STAT/ISGF3 pathway activation in a lymphoma cell.

87. The method of claim 84, wherein the at least one activity is a level of SEAP production in a lymphoma cell.

88. The method of claim 84, wherein the ACC is characterized by at least a 2-fold reduction in at least one of the CP1 and the CP2 activity as compared to the control level.

89. The method of claim 88, wherein the ACC is characterized by at least a 5-fold reduction in at least one CP1 and/or the CP2 activity as compared to the control level.

90. The method of claim 89, wherein the ACC is characterized by at least a 10-fold reduction in at least one activity of the CP1 and/or the CP2 as compared to the control level.

91. The method of claim 90, wherein the ACC is characterized by at least a 500-fold reduction in at least one CP1 and/or the CP2 activity as compared to the control level.

92. The method of any one of claims 84-91, wherein the control level of the at least one activity of the CP1 and/or the CP2, is the activity of the CP1 and/or the CP2 in the ACC following exposure of the ACC to the protease(s).

93. The method of any one of claims 84-92, wherein the control level of the at least one CP1 and/or CP2, is the corresponding CP1 and/or the CP2 activity of a corresponding wildtype mature cytokine.

94. The method of any one of claims 84-93, wherein the ACC is characterized by generating a cleavage product following exposure to the protease(s), wherein the cleavage product comprises the at least one activity of the CP1 and/or the CP2.

95. The method of claim 94, wherein the at least one activity of the CP1 and/or the CP2 is anti-proliferation activity.

96. The method of claim 95, wherein the control level is an EC50 value, and wherein ratio of EC50 (cleavage product) to EC50 (control level) is less than about 10, or less than about 9, or less than about 8, or less than about 7, or less than about 6, or less than about 5, or less than about 4, or less than about 3, or less than about 2, or less than about 1.5, or less than about 1.0.

97. The method of any one of claims 84-96, wherein the at least one of the CP1 and the CP2 activity is a binding affinity of the CP1 and/or the CP2 for its cognate receptor as determined using surface plasmon resonance.

98. A method of treating a subject in need thereof comprising administering a combination of an activatable cytokine construct (ACC) and a PD-1/PD-L1 pathway inhibitor to the subject, wherein the ACC comprises a first monomer construct and a second monomer construct, wherein:

(a) the first monomer construct is a polypeptide comprising a first peptide mask (PM1), a first mature cytokine protein (CP1), a first and a third cleavable moieties (CM1 and CM3), and a first dimerization domain (DD1);

(b) the second monomer construct is a polypeptide comprising a second peptide mask (PM2), a second mature cytokine protein (CP2), a second and a fourth cleavable moieties (CM2 and CM4), and a second dimerization domain (DD2);

(c) the first monomer construct comprises, in an N- to C- terminal direction, the PM1, the CM3, the CP1, the CM1, and the DD1;

and

(d) the ACC is characterized by having a reduced level of interferon activity as compared to a corresponding wildtype interferon or a corresponding pegylated interferon.

99. The method of claim 98, wherein the ACC is further characterized by at least one of:

(i) the PM1 comprises no more than 20 amino acids and binds to the CP1;

(ii) the CM1 and the DD1 directly abut each other;

(iii) the CP1 and the CM1 directly abut each other;

(iv) the CM1 comprises no more than 12 amino acids;

(v) the CM1 and the CM3 each functions as a substrate for a protease; and

(vi) the CP1 is a mature interferon.

100. The method of claim 98 or claim 99, wherein

(i) the DD1 and the DD2 are a pair of human IgG Fc domains;

(ii) the DD1 and the DD2 bind to each other via at least one disulfide bond, thereby forming a homodimer of the first monomer construct and the second monomer construct; or

(iii) both (i) and (ii).

101. The method of any one of claims 98-100, wherein the CP1 is a mature interferon-alpha and the PM1 comprises a sequence that is at least 85% identical to SEQ ID NO: 292.

102. The method of any one of claims 98-101, wherein the CM1 and the CM3 each independently functions as a substrate of urokinase (uPa) and/or a matrix metalloproteinase (MMP).

103. The method of claim 102, wherein the CM1 and the CM3 each independently functions as a substrate of urokinase (uPa) and/or MMP-14.

104. The method of any one of claims 99-103, wherein the mature interferon is a mature human interferon alpha.

105. The method of any one of claims 99-104, wherein the mature interferon alpha is mature interferon alpha-2b.

106. The method of any one of claims 99-105, wherein the mature interferon alpha is a truncated form of a wildtype mature interferon alpha-2b.

107. The method of any one of claims 99-106, wherein the mature interferon comprises a sequence that is at least 95% identical to SEQ ID NO: 1.

108. The method of any one of claims 99-107, wherein the mature interferon comprises the sequence of SEQ ID NO: 1.

109. The method of any one of claims 99-108, wherein the CM1 and the CM3 each comprises no more than 8 amino acids.

110. The method of any one of claims 99-109, wherein the CM1 and the CM3 are the same.

111. The method of any one of claims 99-110, wherein the CM1 and the CM3 each comprises a sequence that is at least 85% identical to SEQ ID NO: 41.

112. The method of any one of claims 99-111, wherein the CM1 and the CM3 each comprises a sequence selected from the group consisting of SEQ ID NO: 41, SEQ ID NO: 68, and SEQ ID NO: 100.

113. The method of any one of claims 99-112, wherein the DD1 and the DD2 are a pair of human IgG4 Fc domains.

114. The method of claim 113, wherein the DD1 and the DD2 are a pair of human IgG4 Fc domains truncated at N-terminus to Cysteine 226 as numbered by EU numbering.

115. The method of claim 113 or 114, wherein the human IgG4 Fc domains comprise a S228P mutation as numbered by EU numbering.

116. The method of any one of claims 99-115, wherein the DD1 and the DD2 each comprises a sequence that is at least 95% identical to SEQ ID NO: 3.

117. The method of any one of claims 99-116, wherein the DD1 and the DD2 each comprises the sequence of SEQ ID NO: 3.

118. The method of any one of claims 99-117, wherein the first and second monomer constructs are covalently bound to each other via at least two disulfide bonds.

119. The method of claim 118, wherein the first and second monomer constructs are covalently bound to each other via at least three disulfide bonds.

120. The method of any one of claims 99-119, wherein:
the first monomer construct further comprises a first signal sequence at the N-terminus, and the second monomer construct further comprises a second signal sequence at the N-terminus.

121. The method of claim 120, wherein the first and second signal sequences each comprises a sequence that is at least 95% identical to SEQ ID NO: 470.

