

USES FOR ATTENUATED IL-2 IMMUNOCONJUGATES

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 63/612,007, which was filed on December 19, 2023, the disclosure of which is hereby incorporated by reference in its entirety.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which is being submitted herewith electronically in XML format and is hereby incorporated by reference in its entirety. Said XML copy, created on December 17, 2024, is named 102085.002049-BIO040-WO01_SequenceListing.xml and is 697 kilobytes in size.

TECHNICAL FIELD

[0003] Disclosed herein are methods of treating a cancer in a subject with an anti-human PD-1 (hPD-1) antibody-attenuated human interleukin-2 (hIL-2) immunoconjugate, alone or in combination with an antagonistic anti-PD-1 antibody.

BACKGROUND

[0004] The past decade has seen dramatic benefits from immuno-oncology therapies for the treatment of cancer. The approval of immunotherapies, such as immune checkpoint inhibitors, adoptive cell therapies and cancer vaccines, having revolutionized the way cancer treatment is approached. These developments have altered the standard of care (SOC) and improved survival for several tumor types. However, while immune checkpoint inhibitors have improved clinical outcomes in a variety of tumor types, only a subset of patients show clinical responses, and a large group of responders develop acquired resistance after an initial response.

[0005] The efficacy of immune checkpoint inhibitors such as PD-1 antagonists requires patients to have a competent immune system and adequate immune cell numbers. Non-responders to PD-1 antagonists typically exhibit low tumor T-cell infiltration and poor proliferative T-cell responses to PD-1 antagonism.

[0006] Human IL-2 (hIL-2) is a Type 1 four α -helical bundle, glycosylated cytokine produced by CD4⁺ T cells and CD8⁺ T cells. Autocrine and paracrine IL-2 signaling occurs

through engagement of either a high-affinity trimeric receptor complex comprising IL-2R α (CD25), IL-2R β (CD122), and IL-2R γ (CD132), or an intermediate-affinity dimeric receptor complex which comprises IL-2R β (CD122) and IL-2R γ (CD132). IL-2 has dual opposing and pleiotropic roles, in that it can both stimulate T cell proliferation to generate T cell effector, T cell memory, and activated NK cells, but can also stimulate suppressive regulatory T cells for maintenance of immune homeostasis. Low-dose IL-2 primarily stimulates regulatory T cells as well as some T effector and NK cells, whereas high-dose IL-2 broadly stimulates cytotoxic T cells, T effector, and NK cells and regulatory T cells. The use of IL-2 in the treatment of autoimmune diseases and as a cancer immunotherapy has, however, been limited by off-target effects and toxicity associated with the administration of IL-2.

SUMMARY

[0007] Disclosed herein are methods of treating a cancer in a subject, the methods comprising administering to the subject:

(A) an anti-human PD-1 (hPD-1) antibody-modified human interleukin-2 (hIL-2) immunoconjugate comprising:

a modified hIL-2 protein comprising a D20A, D20S, D20Q, D20M, D20I, D20V, D20N, D20G, D20T, or D20E substitution at amino acid position 20 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345 and an R38E substitution at amino acid position 38 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345; and

an anti-hPD-1 antibody, or antigen-binding fragment thereof, that immunospecifically binds to hPD-1, wherein the antibody or antigen-binding fragment thereof comprises:

- (i) a heavy chain complementarity determining region 1 (CDR1) comprising the amino acid sequence of SEQ ID NO: 418, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 419, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 420, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 421, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 422, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 423;

- (ii) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 386, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 387, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 388, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 389, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 390, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 391;
- (iii) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 396, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 397, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 398, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 399, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 400, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 401; or
- (iv) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 406, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 407, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 408, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 409, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 410, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 411; and

(B) an antagonistic anti-PD-1 antibody that binds PD-1 in the presence of the immunoconjugate.

[0008] Disclosed herein are methods of treating a renal cell carcinoma, a triple negative breast cancer, a squamous cell carcinoma of the head/neck, a Merkel cell carcinoma, a hepatocellular carcinoma, or a microsatellite instability-high tumor or tumor with deficient DNA mismatch repair in a subject, the methods comprising administering to the subject:

an anti-hPD-1 antibody-modified hIL-2 immunoconjugate comprising:

a modified hIL-2 protein comprising a D20A, D20S, D20Q, D20M, D20I, D20V, D20N, D20G, D20T, or D20E substitution at amino acid position 20 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345 and an R38E substitution at amino acid position 38 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345; and

an anti-hPD-1 antibody, or antigen-binding fragment thereof, that immunospecifically binds to hPD-1, wherein the antibody or antigen-binding fragment thereof comprises:

- (i) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 418, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 419, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 420, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 421, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 422, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 423;
- (ii) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 386, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 387, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 388, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 389, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 390, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 391;
- (iii) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 396, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 397, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 398, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 399, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 400, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 401; or
- (iv) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 406, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 407, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 408, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 409, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 410, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 411.

[0009] Also disclosed herein are uses of

(A) an anti-hPD-1 antibody-modified hIL-2 immunoconjugate comprising:

a modified hIL-2 protein comprising a D20A, D20S, D20Q, D20M, D20I, D20V, D20N, D20G, D20T, or D20E substitution at amino acid position 20 relative to the non-

modified hIL-2 amino acid sequence of SEQ ID NO: 345 and an R38E substitution at amino acid position 38 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345; and

an anti-hPD-1 antibody, or antigen-binding fragment thereof, that immunospecifically binds to hPD-1, wherein the antibody or antigen-binding fragment thereof comprises:

- (i) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 418, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 419, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 420, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 421, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 422, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 423;
- (ii) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 386, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 387, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 388, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 389, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 390, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 391;
- (iii) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 396, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 397, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 398, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 399, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 400, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 401; or
- (iv) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 406, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 407, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 408, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 409, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 410, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 411; and

(B) an antagonistic anti-PD-1 antibody that binds PD-1 in the presence of the immunoconjugate

for the treatment of cancer.