122. The method of claim 121, wherein the first and second signal sequences each comprises the sequence of SEQ ID NO: 470.

123. The method of any one of claims 120-122, wherein:
the first monomer construct further comprises a first spacer positioned between the first signal sequence and the PM1, and the second monomer construct further comprises a second spacer positioned between the second signal sequence and the PM2.

124. The method of claim 123, wherein the first and second spacers each comprises a sequence that is at least 80% identical to SEQ ID NO: 480.

125. The method of claim 124, wherein the first and second spacers each comprises a sequence of SEQ ID NO: 480.

126. The method of any one of claims 99-125, further comprising a linker L1 between the PM1 and the CM3, and/or a linker L2 between the CM3 and the CP1, wherein each of L1 and L2 independently comprises a sequence that is at least 80% identical to SEQ ID NO: 27 (wherein n=1), a sequence that is at least 80% identical to SEQ ID NO: 293, or is absent.

127. The method of claim 126, wherein the L1 comprises the sequence SEQ ID NO: 27 (wherein n=1) and L2 comprises the sequence of SEQ ID NO: 293.

128. The method of any one of claims 99-127, comprising a Linking Region comprising no more than 12 amino acids.

129. The method of claim 128, wherein the Linking Region comprises 7 to 12 amino acids.

130. The method of claim 129, wherein the Linking Region comprises 7 amino acids.

131. The method of any one of claims 99-130, wherein the ACC is characterized by at least a 2000-fold reduction in interferon alpha activity as compared to wildtype interferon alpha.

132. The method of claim 131, wherein the ACC is characterized by at least a 4000-fold reduction in interferon alpha activity as compared to wildtype interferon alpha.

133. The method of claim 132, wherein the ACC is characterized by at least a 5000-fold reduction in interferon alpha activity as compared to wildtype interferon alpha.

134. The method of any one of claims 99-130, wherein the ACC is characterized by at least a 2000-fold reduction in interferon alpha activity as compared to pegylated interferon alpha.

135. The method of any one of claims 99-134, wherein the reduction in interferon activity is determined by comparing the EC50 of the ACC with the EC50 of the wildtype interferon or the pegylated interferon in an anti-proliferation assay in lymphoma cells.

136. The method of any one of claims 99-135, wherein the reduction in interferon activity is determined by comparing the EC50 of the ACC with the EC50 of the wildtype interferon or the pegylated interferon in an assay of induction of secreted embryonic alkaline phosphatase production in interferon-responsive HEK293 cells.

137. The method of any of claims 99-136, wherein the ACC is further characterized by generating a cleavage product following exposure to the protease(s) for which CM1 and CM3 function as a substrate, wherein the ratio of the interferon activity of the corresponding wildtype interferon to the cleavage product is less than about 2.

138. The method of claim 137, wherein the EC50 of the cleavage product is approximately the same as the EC50 of the corresponding wildtype interferon.

139. The method of claim 99, wherein the first and second monomer constructs each comprises a sequence that is at least 95% identical to SEQ ID NO: 290, wherein the ACC is characterized by at least a 1000-fold reduction in interferon activity as compared to wildtype interferon alpha-2b, and wherein the ACC is further characterized by generating

a cleavage product following exposure to uPA, wherein the cleavage product has approximately the same interferon activity as wildtype interferon alpha-2b, wherein interferon activity is measured in an anti-proliferation assay in lymphoma cells or in an assay of induction of secreted embryonic alkaline phosphatase production in interferon-responsive HEK293 cells.

140. A method of treating a subject in need thereof comprising administering a combination of an activatable cytokine construct (ACC) and a PD-1/PD-L1 pathway inhibitor to the subject, wherein the ACC comprises a first monomer construct and a second monomer construct, wherein:

(a) the first monomer construct comprises a first peptide mask (PM1), a first mature cytokine protein (CP1), a first and a third cleavable moieties (CM1 and CM3), and a first dimerization domain (DD1);

(b) the second monomer construct is a polypeptide comprising a second peptide mask (PM2), a second mature cytokine protein (CP2), a second and a fourth cleavable moieties (CM2 and CM4), and a second dimerization domain (DD2);

(c) the first monomer construct is a polypeptide comprising, in an N- to C- terminal direction, the PM1, the CM3, the CP1, the CM1, and the DD1, further wherein:

(i) the PM1 comprises a sequence that is at least 85% identical to SEQ ID NO: 292,

(ii) the CM1 and the DD1 directly abut each other,

(iii) the CM1 comprises a sequence that is at least 85% identical to SEQ ID NO: 41, and

(iv) the CP1 comprises a sequence that is at least 85% identical to SEQ ID NO: 1;

(d) further wherein:

(i) the second monomer construct is the same as the first monomer construct,

(ii) the DD1 and DD2 are a pair of human IgG4 Fc domains;

(e) the DD1 and the DD2 covalently bind to each other via at least one disulfide bond, thereby forming a homodimer of the first monomer construct and the second monomer construct; and

(f) the ACC is characterized by having a reduced level of interferon alpha activity as compared to the interferon alpha activity of PEGylated interferon alpha-2b.

141. The method of claim 140, wherein the first and second monomer constructs each comprises a sequence that is at least 95% identical to SEQ ID NO: 290 or wherein each of the first and second monomer constructs comprises the sequence of SEQ ID NO: 290, wherein the ACC exhibits lower toxicity in vivo compared to either wildtype interferon alpha-2b or PEGylated interferon alpha-2b.

142. The method of any one of claims 1-141, wherein the CM1 and the CM3 each functions as a substrate for a protease that is over-expressed in a tumor tissue.

143. The method of any one of claims 1-142, wherein the PD1/PD-L1 pathway inhibitor is selected from a PD-1 antibody, an activatable PD-1 antibody, a PD-L1 antibody, or an activatable PD-L1 antibody.

144. The method of claim 143, wherein the activatable PD-1 antibody or the activatable PD-L1 antibody comprises: (i) an antibody or an antigen binding fragment thereof (AB) that specifically binds to PD-1 or PD-L1; (ii) a masking moiety (MM) that, when the activatable antibody is in an uncleaved state, inhibits the binding of the AB to PD-1 or PD-L1; and (iii) a cleavable moiety (CM) coupled to the AB, wherein the CM is a polypeptide that functions as a substrate for a protease; and optionally a first linking peptide and/or a second linking peptide.