[0010] Also disclosed are uses of an anti-hPD-1 antibody-modified hIL-2 immunoconjugate comprising:

a modified hIL-2 protein comprising a D20A, D20S, D20Q, D20M, D20I, D20V, D20N, D20G, D20T, or D20E substitution at amino acid position 20 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345 and an R38E substitution at amino acid position 38 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345; and

an anti-hPD-1 antibody, or antigen-binding fragment thereof, that immunospecifically binds to hPD-1, wherein the antibody or antigen-binding fragment thereof comprises:

- (i) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 418, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 419, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 420, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 421, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 422, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 423;
- (ii) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 386, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 387, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 388, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 389, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 390, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 391;
- (iii) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 396, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 397, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 398, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 399, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 400, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 401; or

- (iv) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 406, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 407, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 408, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 409, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 410, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 411

for the treatment of a renal cell carcinoma, a triple negative breast cancer, a squamous cell carcinoma of the head/neck, a Merkel cell carcinoma, a hepatocellular carcinoma, or a microsatellite instability-high tumor or tumor with deficient DNA mismatch repair.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] The summary, as well as the following detailed description, is further understood when read in conjunction with the appended drawings. For the purpose of illustrating the disclosed methods and uses, there are shown in the drawings exemplary embodiments of the methods and uses; however, the methods and uses are not limited to the specific embodiments disclosed. In the drawings:

[0012] FIG. 1A, FIG. 1B, FIG. 1C, FIG. 1D, FIG. 1E, FIG. 1F, FIG. 1G, and FIG. 1H illustrate exemplary antibody-hIL-2 immunoconjugates as described in Example 1 herein. Non-attenuated human IL-2 cytokine (grey rectangle) was fused either directly (df) or via an L6 linker (L6) to either the N-terminus or C-terminus of both heavy chains or both kappa light chains of the antibody.

[0013] FIG. 2A, FIG. 2B, FIG. 2C, FIG. 2D, FIG. 2E, FIG. 2F, FIG. 2G, and FIG. 2H illustrate exemplary antibody-hIL-2 immunoconjugates with hCD25(1-164) extracellular domain designed to interfere with the immunoconjugate's hIL-2 binding to the human IL-2R α . For N-terminal variants, the human CD25/IL-2R α extracellular domain (black triangle) was fused to a non-attenuated hIL-2 cytokine (grey rectangle) via an L20 linker (light grey line). Non-attenuated hIL-2 cytokine was then either directly fused (df) or fused to the antibody with an L6 linker. For C-terminal variants, the hCD25/IL-2R α extracellular domain moiety was either directly fused (df) or fused to the antibody using an L6 linker, followed by an L20 linker and non-attenuated hIL-2 cytokine.

[0014] FIG. 3 illustrates an exemplary 1H3-hIgG1-L6-hIL-2 immunoconjugate that contains a CD25/IL-2R α extracellular domain moiety. The hCD25/IL-2R α extracellular domain

moiety was fused to the 1H3-hIgG1-L6-hIL-2 at the C-terminus of each heavy chain via an L6 linker followed by an L20 linker and hIL-2 cytokine moiety containing substitutions predicted to modulate binding to CD122/IL-2R β as described in Example 2 (attenuated hIL-2).

[0015] FIG. 4A, FIG. 4B, FIG. 4C, and FIG. 4D show the results of experiments analyzing the binding of the anti-hPD-1 antibodies 2H7-hIgG4, C51E6-5-hIgG4, and A2-hIgG4 to the human PD-1 receptor on Jurkat cells in the presence of saturating concentrations of anti-hPD-1 #1-mIgG2b-N297A and anti-hPD-1 #2-mIgG2b-N297A (10 μ M) prior to exposure with anti-hPD-1 antibodies.

[0016] FIG. 5 illustrates exemplary anti-hPD-1-attenuated hIL-2 immunoconjugates either with an L6 linker (L6) (left) or direct fusion (df) (right). Anti-hPD-1 antibodies comprising either hIgG4 or hIgG1 Fc domains, with or without L235E (LE) or L235A/G237A (LAGA) modifications in the Fc domain, were fused to attenuated hIL-2 cytokines at the C-terminus of the antibody heavy chains. Various substitutions in the hIL-2 cytokine were introduced for potency attenuation.

[0017] FIG. 6A and FIG. 6B show the results of competition assays demonstrating that anti-hPD-1 #1-mIgG2b-N297A (**FIG. 6A**) or anti-hPD-1 #2-mIgG2b-N297A (**FIG. 6B**) bind to anti-hPD-1 receptor on Jurkat cells in the presence of saturating concentrations of anti-hPD-1-attenuated hIL-2 immunoconjugates (280 nM).

[0018] FIG. 7 shows the results of competition assays demonstrating that the anti-hPD-1-attenuated hIL-2 immunoconjugates 2H7-hIgG4-df-hIL-2 (D20A/R38E), C51E6-5-L6-hIgG4-hIL-2 (D20A/R38E), and A2-hIgG4-df-hIL-2 (D20A/R38E) do not inhibit the binding of human PD-L1 to the human PD-1 receptor using the PD-1/PD-L1 Blockade Bioassay.

[0019] FIG. 8 shows the results of experiments analyzing the effect of the administration of vehicle, surrogate anti-PD-1 antibodies (anti-mPD-1 RMP1-14 mIgG2b-N297A and anti-mPD-1 RMP1-30 mIgG2b-N297A), and surrogate anti-PD-1-attenuated hIL-2 immunoconjugates (anti-mPD-1 RMP1-14 mIgG2b-N297A-L6-hIL-2 (F42K/Y45R/V69R) or anti-mPD-1 RMP1-30 mIgG2b-N297A-L6-hIL-2 (F42K/Y45R/V69R)) on the growth of established subcutaneous MC38 syngeneic tumors in C57BL/6 mice, as described in Example 18. Test agents were dosed intraperitoneally at 5 mg/kg twice weekly for 4 weeks, starting on day 1. The points on the graph represent mean tumor volumes of an average of 10 mice per group.

[0020] FIG. 9A, FIG. 9B, and FIG. 9C illustrate the results of studies conducted to determine the efficacy of surrogate anti-hPD-1-attenuated hIL-2 immunoconjugate anti-mPD-1 RMP1-30 mIgG2b-N297A-hIL-2 (F42K/Y45R/V69R) in an MC38 murine colon adenocarcinoma model. FIG. 9A depicts the mean subcutaneous tumor volumes (mm³) measured every 3-4 days for 8 days after the first dose of test agents (3 doses on days 1, 4, and 8 at 5 mg/kg). Tumor growth curves represent an average of 15 animals per group. FIG. 9B summarizes results from immunophenotyping tumors by flow cytometry on day 9, showing the proportion of different CD8⁺ T cell subsets as fractions of the total CD8⁺ T cell average absolute counts. FIG. 9C illustrates immunophenotyping results on day 9 which demonstrated that there was a significant expansion of CD8⁺ T effector memory and a trend towards decreased regulatory T cells in tumors (cells/ μ L) following exposure to the surrogate immunoconjugate.