145. The method of any one of claims 1-142, wherein the PD1/PD-L1 pathway inhibitor comprises nivolumab, pembrolizumab, tislelizumab, spartalizumab, camrelizumab, cetrelimab, Balstilimab, Dostarlimab, Prolgolimab, Sasanlimab, zimberelimab, Atezolizumab, Avelumab, Durvalumab, adebrelimab, Lodapolimab, Envafolimab, Cosibelimab, budigalimab, ezabenlimab, finotonlimab, geptanolimab, lodapolimab, penpulimab, pimivalimab, pucotenlimab, serplulimab. Sintilimab, toripalimab,

zeluvalimab, iparomlimab, nofazinlimab, rulonilimab, garivulimab, manelimab, opucolimab, sudubrilimab, sugemalimab, socazolimab, or tagitanlimab.

146. The method of any one of claims 1-142 or 145, wherein the PD1/PD-L1 pathway inhibitor comprises pacmilimab (CX-072), CX-075, CX-171, or CX-188.

147. The method of any one of claims 1-146, wherein the subject is in need of reducing, inhibiting, and/or delaying the onset or progression of PD-1 or PD-L1 in the subject.

148. The method of any one of claims 1-146, wherein the subject is in need of alleviating a symptom associated with aberrant expression and/or activity of PD-1 or PD-L1 in the subject.

149. The method of any one of claims 1-148, wherein the subject has been identified or diagnosed as having a cancer.

150. The method of claim 149, wherein the cancer is a lymphoma.

151. The method of claim 150, wherein the lymphoma is Burkitt's lymphoma.

152. The method of any one of claims 1-151, wherein the method comprises augmenting or potentiating therapeutic efficacy and/or therapeutic index relative to a conventional cytokine therapy in the subject.

153. The method of any one of claims 1-151, wherein the method comprises augmenting or potentiating therapeutic efficacy and/or therapeutic index relative to a conventional PD1/PDL1 inhibitor therapy in the subject.

154. The method of any one of claims 1-151, wherein the method comprises augmenting or potentiating therapeutic efficacy and/or therapeutic index relative to a conventional cytokine and PD1/PDL1 inhibitor combination therapy in the subject.

155. The method of any one of claims 1-149, wherein the method comprises augmenting or potentiating therapeutic efficacy and/or therapeutic index relative to administering the ACC alone.

156. A combination or composition comprising the ACC and the PD-1/PD-L1 pathway inhibitor as claimed in any one of claims 1-148.

157. The combination or composition of claim 156, wherein the combination or composition is a pharmaceutical composition.

158. The combination or composition of claim 156, wherein the combination or composition is for use in therapy.

159. The combination of composition of claim 156, wherein the combination or composition is for use in treating cancer.

160. The combination or composition of claim 156, wherein the combination or composition is for use in treating an infection.

161. A container, vial, syringe, injector pen, or kit comprising at least one dose of the combination or composition of claims 156-160.

162. A method of treating a subject in need thereof comprising administering a combination of an activatable cytokine construct (ACC) and a PD-1/PD-L1 pathway inhibitor to the subject, wherein the ACC includes a first monomer construct and a second monomer construct, wherein:

(a) the first monomer construct comprises a first mature cytokine protein (CP1), a first cleavable moiety (CM1), and a first dimerization domain (DD1),

wherein the CM1 is positioned between the CP1 and the DD1; and

(b) the second monomer construct comprises a second mature cytokine protein (CP2), a second cleavable moiety (CM2), and a second dimerization domain (DD2),

wherein the CM2 is positioned between the CP2 and the DD2; or

(a) the first monomer construct comprises a first mature cytokine protein (CP1), a first dimerization domain (DD1), and

(b) the second monomer construct comprises a second mature cytokine protein (CP2), a cleavable moiety (CM), and a second dimerization domain (DD2), wherein the CM is positioned between the CP2 and the DD2, wherein the CM functions as a substrate for a protease; or

(a) the first monomer construct comprises a first mature cytokine protein (CP1), a cleavable moiety (CM), and a first dimerization domain (DD1), wherein the CM is positioned between the CP1 and the DD1, and

(b) the second monomer construct comprises a second mature cytokine protein (CP2), and a second dimerization domain (DD2),

wherein the CM functions as a substrate for a protease; or

(a) the first monomer construct comprises a first mature cytokine protein (CP1), and a first dimerization domain (DD1), and

(b) the second monomer construct comprises a second mature cytokine protein (CP2), and a second dimerization domain (DD2), wherein the CP1, the CP2, or both CP1 and CP2 include(s) an amino acid sequence that functions as a substrate for a protease;

further wherein (c) the DD1 and the DD2 bind each other thereby forming a dimer of the first monomer construct and the second monomer construct; and

further wherein (d) the ACC is characterized by having a reduced level of at least one CP1 and/or CP2 activity as compared to a control level of the at least one CP1 and/or CP2 activity.

163. The method of claim 162, wherein the first monomer construct comprises a first polypeptide that comprises the CP1, the CM1, and the DD1.

164. The method of claim 162 or 163, wherein the second monomer construct comprises a second polypeptide that comprises the CP2, the CM2, and the DD2.

165. The method of any one of claims 162-164, wherein the DD1 and the DD2 are a pair selected from the group consisting of: a pair of Fc domains, a sushi domain from an alpha chain of human IL-15 receptor (IL15Rα) and a soluble IL-15; barnase and barnstar; a PKA and an AKAP; adapter/docking tag modules based on mutated RNase I fragments; an epitope and sdAb; an epitope and scFv; and SNARE modules based on interactions of the proteins syntaxin, synaptotagmin, synaptobrevin, and SNAP25, an antigen-binding domain and an epitope.

166. The method of any one of claims 162-165, wherein the DD1 and the DD2 are a pair of Fc domains.

167. The method of claim 166, wherein the pair of Fc domains is a pair of human Fc domains.

168. The method of claim 167, wherein the human Fc domains are human IgG1 Fc domains, human IgG2 Fc domains, human IgG3 Fc domains, or human IgG4 Fc domains.

169. The method of claim 168, wherein the human Fc domains are human IgG4 Fc domains.

170. The method of claim 167, wherein the human Fc domains comprise a sequence that is at least 80% identical to SEQ ID NO: 3.

171. The method of claim 167, wherein the human Fc domains comprise a sequence that is at least 90% identical to SEQ ID NO: 3.

172. The method of claim 167, wherein the human Fc domains comprise SEQ ID NO: 3.

173. The method of claim 162, wherein the DD1 and the DD2 comprise SEQ ID NOs: 287 and 288, respectively.

174. The method of any one of claims 162-173, wherein the DD1 and the DD2 are the same.

175. The method of claim 165, wherein the DD1 comprises an antigen-binding domain and DD2 comprises a corresponding epitope.

176. The method of claim 175, wherein the antigen-binding domain is an anti-His tag antigen-binding domain and wherein the DD2 comprises a His tag.

177. The method of claim 175, wherein the antigen-binding domain is a single chain variable fragment (scFv).

178. The method of claim 175, wherein the antigen-binding domain is a single domain antibody (sdAb).

179. The method of claim 165, wherein at least one of the DD1 and the DD2 comprises a dimerization domain substituent selected from the group consisting of a non-polypeptide polymer and a small molecule.

180. The method of claim 179, wherein the DD1 and the DD2 comprise non-polypeptide polymers covalently bound to each other.

181. The method of claim 180, wherein the non-polypeptide polymer is a sulfur-containing polyethylene glycol, and wherein the DD1 and the DD2 are covalently bound to each other via one or more disulfide bonds.

182. The method of claim 179, wherein at least one of the DD1 and the DD2 comprises a small molecule.

183. The method of claim 182, wherein the small molecule is biotin.

184. The method of claim 183, wherein DD1 comprises biotin and DD2 comprises an avidin.

185. The method of any one of claims 162-184, wherein the CP1 and the CP2 are mature cytokines.

186. The method of any one of claims 162-184, wherein the CP1 and the CP2 comprise a signal peptide.

187. The method of any one of claims 162-186, wherein the CP1 and the CP2 are the same.

188. The method of any one of claims 162-186, wherein the CP1 and the CP2 are different.

189. The method of any one of claims 162-186, wherein the CP1 and/or the CP2 is/are an interferon.

190. The method of claim 189, wherein the CP1 and the CP2 are an interferon.

191. The method of claim 189, wherein the CP1 and the CP2 are different interferons.

192. The method of claim 189, wherein the CP1 and the CP2 are the same interferon.

193. The method of any one of claims 189-192, wherein the interferon(s) is/are a human wildtype mature interferon.

194. The method of any one of claims 189-193, wherein the interferon(s) is/are selected from the group consisting of: interferon-alpha, interferon-beta, interferon-omega, and interferon-tau.

195. The method of claim 194, wherein the interferons is/are an interferon-alpha.

196. The method of claim 195, wherein the interferon(s) is/are selected from the group consisting of: interferon alpha-2a, interferon alpha-2b, and interferon alpha-n3.

197. The method of claim 196, wherein the interferon(s) is/are interferon alpha-2b.

198. The method of claim 197, wherein the CP1 and/or the CP2 comprises a sequence that is at least 80% identical to SEQ ID NO: 1.

199. The method of claim 198, wherein the CP1 and/or the CP2 comprises a sequence that is at least 90% identical to SEQ ID NO: 1.

200. The method of claim 199, wherein the CP1 and/or the CP2 comprises the sequence of SEQ ID NO: 1.

201. The method of claim 194, wherein the interferon is an interferon beta.

202. The method of claim 201, wherein the interferon beta is selected from the group consisting of interferon beta-1a, and interferon beta-1b.

203. The method of any one of claims 162-202, wherein the CP1 and/or the CP2 comprises an IFab domain.

204. The method of any one of claims 162-189, wherein the CP1 and/or the CP2 comprises an interleukin.

205. The method of claim 204, wherein the interleukin is selected from the group consisting of IL-1α, IL-1β, IL-1RA, IL-18, IL-2, IL-4, IL-7, IL-9, IL-13, IL-15, IL-3, IL-5, IL-6, IL-11, IL-12, IL-10, IL-20, IL-21, IL-14, IL-16, and IL-17.

206. The method of any one of claims 162-205, wherein each of the CM1 and the CM2 comprises a total of about 3 amino acids to about 15 amino acids.

207. The method of any one of claims 162-206, wherein one or more of the CM1, the CM2, the CM3, and the CM4 comprise substrates for different proteases.

208. The method of any one of claims 162-207, wherein the CM1, the CM2, and the CM3 comprise substrates for the same protease.

209. The method of any one of claims 162-208, wherein the protease(s) is/are selected from the group consisting of: ADAM8, ADAM9, ADAM10, ADAM12, ADAM15, ADAM17/TACE, ADAMDEC1, ADAMTS1, ADAMTS4, ADAMTS5, BACE, Renin, Cathepsin D, Cathepsin E, Caspase 1, Caspase 2, Caspase 3, Caspase 4, Caspase 5, Caspase 6, Caspase 7, Caspase 8, Caspase 9, Caspase 10, Caspase 14, Cathepsin B, Cathepsin C, Cathepsin K, Cathespin L, Cathepsin S, Cathepsin V/L2, Cathepsin X/Z/P, Cruzipain, Legumain, Otubain-2, KLK4, KLK5, KLK6, KLK7, KLK8, KLK10, KLK11, KLK13, KLK14, Meprin, Neprilysin, PSMA, BMP-1, MMP-1, MMP-2, MMP-3, MMP-7, MMP-9, MMP-10, MMP-11, MMP-12, MMP-13, MMP-14, MMP-15, MMP-16, MMP-17, MMP-19, MMP-20, MMP-23, MMP-24, MMP-26, MMP-27, activated protein C, cathepsin A, cathepsin G, Chymase, FVIIa, FIXa, FXa, FXIa, FXIIa, Elastase, Granzyme B, Guanidinobenzoatase, HtrA1, human neutrophil lyase, lactoferrin, marapsin, NS3/4A, PACE4, Plasmin, PSA, tPA, thrombin, tryptase, uPA, DESC1, DPP-4, FAP, Hepsin, Matriptase-2, MT-SP1/Matripase, TMPRSS2, TMPRSS3, and TMPRSS4.

210. The method of claim 209, wherein the protease(s) is/are selected from the group consisting of: uPA, legumain, MT-SP1, ADAM17, BMP-1, TMPRSS3, TMPRSS4, MMP-2, MMP-9, MMP-12, MMP-13, and MMP-14.