[0021] FIG. 10 shows the results from an experiment analyzing the acceleration of Graft vs Host Disease in NOD-*Prkdc*^{em26Cd52}*IL-2rg*^{em26Cd22}/NjuCrI (NCG) mice exposed to anti-hPD-1-attenuated hIL-2 immunoconjugates, as demonstrated by significant body weight decrease in an NCG-PBMC model.

[0022] FIG. 11A and FIG. 11B show the results of an experiment analyzing the dose-dependent expansion of cells/mL of blood CD8⁺ Effector Memory T cells (FIG. 11A) and CD4⁺ Effector Memory T cells (FIG. 11B) of NOD-*Prkdc*^{em26Cd52}*IL-2rg*^{em26Cd22}/NjuCrI (NCG) mice treated with 2H7-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) in the NCG-PBMC model.

[0023] FIG. 12 shows a decrease in cells/mL of blood regulatory T cells of NOD-*Prkdc*^{em26Cd52}*IL-2rg*^{em26Cd22}/NjuCrI (NCG) mice treated with 2H7-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) in the NCG-PBMC model.

[0024] FIG. 13A and FIG. 13B show that H7-632-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) (designated "H7-767") (FIG. 13B) continues to bind to the human PD-1 receptor on Jurkat cells in the presence of saturating concentrations of anti-hPD-1 #1-mIgG2b-N297A and anti-hPD-1 #2-mIgG2b-N297A (10 μ M) prior to exposure.

[0025] FIG. 14A and FIG. 14B are graphs showing the binding of recombinant human PD-1 captured by H7-767 immobilized to a CM5 sensor chip followed by binding of either (FIG. 14A) H7-767, KEYTRUDA®, or OPDIVO® or (FIG. 14B) PD-L1 or PD-L2, as evaluated by surface plasmon resonance (SPR).

[0026] FIG. 15 demonstrates that H7-632-hIgG1-LAGA and H7-767 do not inhibit the binding of human PD-L1 to the human PD-1 receptor using an hPD-1/hPD-L1 Blockade Bioassay.

[0027] FIG. 16A, FIG. 16B, FIG. 16C, and FIG. 16D are graphs showing the binding of anti-hPD-1-attenuated hIL-2 immunoconjugates 2H7-hIgG4-df-hIL-2 (D20A/R38E), C51E6-5-hIgG4-df-hIL-2 (D20A/R38E), and A2-hIgG4-df-hIL-2 (D20A/R38E) to the human PD-1 receptor on Jurkat cells in the presence of saturating concentrations of anti-hPD-1 #1-mIgG2b-N297A and anti-hPD-1 #2-mIgG2b-N297A (10 μ M) prior to exposure with anti-hPD-1-attenuated hIL-2 immunoconjugates, as assessed by flow cytometry.

[0028] FIG. 17 is a graph showing the binding of 2H7-hIgG4-df-hIL-2 (D20A/R38E), C51E6-5-hIgG4-df-hIL-2 (D20A/R38E), A2-hIgG4-df-hIL-2 (D20A/R38E) and the irrelevant antibody control 1H3-hIgG4-df-hIL-2 (D20A/R38E) to HEK-293T cells recombinantly expressing cynomolgus PD-1, as assessed by flow cytometry.

[0029] FIG. 18A, FIG. 18B, FIG. 18C, and FIG. 18D show the antagonist activity of anti-hPD-1-attenuated hIL-2 immunoconjugates 2H7-hIgG4-df-hIL-2 (D20A/R38E), C51E6-5-hIgG4-df-hIL-2 (D20A/R38E), and A2-hIgG4-df-hIL-2 (D20A/R38E) in the presence of anti-hPD-1 #1 or anti-hPD-1 #2. FIG. 18A and FIG. 18B show results from the titration of anti-hPD-1 #1 or anti-hPD-1 #2 in the presence of fixed concentration anti-hPD-1-attenuated hIL-2 immunoconjugates. FIG. 18C and FIG. 18D show the results from the converse experiment in which anti-hPD-1-attenuated hIL-2 immunoconjugates were titrated with a fixed concentration of 100 nM of anti-hPD-1 #1 (FIG. 18C) or 100 nM of anti-hPD-1 #2 (FIG. 18D).

[0030] FIG. 19 shows the effect of the administration of various test agents including a surrogate anti-mouse PD-1/attenuated IL-2 immunoconjugate on the growth of established subcutaneous MC38 syngeneic tumors in C57BL/6 mice. Each growth curve represents the mean tumor volume of ten mice per treatment group.

[0031] FIG. 20 shows the ability of MC38 tumor cells to grow in tumor naïve mice compared to mice from the MC38 primary tumor study illustrated in FIG. 19 that were previously dosed with anti-mPD-1-hIL-2 F42K/Y45R/V69R and which had demonstrated complete long-term regression of the established primary tumor. Animals from both cohorts (10 mice per group) were subcutaneously implanted with 5×10^5 MC38 tumor cells on the left flank contralateral to the location of the primary tumor. Mice previously exposed to the surrogate

agent anti-mPD-1-hIL-2 F42K/Y45R/V69R demonstrated no tumor growth as they had developed a sustained immunity, whilst corresponding naïve mice controls demonstrated the typical growth of tumors in their flanks.

[0032] FIG. 21 shows the change in MC38 tumor volume over time in mice treated with an anti-mouse PD-1 RMP1-14, anti-mouse PD-1 RMP1-30-hIL-2 F42K/Y45R/V69R, or a combination of anti-mouse PD-1 RMP1-14 and anti-mouse PD-1 RMP1-30-hIL-2 F42K/Y45R/V69R.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

[0033] The disclosed methods and uses may be understood more readily by reference to the following detailed description taken in connection with the accompanying figures, which form a part of this disclosure. It is to be understood that the disclosed methods and uses are not limited to the specific methods and uses described and/or shown herein, and that the terminology used herein is for the purpose of describing particular embodiments by way of example only and is not intended to be limiting of the claimed methods and uses.

[0034] Unless specifically stated otherwise, any description as to a possible mechanism or mode of action or reason for improvement is meant to be illustrative only, and the disclosed methods and uses are not to be constrained by the correctness or incorrectness of any such suggested mechanism or mode of action or reason for improvement.