211. The method of any one or combination of claim 162-208, wherein the CM1, CM2, CM3, and/or the CM4 comprise a sequence selected from the group consisting of: LSGRSDNH (SEQ ID NO: 5), TGRGPSWV (SEQ ID NO: 6), PLTGRSGG (SEQ ID NO: 7), TARGPSFK (SEQ ID NO: 8), NTLSGRSENHSG (SEQ ID NO: 9), NTLSGRSGNHGS (SEQ ID NO: 10), TSTSGRSANPRG (SEQ ID NO: 11), TSGRSANP (SEQ ID NO: 12), VHMPLGFLGP (SEQ ID NO: 13), AVGLLAPP (SEQ ID NO: 14), AQNLLGMV (SEQ ID NO: 15), QNQALRMA (SEQ ID NO: 16), LAAPLGLL (SEQ ID NO: 17),

STFPFGMF (SEQ ID NO: 18), ISSGLLSS (SEQ ID NO: 19), PAGLWLDP (SEQ ID NO: 20), VAGRSMRP (SEQ ID NO: 21), VVPEGRRS (SEQ ID NO: 22), ILPRSPAF (SEQ ID NO: 23), MVLGRSLL (SEQ ID NO: 24), QGRAITFI (SEQ ID NO: 25), SPRSIMLA (SEQ ID NO: 26), SMLRSMPL (SEQ ID NO: 27), ISSGLLSGRSDNH (SEQ ID NO: 28), AVGLLAPPGGLSGRSDNH (SEQ ID NO: 29), ISSGLLSSGGSGGSLSGRSDNH (SEQ ID NO: 30), LSGRSGNH (SEQ ID NO: 31), SGRSANPRG (SEQ ID NO: 32), LSGRSDDH (SEQ ID NO: 33), LSGRSDIH (SEQ ID NO: 34), LSGRSDQH (SEQ ID NO: 35), LSGRSDTH (SEQ ID NO: 36), LSGRSDYH (SEQ ID NO: 37), LSGRSDNP (SEQ ID NO: 38), LSGRSANP (SEQ ID NO: 39), LSGRSANI (SEQ ID NO: 40), LSGRSDNI (SEQ ID NO: 41), MIAPVAYR (SEQ ID NO: 42), RPSPMWAY (SEQ ID NO: 43), WATPRPMR (SEQ ID NO: 44), FRLLDWQW (SEQ ID NO: 45), ISSGL (SEQ ID NO: 46), ISSGLLS (SEQ ID NO: 47), ISSGLL (SEQ ID NO: 48), ISSGLLSGRSANPRG (SEQ ID NO: 49), AVGLLAPPTSGRSANPRG (SEQ ID NO: 50), AVGLLAPPSGRSANPRG (SEQ ID NO: 51), ISSGLLSGRSDDH (SEQ ID NO: 52), ISSGLLSGRSDIH (SEQ ID NO: 53), ISSGLLSGRSDQH (SEQ ID NO: 54), ISSGLLSGRSDTH (SEQ ID NO: 55), ISSGLLSGRSDYH (SEQ ID NO: 56), ISSGLLSGRSDNP (SEQ ID NO: 57), ISSGLLSGRSANP (SEQ ID NO: 58), ISSGLLSGRSANI (SEQ ID NO: 59), AVGLLAPPGGLSGRSDDH (SEQ ID NO: 60), AVGLLAPPGGLSGRSDIH (SEQ ID NO: 61), AVGLLAPPGGLSGRSDQH (SEQ ID NO: 62), AVGLLAPPGGLSGRSDTH (SEQ ID NO: 63), AVGLLAPPGGLSGRSDYH (SEQ ID NO: 64), AVGLLAPPGGLSGRSDNP (SEQ ID NO: 65), AVGLLAPPGGLSGRSANP (SEQ ID NO: 66), AVGLLAPPGGLSGRSANI (SEQ ID NO: 67), ISSGLLSGRSDNI (SEQ ID NO: 68), AVGLLAPPGGLSGRSDNI (SEQ ID NO: 69), GLSGRSDNHGGAVGLLAPP (SEQ ID NO: 70), GLSGRSDNHGGVHMPLGFLGP (SEQ ID NO: 71), LSGRSDNHGGVHMPLGFLGP (SEQ ID NO: 72), ISSGLSS (SEQ ID NO: 73), PVGYTSSL (SEQ ID NO: 74), DWLYWPGI (SEQ ID NO: 75), LKAAPRWA (SEQ ID NO: 76), GPSHLVLT (SEQ ID NO: 77), LPGGLSPW (SEQ ID NO: 78), MGLFSEAG (SEQ ID NO: 79), SPLPLRVP (SEQ ID NO: 80), RMHLRSLG (SEQ ID NO: 81), LLAPSHRA (SEQ ID NO: 82), GPRSFGL (SEQ ID NO: 83), GPRSFG (SEQ ID NO: 84), SARGPSRW (SEQ ID NO: 85), GGWHTGRN (SEQ ID NO: 86), HTGRSGAL

(SEQ ID NO: 87), AARGPAIH (SEQ ID NO: 88), RGPAFNPM (SEQ ID NO: 89), SSRGPAYL (SEQ ID NO: 90), RGPATPIM (SEQ ID NO: 91), RGPA (SEQ ID NO: 92), GGQPSGMWGW (SEQ ID NO: 93), FPRPLGITGL (SEQ ID NO: 94), SPLTGRSG (SEQ ID NO: 95), SAGFSLPA (SEQ ID NO: 96), LAPLGLQRR (SEQ ID NO: 97), SGGPLGVR (SEQ ID NO: 98), PLGL (SEQ ID NO: 99), and SGRSDNI (SEQ ID NO: 100).

212. The method of claim 211, wherein the CM1, the CM2, the CM3 and/or the CM4 comprises a sequence selected from the group consisting of: ISSGLLSGRSDNH (SEQ ID NO: 28), LSGRSDDH (SEQ ID NO: 33), ISSGLLSGRSDQH (SEQ ID NO: 54), SGRSDNI (SEQ ID NO: 100), and ISSGLLSGRSDNI (SEQ ID NO: 68).

213. The method of any one of claims 162-211, wherein the protease(s) is/are produced by a tumor in a subject.

214. The method of claim 213, wherein the subject has been diagnosed or identified as having a cancer.

215. The method of any one of claims 162-214, wherein the CP1 and the CM1 directly abut each other in the first monomer construct.

216. The method of any one of claims 162-215, wherein the CM1 and the DD1 directly abut each other in the first monomer construct.

217. The method of any one of claims 162-217, wherein the CP2 and the CM2 directly abut each other in the second monomer construct.

218. The method of any one of claims 162-217, wherein the CM2 and the DD2 directly abut each other in the second monomer construct.

219. The method of any one of claims 162-214, wherein the first monomer construct comprises at least one linker.

220. The method of claim 219, wherein the at least one linker is a linker L1 disposed between the PM1 and the CM3 and/or a linker L2 disposed between the CM3 and the CP1.