[0035] Throughout this text, the descriptions refer to methods of treatment and uses. Where the disclosure describes or claims a feature or embodiment associated with methods of treatment, such a feature or embodiment is equally applicable to the uses. Likewise, where the disclosure describes or claims a feature or embodiment associated with uses, such a feature or embodiment is equally applicable to the methods of treatment. Uses included within the scope of this disclosure include, but are not limited to, Swiss-style uses, first medical uses, second/further medical uses, and uses pursuant to EPC2000.

[0036] Where a range of numerical values is recited or established herein, the range includes the endpoints thereof and all the individual integers and fractions within the range, and also includes each of the narrower ranges therein formed by all the various possible combinations of those endpoints and internal integers and fractions to form subgroups of the larger group of values within the stated range to the same extent as if each of those narrower ranges was explicitly recited. Where a range of numerical values is stated herein as being greater

than a stated value, the range is nevertheless finite and is bounded on its upper end by a value that is operable within the context of the herein disclosure. Where a range of numerical values is stated herein as being less than a stated value, the range is nevertheless bounded on its lower end by a non-zero value. It is not intended that the scope of the methods and uses be limited to the specific values recited when defining a range. All ranges are inclusive and combinable.

[0037] When values are expressed as approximations, by use of the antecedent “about,” it will be understood that the particular value forms another embodiment. Reference to a particular numerical value includes at least that particular value, unless the context clearly dictates otherwise. The term “about” when used in reference to numerical ranges, cutoffs, or specific values is used to indicate that the recited values may vary by up to as much as 10% from the listed value. Thus, the term “about” is used to encompass variations of $\pm 10\%$ or less, variations of $\pm 5\%$ or less, variations of $\pm 1\%$ or less, variations of $\pm 0.5\%$ or less, or variations of $\pm 0.1\%$ or less from the specified value.

[0038] It is to be appreciated that certain features of the disclosed methods and uses which are, for clarity, described herein in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the disclosed methods and uses that are, for brevity, described in the context of a single embodiment, may also be provided separately or in any subcombination.

[0039] As used herein, the singular forms “a,” “an,” and “the” include the plural.

[0040] Various terms relating to aspects of the description are used throughout the specification and claims. Such terms are to be given their ordinary meaning in the art unless otherwise indicated. Other specifically defined terms are to be construed in a manner consistent with the definitions provided herein.

[0041] The term “comprising” is intended to include examples encompassed by the terms “consisting essentially of” and “consisting of”; similarly, the term “consisting essentially of” is intended to include examples encompassed by the term “consisting of.”

[0042] The term “antibody molecule” is meant in a broad sense and includes full length immunoglobulin molecules and antigen-binding fragments thereof.

[0043] Immunoglobulins can be assigned to five major classes, namely IgA, IgD, IgE, IgG, and IgM, depending on the heavy chain constant domain amino acid sequence. IgA and IgG are further sub-classified as the isotypes IgA1, IgA2, IgG1, IgG2, IgG3, and IgG4.

Antibody light chains of any vertebrate species can be assigned to one of two clearly distinct types, namely kappa (κ) and lambda (λ), based on the amino acid sequences of their constant domains.

[0044] “Antigen-binding fragment” refers to a portion of an immunoglobulin molecule that retains the antigen binding properties of the parental full length antibody (*i.e.*, “antigen-binding fragment thereof”). Exemplary antigen binding fragments can have: heavy chain complementarity determining regions (CDR) 1, 2, and/or 3; light chain CDR 1, 2, and/or 3; a heavy chain variable region (VH); a light chain variable region (VL); and combinations thereof. Antigen binding fragments include: a Fab fragment, a monovalent fragment consisting of the VL, VH, constant light (CL), and constant heavy 1 (CH1) domains; a F(ab)₂ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; a Fd fragment consisting of the VH and CH1 domains; a Fv fragment consisting of the VL and VH domains of a single arm of an antibody; and a domain antibody (dAb) fragment (Ward *et al.*, Nature 341:544- 546, 1989), which consists of a VH domain or a VL domain. VH and VL domains can be engineered and linked together via a synthetic linker to form various types of single chain antibody designs where the VH/VL domains pair intramolecularly, or intermolecularly in those cases when the VH and VL domains are expressed by separate single chain antibody constructs, to form a monovalent antigen binding site, such as single chain Fv (scFv) or diabody, described for example in Int’l Pat. Pub. Nos. WO1998/44001, WO1988/01649, WO1994/13804, and WO1992/01047. These antibody fragments are obtained using techniques well known to those of skill in the art, and the fragments are screened for utility in the same manner as are full length antibodies.

[0045] The phrase “immunospecifically binds” refers to the ability of the disclosed antibody molecules to preferentially bind to its target (hPD-1 in the case of anti-hPD-1 antibody molecules) without preferentially binding other molecules in a sample containing a mixed population of molecules. Antibody molecules that immunospecifically bind hPD-1 are substantially free of other antibodies having different antigenic specificities (*e.g.*, an anti-hPD-1 antibody is substantially free of antibodies that specifically bind antigens other than hPD-1). Antibody molecules that immunospecifically bind hPD-1, however, can have cross-reactivity to other antigens, such as orthologs of hPD-1, including *Macaca fascicularis* (cynomolgus monkey) PD-1. The antibody molecules disclosed herein are able to immunospecifically bind both

naturally-produced hPD-1 and to PD-1 which is recombinantly produced in mammalian or prokaryotic cells.

[0046] An antibody variable region consists of four “framework” regions interrupted by three “antigen binding sites.” The antigen binding sites are defined using various terms: (i) Complementarity Determining Regions (CDRs), three in the VH (HCDR1, HCDR2, HCDR3), and three in the VL (LCDR1, LCDR2, LCDR3) are based on sequence variability (Wu and Kabat J Exp Med 132:211-50, 1970; Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md., 1991); and (ii) “Hypervariable regions” (“HVR” or “HV”), three in the VH (H1, H2, H3) and three in the VL (L1, L2, L3) refer to the regions of the antibody variable domains which are hypervariable in structure as defined by Chothia and Lesk (Chothia and Lesk Mol Biol 196:901-17, 1987). The AbM definition of CDRs is also widely used; it is a compromise between Kabat and Chothia numbering schemes and is so-called because it was used by Oxford Molecular’s AbM antibody modelling software (Rees, A.R., Searle, S.M.J., Henry, A.H. and Pedersen, J.T. (1996) In Sternberg M.J.E. (ed.), Protein Structure Prediction. Oxford University Press, Oxford, 141–172). Other terms include “IMGT-CDRs” (Lefranc *et al.*, Dev Comparat Immunol 27:55-77, 2003) and “Specificity Determining Residue Usage” (SDRU) (Almagro Mol Recognit 17:132-43, 2004). The International ImMunoGeneTics (IMGT) database (www.imgt.org) provides a standardized numbering and definition of antigen-binding sites. The correspondence between CDRs, HVs and IMGT delineations is described in Lefranc *et al.*, Dev Comparat Immunol 27:55-77, 2003.