221. The method of claim 219, wherein the second monomer construct comprises at least one linker.

222. The method of claim 221, wherein the at least one linker is a linker L3 disposed between the PM2 and the CM4 and/or a linker L4 disposed between the CM4 and the CP2.

223. The method of claim 222, wherein the first monomer construct comprises a linker L1 and the second monomer construct comprises a linker L3.

224. The method of claim 223, wherein L1 and L3 are the same.

225. The method of claim 222, wherein the first monomer construct comprises a linker L2 and the second monomer construct comprises a linker L4.

226. The method of claim 225, wherein L2 and L4 are the same.

227. The method of any one of claims 219-226, wherein each linker has a total length of 1 amino acid to about 15 amino acids.

228. The method of claim 227, wherein each linker has a total length of at least 5 amino acids.

229. The method of any one of claims 219-225, wherein each linker is independently selected from the group consisting of GSSGGSGGSGG (SEQ ID NO: 210); GGGS (SEQ ID NO: 2); GGGSGGGS (SEQ ID NO: 211); GGGSGGGSGGGS (SEQ ID NO: 212); GGGGSGGGGSGGGGS (SEQ ID NO: 213); GGGGSGGGGSGGGGSGGGGSGGGGS

(SEQ ID NO: 214); GGGGSGGGGS (SEQ ID NO: 215); GGGGS (SEQ ID NO: 216); GS; GGGGSGS (SEQ ID NO: 217); GGGGSGGGGSGGGGSGS (SEQ ID NO: 218); GGSLDPKGGGGS (SEQ ID NO: 219); PKSCDKTHTCPPCPAPELLG (SEQ ID NO: 220); SKYGPPCPPCPAPEFLG (SEQ ID NO: 221); GKSSGSGSESKS (SEQ ID NO: 222); GSTSGSGKSSEGKG (SEQ ID NO: 223); GSTSGSGKSSEGSGSTKG (SEQ ID NO: 224); GSTSGSGKPGSGEGSTKG (SEQ ID NO: 225); GSTSGSGKPGSSEGST (SEQ ID NO: 226); (GS)n, (GGS)n, (GSGGS)n (SEQ ID NO: 227), (GGGS)n (SEQ ID NO: 228), (GGGGS)n (SEQ ID NO: 216), wherein each n is an integer of at least one; GGSG (SEQ ID NO: 229); GGSGG (SEQ ID NO: 230); GSGSG (SEQ ID NO: 231; GSGGG (SEQ ID NO: 232); GGGSG (SEQ ID NO: 233); GSSSG (SEQ ID NO: 234); GGGGSGGGGSGGGGS (SEQ ID NO: 213); GGGGSGGGGSGGGGSGGGGS (SEQ ID NO: 214); GSTSGSGKPGSSEGST (SEQ ID NO: 226); SGGG (SEQ ID NO: 296); and SGGGG (SEQ ID NO: 459).

230. The method of claim 229, wherein the linker comprises a sequence of GGGS (SEQ ID NO: 2).

231. The method of any one of claims 162-230, wherein the first monomer construct comprises in a N- to C- terminal direction, the PM1, the CM3, the CP1, the CM1, and the DD1.

232. The method of any one of claims 162-230, wherein the first polypeptide comprises in a C- to N-terminal direction, the PM1, the CM3, the CP1, the CM1, and the DD1.

233. The method of any one of claims 162-232, wherein the second polypeptide comprises in a N- to C-terminal direction, the CP2, CM2, and the DD2.

234. The method of any one of claims 162-233, wherein the second polypeptide comprises in a C- to N-terminal direction, the CP2, CM2, and the DD2.

235. The method of any one of claims 162-187, 189, 190, or 192-234, wherein the first monomer construct and the second monomer construct are the same.

236. The method of any one of claims 162-230, wherein the first monomer construct comprises in a N- to C- terminal direction, the PM1, an optional linker, the CM3, an optional linker, the CP1, the CM1, and the DD1, wherein the CP1 and the CM1 directly abut each other, wherein the CM1 and the DD1 directly abut each other, wherein the CM1 is a peptide of not more than 10 amino acids, wherein the second monomer construct is the same as the first monomer construct, and wherein the first and second monomer constructs are covalently bound to each other via at least two disulfide bonds.

237. The method of claim 236, wherein the DD1 and the DD2 are each a human Fc domain having an N-terminus at Cysteine 216, as numbered according to EU numbering.

238. The method of claim 236 or 237, wherein the CM1 is a peptide of not more than 7 amino acids.

239. The method of any one or combination of claim 236-238, wherein the CP1 and the CP2 comprise an amino acid sequence that is at least 90% identical to SEQ ID NO: 1.

240. The method of any one of claims 162-239, wherein the ACC is characterized by having a reduced level of at least one CP1 and/or CP2 activity as compared to a control level of at least one CP1 and/or CP2 activity.

241. The method of claim 240, wherein the at least one of the CP1 and the CP2 activity is a level of proliferation of lymphoma cells.

242. The method of claim 240, wherein the at least one of the CP1and the CP2 activity is the level of JAK/STAT/ISGF3 pathway activation in a lymphoma cell.

243. The method of claim 240, wherein the at least one activity is a level of SEAP production in a lymphoma cell.

244. The method of claim 240, wherein the ACC is characterized by at least a 2-fold reduction in at least one of the CP1 and the CP2 activity as compared to the control level.

245. The method of claim 244, wherein the ACC is characterized by at least a 5-fold reduction in at least one CP1 and/or the CP2 activity as compared to the control level.

246. The method of claim 245, wherein the ACC is characterized by at least a 10-fold reduction in at least one activity of the CP1 and/or the CP2 as compared to the control level.

247. The method of claim 246, wherein the ACC is characterized by at least a 500-fold reduction in at least one CP1 and/or the CP2 activity as compared to the control level.

248. The method of any one of claims 240-247, wherein the control level of the at least one activity of the CP1 and/or the CP2, is the activity of the CP1 and/or the CP2 in the ACC following exposure of the ACC to the protease(s).

249. The method of any one of claims 240-248, wherein the control level of the at least one CP1 and/or CP2, is the corresponding CP1 and/or the CP2 activity of a corresponding wildtype mature cytokine.

250. The method of any one of claims 240-249, wherein the ACC is characterized by generating a cleavage product following exposure to the protease(s), wherein the cleavage product comprises the at least one activity of the CP1 and/or the CP2.

251. The method of claim 250, wherein the at least one activity of the CP1 and/or the CP2 is anti-proliferation activity.

252. The method of claim 251, wherein the control level is an EC50 value, and wherein ratio of EC50 (cleavage product) to EC50 (control level) is less than about 10, or less than about 9, or less than about 8, or less than about 7, or less than about 6, or less than about 5, or less than about 4, or less than about 3, or less than about 2, or less than about 1.5, or less than about 1.0.

253. The method of any one of claims 240-252, wherein the at least one of the CP1 and the CP2 activity is a binding affinity of the CP1 and/or the CP2 for its cognate receptor as determined using surface plasmon resonance.

254. The method of claim 162, wherein the first and second monomer constructs each comprises a sequence that is at least 95% identical to SEQ ID NO: 290 or wherein each of the first and second monomer constructs comprises the sequence of SEQ ID NO: 290, wherein the ACC exhibits lower toxicity in vivo compared to either wildtype interferon alpha-2b or PEGylated interferon alpha-2b.

255. The method of any one of claims 162-254, wherein the CM1 and the CM2 each functions as a substrate for a protease that is over-expressed in a tumor tissue.

256. The method of any one of claims 162-255, wherein the PD1/PD-L1 pathway inhibitor is selected from a PD-1 antibody, an activatable PD-1 antibody, a PD-L1 antibody, or an activatable PD-L1 antibody.

257. The method of claim 256, wherein the activatable PD-1 antibody or the activatable PD-L1 antibody comprises: (i) an antibody or an antigen binding fragment thereof (AB) that specifically binds to PD-1 or PD-L1; (ii) a masking moiety (MM) that, when the activatable antibody is in an uncleaved state, inhibits the binding of the AB to PD-1 or PD-L1; and (iii) a cleavable moiety (CM) coupled to the AB, wherein the CM is a polypeptide that functions as a substrate for a protease; and optionally a first linking peptide and/or a second linking peptide.

258. The method of any preceding claim, wherein the PD1/PD-L1 pathway inhibitor comprises nivolumab, pembrolizumab, tislelizumab, spartalizumab, camrelizumab, cetrelimab, Balstilimab, Dostarlimab, Prolgolimab, Sasanlimab, zimberelimab, Atezolizumab, Avelumab, Durvalumab, adebrelimab, Lodapolimab, Envafolimab, Cosibelimab, budigalimab, ezabenlimab, finotonlimab, geptanolimab, lodapolimab, penpulimab, pimivalimab, pucotenlimab, serplulimab. Sintilimab, toripalimab, zeluvalimab, iparomlimab, nofazinlimab, rulonilimab, garivulimab, manelimab, opucolimab, sudubrilimab, sugemalimab, socazolimab, or tagitanlimab.

259. The method of any preceding claim, wherein the PD1/PD-L1 pathway inhibitor comprises pacmilimab (CX-072), CX-075, CX-171, or CX-188.

260. The method of any preceding claim, wherein the PD1/PD-L1 pathway inhibitor is a PD-1 pathway inhibitor, optionally a PD-1 antibody or an activatable PD-1 antibody, optionally wherein the PD-1 pathway inhibitor is an antibody comprising one or more sequences in Tables 7-9 of WO2017011580A2.

261. The method of any preceding claim, wherein the PD1/PD-L1 pathway inhibitor is a PD-L1 pathway inhibitor, optionally a PD-L1 antibody or an activatable PD-L1 antibody, optionally wherein the PD-L1 pathway inhibitor is an antibody comprising one or more sequences in Tables 15-17 of WO2016149201A2.

262. The method of claim 256, wherein the activatable PD-1 antibody or the activatable PD-L1 antibody comprises: (i) an antibody or an antigen binding fragment thereof (AB) that specifically binds to PD-1 or PD-L1; (ii) a masking moiety (MM) that, when the activatable antibody is in an uncleaved state, inhibits the binding of the AB to PD-1 or PD-L1; and (c) a cleavable moiety (CM) coupled to the AB, wherein the CM is a polypeptide that functions as a substrate for a protease; and optionally a first linking peptide and/or a second linking peptide.

263. The method of claim 262, wherein the activatable anti-PD-1 antibody comprises a MM comprising an amino acid sequence selected from the group consisting of AMSGCSWSAFCPYLA (SEQ ID NO: 550), DVNCAIWYSVCITVP (SEQ ID NO: 551), LVCPLYALSSGVCMG (SEQ ID NO: 552), SVNCRIWSAVCAGYE (SEQ ID NO: 553), MLVCSLQPTAMCERV (SEQ ID NO: 554), APRCYMFASYCKSQY (SEQ ID NO: 555), VGPCELTPKPVCNTY (SEQ ID NO: 556), ETCNQYERSSGLCFA (SEQ ID NO: 557), APRTCYTYQCSSFYT (SEQ ID NO: 558), GLCSWYLSSSGLCVD (SEQ ID NO: 559), VPWCQLTPRVMCMWA (SEQ ID NO: 560), NWLDCQFYSECSVYG (SEQ ID NO: 561), SCPLYVMSSFGGCWD (SEQ ID NO: 562), MSHCWMFSSSCDGVK (SEQ ID NO: 563), VSYCTWLIEVICLRG (SEQ ID NO: 564), VLCAAYALSSGICGG (SEQ ID NO: 565), TTCNLYQQSSMFCNA (SEQ ID NO: 566), APRCYMFASYCKSQY (SEQ ID NO: 567), PCDQNPYFYPYVCHA (SEQ ID NO: 568), SVCPMYALSSMLCGA (SEQ ID NO: 569), LSVECYVFSRCSSLP (SEQ ID NO: 570), FYCTYLVSLTCHPQ (SEQ ID NO: 571), SMAGCQWSSFCVQRD (SEQ ID NO: 572), IYSCYMFASRCTSDK (SEQ ID NO: 573), SRCSVYEVSSGLCDW (SEQ ID NO: 574), GMCSAYAYSSKLCTI (SEQ ID NO: 575), MTTNTCNLLCQQFLT (SEQ ID NO: 576), FQPCLMFASSCFTSK (SEQ ID NO: 577), WNCHPAGVGPVFCEV (SEQ ID NO: 578), ALCSMYLASSGLCNK (SEQ ID NO: 579), NYLSCQFFQNCYETY (SEQ ID NO: 580), GWCLFSDMWLGLCSA (SEQ ID NO: 581), EFCARDWLPYQCSSF (SEQ ID NO: 582), and TSYCSIEHYPCNTHH (SEQ ID NO: 583).