[0047] “Framework” or “framework sequences” are the remaining sequences of a variable region other than those defined to be antigen binding sites. Because the antigen binding sites can be defined by various terms as described above, the exact amino acid sequence of a framework depends on how the antigen-binding site was defined.

[0048] “Human antibody,” “fully human antibody,” and like terms refers to an antibody having heavy and light chain variable regions in which both the framework and the antigen binding sites are derived from sequences of human origin. If the antibody contains a constant region, the constant region also is derived from sequences of human origin. A human antibody comprises heavy and/or light chain variable regions that are “derived from” sequences of human origin if the variable regions of the antibody are obtained from a system that uses human

germline immunoglobulin or rearranged immunoglobulin genes. Such systems include human immunoglobulin gene libraries displayed on phage, and transgenic non-human animals such as mice or chicken carrying human immunoglobulin loci as described herein. “Human antibody” may contain amino acid differences when compared to the human germline or rearranged immunoglobulin sequences due to, for example, naturally occurring somatic mutations or intentional introduction of substitutions in the variable domain (framework and antigen binding sites), or constant domain. Typically, a “human antibody” is at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical in amino acid sequence to an amino acid sequence encoded by a human germline or rearranged immunoglobulin gene. In some cases, a “human antibody” may contain consensus framework sequences derived from human framework sequence analyses, for example as described in Knappik *et al.*, J Mol Biol 296:57-86, 2000, or synthetic HCDR3 incorporated into human immunoglobulin gene libraries displayed on phage, as described in, for example, Shi *et al.*, J Mol Biol 397:385-96, 2010 and Int’l Pat. Pub. No. WO2009/085462. Antibodies in which antigen binding sites are derived from a non-human species are not included in the definition of “human antibody.”

[0049] Human antibodies, while derived from human immunoglobulin sequences, may be generated using systems such as phage display incorporating synthetic CDRs and/or synthetic frameworks, or can be subjected to *in vitro* mutagenesis to improve antibody properties in the variable regions or the constant regions or both, resulting in antibodies that do not naturally exist within the human antibody germline repertoire *in vivo*.

[0050] “Recombinant antibody” includes all antibodies that are prepared, expressed, created, or isolated by recombinant means, such as: antibodies isolated from an animal (*e.g.*, a mouse) that is transgenic or transchromosomal for human immunoglobulin genes or a hybridoma prepared therefrom (described further below); antibodies isolated from a host cell transformed to express the antibody; antibodies isolated from a recombinant, combinatorial antibody library; and antibodies prepared, expressed, created, or isolated by any other means that involve splicing of human immunoglobulin gene sequences to other DNA sequences, or antibodies that are generated *in vitro* using Fab arm exchange.

[0051] “Monoclonal antibody” refers to a population of antibody molecules of a single molecular composition. A monoclonal antibody composition displays a single binding

specificity and affinity for a particular epitope, or in a case of a bispecific monoclonal antibody, a dual binding specificity to two distinct epitopes. Monoclonal antibody therefore refers to an antibody population with single amino acid composition in each heavy and each light chain, except for possible well known alterations such as removal of C-terminal lysine from the antibody heavy chain. Monoclonal antibodies may have heterogeneous glycosylation within the antibody population. Monoclonal antibody may be monospecific or multispecific, or monovalent, bivalent or multivalent. A bispecific antibody is included in the term monoclonal antibody.

[0052] “Epitope” refers to a portion of an antigen to which an antibody specifically binds. Epitopes usually consist of chemically active (such as polar, non-polar, or hydrophobic) surface groupings of moieties such as amino acids or polysaccharide side chains and can have specific three-dimensional structural characteristics, as well as specific charge characteristics. An epitope can be composed of contiguous and/or discontinuous amino acids that form a conformational spatial unit. For a discontinuous epitope, amino acids from differing portions of the linear sequence of the antigen come in close proximity in 3-dimensional space through the folding of the protein molecule.

[0053] “Variant” refers to a polypeptide or a polynucleotide that differs from a reference polypeptide or a reference polynucleotide by one or more modifications for example, substitutions, insertions, or deletions. The term “mutation” as used herein is intended to mean one or more intentional substitutions which are made to a polypeptide or polynucleotide.

[0054] “Antagonistic anti-PD-1 antibody,” as used herein, refers to an antibody that binds to PD-1 and acts to at least partially inhibit the interaction between PD-1 and its ligands PD-L1 and/or PD-L2.

[0055] “Antagonistic anti-PD-1 antibody that binds PD-1 in the presence of the immunoconjugate” means that at least a portion of the antagonistic anti-PD-1 antibody detectably binds to PD-1 which had previously been exposed to the immunoconjugate, for example using a method as described in Protocol B described herein.

[0056] “Non-antagonist anti-hPD-1 antibody” refers to an anti-human PD-1 antibody that does not inhibit the ligand-induced signaling mediated by interaction between PD-1 and its ligands PD-L1 and/or PD-L2 as measured using a cell based assay or SPR as described herein.

[0057] “Treat,” “treatment,” and like terms refer to both therapeutic treatment and prophylactic or preventative measures, and includes reducing the severity and/or frequency of symptoms, eliminating symptoms and/or the underlying cause of the symptoms, reducing the frequency or likelihood of symptoms and/or their underlying cause, and improving or remediating damage caused, directly or indirectly, by the cancer. Treatment also includes prolonging survival as compared to the expected survival of a subject not receiving treatment. Subjects to be treated include those that have the cancer as well as those prone to have the cancer or those in which the cancer is to be prevented.

[0058] As used herein, “administering to the subject” and similar terms indicate a procedure by which the disclosed immunoconjugates (monotherapies) or immunoconjugates and antagonistic anti-PD-1 antibodies (combination therapies) are injected into a subject such that target cells, tissues, or segments of the body of the subject are contacted with the disclosed immunoconjugates or immunoconjugates and antagonistic anti-PD-1 antibodies.