264. The method of claim 262, wherein the activatable anti-PD-L1 antibody comprises a masking moiety (MM) comprising an amino acid sequence selected from the group consisting of YCEVSELFVLPWCMG (SEQ ID NO: 584), SCLMHPHYAHDYCYV (SEQ ID NO: 585), LCEVLMLLQHPWCMG (SEQ ID NO: 586), IACRHFMEQLPFCHH (SEQ ID NO: 587), FGPRCGEASTCVPYE (SEQ ID NO: 588), LYCDSWGAGCLTRP (SEQ ID NO: 589), GIALCPSHFCQLPQT (SEQ ID NO: 590), DGPRCFVSGECSPIG (SEQ ID NO: 591), LCYKLDYDDRSYCHI (SEQ ID NO: 592), PCHPHPYDARPYCNV (SEQ ID NO: 593), PCYWHPFFAYRYCNT (SEQ ID NO: 594), VCYYMDWLGRNWCSS (SEQ ID NO: 595), LCDLFKLREFPYCMG (SEQ

ID NO: 596), YLPCHFVPIGACNNK (SEQ ID NO: 597), FCHMGVVVPQCANY (SEQ ID NO: 598), ACHPHPYDARPYCNV (SEQ ID NO: 599), PCHPAPYDARPYCNV (SEQ ID NO: 600), PCHPHAYDARPYCNV (SEQ ID NO: 601), PCHPHPADARPYCNV (SEQ ID NO: 602), PCHPHPYAARPYCNV (SEQ ID NO: 603), PCHPHPYDAAPYCNV (SEQ ID NO: 604), PCHPHPYDARPACNV (SEQ ID NO: 605), PCHPHPYDARPYCAV (SEQ ID NO: 606), PCHAHPYDARPYCNV (SEQ ID NO: 607), and PCHPHPYDARAYCNV (SEQ ID NO: 608).

265. The method of any one of claims 162-264, wherein the subject is in need of reducing, inhibiting, and/or delaying the onset or progression of PD-1 or PD-L1 in the subject.

266. The method of any one of claims 162-264, wherein the subject is in need of alleviating a symptom associated with aberrant expression and/or activity of PD-1 or PD-L1 in the subject.

267. The method of any one of claims 162-266, wherein the subject has been identified or diagnosed as having a cancer.

268. The method of claim 267, wherein the cancer is a lymphoma.

269. The method of claim 268, wherein the lymphoma is Burkitt's lymphoma.

270. The method of any one of claims 162-269, wherein the method comprises augmenting or potentiating therapeutic efficacy and/or therapeutic index relative to a conventional cytokine therapy in the subject.

271. The method of any one of claims 162-269, wherein the method comprises augmenting or potentiating therapeutic efficacy and/or therapeutic index relative to a conventional PD1/PDL1 inhibitor therapy in the subject.

272. The method of any one of claims 162-269, wherein the method comprises augmenting or potentiating therapeutic efficacy and/or therapeutic index relative to a conventional cytokine and PD1/PDL1 inhibitor combination therapy in the subject.

273. The method of any one of claims 162-269, wherein the method comprises augmenting or potentiating therapeutic efficacy and/or therapeutic index relative to administering the ACC alone.

274. A combination or composition comprising the ACC and the PD-1/PD-L1 pathway inhibitor as claimed in any one of claims 162-262.

275. The combination or composition of claim 274, wherein the combination or composition is a pharmaceutical composition.

276. A container, vial, syringe, injector pen, or kit comprising at least one dose of the combination or composition of claims 274 or 275.

277. The method of any preceding claim, wherein the ACC and the PD-1/PD-L1 pathway inhibitor are administered simultaneously or sequentially.

278. The method of any preceding claim, wherein the ACC and the PD-1/PD-L1 pathway inhibitor are administered separately.

279. A method of treating a subject in need thereof comprising administering a combination of an activatable cytokine construct (ACC) and a PD-1/PD-L1 pathway inhibitor to the subject, wherein the ACC comprises a first monomer construct and a second monomer construct, wherein:

(a) the first monomer construct comprises a first peptide mask (PM1), a first mature cytokine protein (CP1), a first and a third cleavable moieties (CM1 and CM3), and a first dimerization domain (DD1), wherein the CM1 is positioned between the CP1 and the DD1 and the CM3 is positioned between the PM1 and the CP1; and

(b) the second monomer construct comprises a second mature cytokine protein (CP2), a second cleavable moiety (CM2), and a second dimerization domain (DD2), wherein the CM2 is positioned between the CP2 and the DD2;

wherein the DD1 and the DD2 bind to each other thereby forming a dimer of the first monomer construct and the second monomer construct,

the ACC is characterized in that it has at least one of the following characteristics:

(i) a structural arrangement in an N- to C-terminal direction comprising: PM1-CM3-CP1-CM1-DD1 and CP2-CM2-DD2, wherein DD1 and DD2 are dimerized;

(ii) wherein the first monomer construct is characterized in that the CP1 and the DD1 are linked by a linking region of no more than 18 amino acids such that the linking region of no more than 18 amino acids includes the CM3;

(iii) wherein the second monomer construct is characterized in that the CP2 and the DD2 are linked by a linking region of no more than 18 amino acids such that the linking region of no more than 18 amino acids includes the CM2;

(iv) wherein each of PM1 and PM2 is less than 40 amino acids;

(v) wherein each of PM1 and PM2 is between 13 and 49 amino acids; and/or

(vi) wherein each of PM1 and PM2 is not a receptor for the CP1 and the CP2 and wherein each of PM1 and PM2 is not a fragment of receptor for the CP1 and the CP2.

280. The method of claim 279, wherein the first monomer construct is characterized in that the CP1 and the DD1 are linked by a linking region of no more than 12 amino acids such that the linking region of no more than 12 amino acids includes the CM3.

281. The method of claims 279-280, wherein the second monomer construct is characterized in that the CP2 and the DD2 are linked by a linking region of no more than 12 amino acids such that the linking region of no more than 12 amino acids includes the CM2.

282. The method of any preceding claim, comprising a mask linking region between PM1 and CP1 that comprises 15, 16, 17, 18, 19, 20, 21, or 22 amino acids.

283. The method of any preceding claim, comprising a mask linking region between PM2 and CP2 that comprises 15, 16, 17, 18, 19, 20, 21, or 22 amino acids.

284. The method of any preceding claim, wherein the first monomer construct has only one peptide mask.

285. The method of any preceding claim, wherein the second monomer construct has only one peptide mask.

286. The method of any preceding claim, wherein the first monomer construct has only one peptide mask and the second monomer construct has only one peptide mask.