[0059] The phrase “therapeutically effective amount” refers to an amount of the immunoconjugate (monotherapy) or immunoconjugate and antagonistic anti-PD-1 antibodies (combination therapy), as described herein, effective to achieve a particular biological or therapeutic result such as, but not limited to, biological or therapeutic results disclosed, described, or exemplified herein. The therapeutically effective amount may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the immunoconjugate (monotherapy) or immunoconjugate and antagonistic anti-PD-1 antibodies (combination therapy) to cause a desired response in a subject. Exemplary indicators of a therapeutically effect amount include, for example, improved well-being of the patient, reduction of a cancer symptom, arrested or slowed progression of cancer symptoms, and/or absence of cancer symptoms.

[0060] The term “subject” as used herein is intended to mean any animal, in particular, mammals. Thus, the methods are applicable to human and nonhuman animals, although most preferably used with humans. “Subject” and “patient” are used interchangeably herein.

[0061] The disclosed modified hIL-2 proteins are also referred to as “attenuated” hIL-2 herein. As described herein the term “reduced potency” and related terms such as “reduction in potency” or “attenuation” of IL-2 activity refer to a reduction in potency of the modified hIL-2 as determined by an increased EC₅₀ value relative to the EC₅₀ value for a non-modified-hIL-2 in

an IL-2-dependent assay. As described herein the reduction in potency of the modified hIL-2 will be on both the high affinity and on the intermediate affinity IL-2 receptors. The IL-2-dependent assay for determining potency may be an engineered human erythroleukemic TF1 (TF1+IL-2R β) or a human natural killer NK-92 cell proliferation assay as described herein. In one embodiment, the IL-2-dependent assay for determining potency is an engineered human erythroleukemic TF1 (TF1+IL-2R β) cell proliferation assay. In another embodiment, the IL-2-dependent assay for determining potency is a human natural killer NK-92 cell proliferation assay. Other IL-2-dependent assays for determining potency may also be a TF1+IL-2R β or a human natural killer NK-92 pSTAT5 assay as described herein. The non-modified-hIL-2 may be a prokaryote-expressed hIL-2 such as Proleukin® (which has the native human IL-2 amino acid sequence apart from a C125S substitution to remove an unbound cysteine, and which does not bear the normal human carbohydrate expression on residue T3), or the non-modified-hIL-2 may be an hIL-2 with the amino acid sequence of SEQ ID NO: 345 or with the amino acid sequence of SEQ ID NO: 345 with a C125S substitution, which is expressed in a mammalian cell line, such as a CHO or HEK cell line.

[0062] Immunoconjugate and fusion protein are used interchangeably herein.

Combination Therapy

[0063] Standard of care cancer treatments may include the administration of a PD-1 antagonist checkpoint inhibitor (such as the antagonistic anti-PD-1 antibodies nivolumab, pembrolizumab, cemiplimab, dostarlimab, or retifanlimab) to antagonize PD-1 in tumor-resident T cells. Treatment with nivolumab or pembrolizumab, for example, may initially result in enhanced responses against the tumor by effector T cells, but in many cases these responses decrease over time as the chronically stimulated intratumoral T cells develop an “exhausted” phenotype characterized by reduced proliferative potential, reduced cytotoxic activity, and increased immune checkpoint molecule expression. The immunoconjugates described herein do not prevent antagonistic anti-PD-1 antibodies such as nivolumab or pembrolizumab from binding and antagonizing the PD-1 receptor. The mechanism of action of the immunoconjugates described herein and antagonistic anti-PD-1 antibodies is different and complementary. Specifically, the primary mechanism of action of PD-1 antagonists, such as antagonistic anti-PD-1 antibodies, is to prevent the immune inhibitory signal delivered through the interaction of PD-1

with PD-L1, which leads to maintaining T cells in, or restoring T cells to, their activated state. The mechanism of action of the immunoconjugates described herein, on the other hand, is via T cell-selective IL-2 signalling, which primarily induces T cell proliferation, and only subsequently promotes activation. The different modes of action and the potential for each agent to bind and be active at the same time provides a rationale for combining the therapies to enhance clinical outcomes in, for example, acquired resistance cases for PD-(L)1 blockade therapies. This attribute enables the clinical combination of the disclosed immunoconjugates with antagonistic anti-PD-1 antibodies to enhance therapy. In tumors which initially responded to checkpoint inhibitors but have subsequently developed T cell exhaustion, for example, the administration of the disclosed immunoconjugates, which deliver the modified hIL-2 to PD-1-expressing cells, can restimulate tumor resident T cells to take on a non-exhausted phenotype and may encourage T cells to become responsive to checkpoint inhibitors again. In some embodiments, an antagonistic anti-PD-1 antibody and the immunoconjugate can be delivered concurrently or sequentially as single agents as described herein so that each agent can be administered at a concentration and for a period which optimizes the subject's anti-tumor responses.

[064] Disclosed herein are methods of treating a cancer in a subject, the methods comprising administering to the subject:

(A) an anti-human PD-1 (hPD-1) antibody-modified human interleukin-2 (hIL-2) immunoconjugate comprising:

a modified hIL-2 protein comprising a substitution at amino acid position 20 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345 and a substitution at amino acid position 38 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345; and

an anti-hPD-1 antibody, or antigen-binding fragment thereof, that immunospecifically binds to hPD-1, wherein the antibody or antigen-binding fragment thereof comprises:

- (i) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 418, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 419, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 420, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 421, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 422, and a light chain

CDR3 comprising the amino acid sequence of SEQ ID NO: 423 (referred to herein as “H7-632”);

- (ii) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 386, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 387, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 388, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 389, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 390, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 391 (referred to herein as “2H7”);
- (iii) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 396, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 397, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 398, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 399, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 400, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 401 (referred to herein as “C51E6-5”); or
- (iv) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 406, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 407, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 408, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 409, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 410, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 411 (referred to herein as “A2”); and

(B) an antagonistic anti-PD-1 antibody that binds PD-1 in the presence of the immunoconjugate.

[065] Suitable substitutions at amino acid position 20 of the modified hIL-2 portion of the immunoconjugates include, for example, any of a D20A, D20S, D20Q, D20M, D20I, D20V, D20N, D20G, D20T, or D20E substitution relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345.

[066] Suitable substitutions at amino acid position 38 of the modified hIL-2 portion of the immunoconjugates include, for example, any of an R38E, R38N, R38G, R38H, R38I, R38L,

R38M, R38F, R38P, R38S, R38T, R38W, R38Y, R38V, R38A, R38Q, R38D, or a R38K substitution relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345.

[0067] In some embodiments, any one of the D20A, D20S, D20Q, D20M, D20I, D20V, D20N, D20G, D20T, or D20E substitutions can be combined with an R38E substitution.

[0068] Thus, disclosed herein are methods of treating a cancer in a subject, the methods comprising administering to the subject:

(A) an anti-hPD-1 antibody-modified hIL-2 immunoconjugate comprising:

a modified hIL-2 protein comprising a D20A, D20S, D20Q, D20M, D20I, D20V, D20N, D20G, D20T, or D20E substitution at amino acid position 20 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345 and an R38E substitution at amino acid position 38 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345; and

an anti-hPD-1 antibody, or antigen-binding fragment thereof, that immunospecifically binds to hPD-1, wherein the antibody or antigen-binding fragment thereof comprises:

- (i) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 418, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 419, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 420, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 421, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 422, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 423 (referred to herein as “H7-632”);
- (ii) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 386, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 387, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 388, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 389, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 390, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 391 (referred to herein as “2H7”);
- (iii) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 396, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 397, a

heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 398, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 399, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 400, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 401 (referred to herein as “C51E6-5”); or

- (iv) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 406, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 407, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 408, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 409, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 410, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 411 (referred to herein as “A2”); and

(B) an antagonistic anti-PD-1 antibody that binds PD-1 in the presence of the immunoconjugate.

[0069] The modified hIL-2 protein portion of the immunoconjugates can comprise the amino acid sequence of any one of SEQ ID NOs: 134-150, 307, 344, 607-611, 614, 617, or 620. The modified hIL-2 protein portion of the immunoconjugates can comprise the amino acid sequence of any one of SEQ ID NOs: 134-150, 307, 344, 608, 611, 614, or 620. The modified hIL-2 protein portion of the immunoconjugates can comprise the amino acid sequence of any one of SEQ ID NOs: 149, 307, 607-611, 614, 617, or 620. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 134. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 135. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 136. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 137. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 138. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 139. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 140. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 141. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 142. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO:

143. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 144. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 145. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 146. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 147. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 148. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 149. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 150. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 307. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 344. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 607. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 608. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 609. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 610. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 611. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 614. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 617. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 620. The modified hIL-2 protein of any one of amino acid sequences SEQ ID NOs: 134-150, 307, 344, 607-611, 614, 617, or 620 can further comprise a T3A substitution and/or a C125A substitution. In some embodiments, the modified hIL-2 protein of any one of amino acid sequences SEQ ID NOs: 134-150, 307, 344, 607-611, 614, 617, or 620 further comprises a T3A substitution. In some embodiments, the modified hIL-2 protein of any one of amino acid sequences SEQ ID NOs: 134-150, 307, 344, 607-611, 614, 617, or 620 further comprises a C125A substitution. In some embodiments, the modified hIL-2 protein of any one of amino acid sequences SEQ ID NOs: 134-150, 307, 344, 607-611, 614, 617, or 620 further comprises a T3A substitution and a C125A substitution.

[0070] The modified hIL-2 protein portion of the immunoconjugates can comprise a D20A substitution relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345 and a R38E substitution relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO:

345. The disclosed methods of treating a cancer in a subject can comprise administering to the subject:

- (A) an anti-hPD-1 antibody-modified hIL-2 immunoconjugate comprising:
 - a modified hIL-2 protein comprising a D20A substitution at amino acid position 20 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345 and an R38E substitution at amino acid position 38 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345; and
 - an anti-hPD-1 antibody, or antigen-binding fragment thereof, that immunospecifically binds to hPD-1, wherein the antibody or antigen-binding fragment thereof comprises:
 - (i) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 418, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 419, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 420, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 421, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 422, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 423 (referred to herein as “H7-632”);
 - (ii) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 386, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 387, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 388, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 389, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 390, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 391 (referred to herein as “2H7”);
 - (iii) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 396, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 397, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 398, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 399, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 400, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 401 (referred to herein as “C51E6-5”); or

- (iv) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 406, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 407, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 408, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 409, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 410, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 411 (referred to herein as "A2"); and

(B) an antagonistic anti-PD-1 antibody that binds PD-1 in the presence of the immunoconjugate.

[0071] The modified hIL-2 protein portion of the immunoconjugates can further comprise a substitution at amino acid position 3 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345. A suitable substitution includes, for example, a T3A. In some embodiments, the modified hIL-2 protein portion of the immunoconjugates comprise a T3A substitution, a D20A substitution, and a R38E substitution. In some aspects, the modified hIL-2 protein portion of the immunoconjugates comprise the amino acid sequence of SEQ ID NO: 216.

[0072] Alternatively, the modified hIL-2 protein portion of the immunoconjugates can further comprise a deletion of amino acid position 3 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345. In some embodiments, the modified hIL-2 protein portion of the immunoconjugates comprise a deletion of amino acids 1-3, a D20A substitution, and a R38E substitution. In some aspects, the modified hIL-2 protein portion of the immunoconjugates comprise the amino acid sequence of SEQ ID NO: 218.

[0073] The modified hIL-2 protein portion of the immunoconjugates can further comprise a deletion or substitution at amino acid position 125 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345. The substitution at amino acid position 125 can be C125A. In some embodiments, the modified hIL-2 protein portion of the immunoconjugates comprise a D20A substitution, a R38E substitution, and a C125A substitution. In some embodiments, the modified hIL-2 protein portion of the immunoconjugates comprise the amino acid sequence of SEQ ID NO: 215. In some embodiments, the modified hIL-2 protein portion of the immunoconjugates comprise a T3A substitution, a D20A substitution, a R38E substitution, and a C125A substitution. In some embodiments, the modified hIL-2 protein portion of the immunoconjugates comprise the amino acid sequence of SEQ ID NO: 217. In some

embodiments, the modified hIL-2 protein portion of the immunoconjugates comprise a deletion of amino acids 1-3, a D20A substitution, a R38E substitution, and a C125A substitution. In some embodiments, the modified hIL-2 protein portion of the immunoconjugates comprise the amino acid sequence of SEQ ID NO: 219.

[0074] The modified hIL-2 protein portion of the immunoconjugates can exhibit a reduction in potency of at least about 200-fold, at least about 500-fold, at least about 1,000-fold, at least about 2,000-fold, at least about 5,000-fold, at least about 6,500-fold, or at least about 10,000-fold on the high affinity IL-2 receptor (hIL-2R $\alpha\beta\gamma$) relative to a non-modified hIL-2, for example as quantified by a comparison in EC₅₀ values in an hIL-2-dependent cell proliferation assay described herein. In some embodiments, the modified hIL-2 protein portion of the immunoconjugates can exhibit a reduction in potency of greater than about 10,000-fold on the high affinity IL-2 receptor (hIL-2R $\alpha\beta\gamma$) relative to a non-modified hIL-2. A greater reduction in hIL-2 potency on the high affinity hIL-2 receptor may be possible and acceptable for the modified hIL-2 proteins described herein, but such a reduction may not be quantifiable with the methods described herein due to limits of the cell proliferation assay conditions.

[0075] In addition, the modified hIL-2 protein portion of the immunoconjugates can exhibit a reduction in potency of at least about 200-fold, at least about 500-fold, at least about 1,000-fold, at least about 2,000-fold, at least about 5,000-fold, at least about 6,500-fold, or at least about 10,000-fold on the intermediate affinity IL-2 receptor (hIL-2R $\beta\gamma$) relative to a non-modified hIL-2, for example as quantified by a comparison in EC₅₀ values in an hIL-2-dependent cell proliferation assay described herein. In some embodiments, the modified hIL-2 protein portion of the immunoconjugates can exhibit a reduction in potency of greater than about 10,000-fold on the intermediate affinity IL-2 receptor (hIL-2R $\beta\gamma$) relative to a non-modified hIL-2.

[0076] The modified hIL-2 protein portion of the immunoconjugates can exhibit a reduction in potency of up to about 10,000-fold on the high affinity IL-2 receptor (hIL-2R $\alpha\beta\gamma$) and a reduction in potency of up to about 10,000-fold on the intermediate affinity IL-2 receptor (hIL-2R $\beta\gamma$) relative to a non-modified hIL-2, for example as quantified by a comparison in EC₅₀ values in an hIL-2-dependent cell proliferation assay described herein. The modified hIL-2 protein portion of the immunoconjugates can exhibit a reduction in potency of greater than about 10,000-fold on the high affinity IL-2 receptor (hIL-2R $\alpha\beta\gamma$) and a reduction in potency of greater

than about 10,000-fold on the intermediate affinity IL-2 receptor (hIL-2R $\beta\gamma$) relative to a non-modified hIL-2.

[0077] The modified hIL-2 protein can be fused to the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate at the N-terminus of an antibody light chain, the C-terminus of an antibody light chain, the N-terminus of an antibody heavy chain, the C-terminus of an antibody heavy chain, the N-terminus of the antigen-binding fragment, or the C-terminus of the antigen-binding fragment. In some embodiments, the modified hIL-2 protein portion of the immunoconjugates is directly fused by a peptide bond to the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate. The modified hIL-2 protein portion of the immunoconjugates can be, for example, directly fused by a peptide bond to the C-terminal amino acid residue of the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate. In some embodiments, the modified hIL-2 protein is fused to the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate through a linker.

[0078] Fusion of the modified hIL-2 proteins to the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate can rescue the modified hIL-2 proteins' ability to activate the intermediate affinity IL-2 receptor. In some embodiments, the immunoconjugate is able to activate the intermediate affinity IL-2 receptor to a degree that is comparable to wild type hIL-2 activation of the intermediate affinity IL-2 receptor.

[0079] In some embodiments, the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugates comprise a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 418, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 419, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 420, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 421, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 422, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 423 (referred to herein as "H7-632").

[0080] In some embodiments, the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugates comprise a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 386, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 387, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 388, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 389, a light chain

CDR2 comprising the amino acid sequence of SEQ ID NO: 390, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 391 (referred to herein as “2H7”).

[0081] In some embodiments, the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugates comprise a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 396, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 397, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 398, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 399, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 400, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 401 (referred to herein as “C51E6-5”).

[0082] In some embodiments, the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugates comprise a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 406, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 407, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 408, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 409, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 410, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 411 (referred to herein as “A2”).

[0083] The anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugates can comprise a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 416 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 417 (referred to herein as “H7-632”).

[0084] The anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugates can comprise a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 384 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 385 (referred to herein as “2H7”).

[0085] The anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugates can comprise a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 394 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 395 (referred to herein as “C51E6-5”).

[0086] The anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugates can comprise a heavy chain variable region comprising the amino acid

sequence of SEQ ID NO: 404 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 405 (referred to herein as “A2”).

[0087] The anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugates can comprise an IgG1 heavy chain constant region.

[0088] The anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugates can have substitutions or deletions within the constant region to minimize Fc-mediated immune effector function, such as FcγRIIIA-mediated antibody-dependent cell-mediated cytotoxicity (ADCC), FcγRI- and FcγRIIa-dependent antibody-dependent cellular phagocytosis (ADCP), and C1q binding-mediated complement-dependent cytotoxicity (CDC). In some embodiments, the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugates comprises a L235A substitution, wherein the amino acid numbering is according to EU numbering. In some embodiments, the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugates comprises a G237A substitution, wherein the amino acid numbering is according to EU numbering. In some embodiments, the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugates comprises an L235A and a G237A substitution, wherein the amino acid numbering is according to EU numbering.

[0089] The anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate can comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 414 and a light chain comprising the amino acid sequence of SEQ ID NO: 415 (referred to herein as “H7-632-hIgG1-LAGA”).

[0090] The anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate can comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 424 and a light chain comprising the amino acid sequence of SEQ ID NO: 425 (referred to herein as “2H7-hIgG4”).

[0091] The anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate can comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 426 and a light chain comprising the amino acid sequence of SEQ ID NO: 427 (referred to herein as “C51E6-5-hIgG4”).

[0092] The anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate can comprise a heavy chain comprising the amino acid sequence of SEQ ID

NO: 428 and a light chain comprising the amino acid sequence of SEQ ID NO: 429 (referred to herein as “A2-hIgG4”).

[0093] The immunoconjugates can have one or more of the following properties:

- Binds to PD-1 but does not inhibit PD-L1 binding to PD-1;
- Binds to PD-1 in the presence of standard-of-care anti-PD-1 antibodies used in the clinic (*e.g.*, pembrolizumab (KEYTRUDA[®]) or nivolumab (OPDIVO[®]));
- Is highly selective for PD-1 and does not immunospecifically bind other related B7 family members;
- Binds PD-1 on activated human T cells ($EC_{50} \sim 0.1-0.2$ nM in a flow binding assay);
- The modified hIL-2 protein portion of the immunoconjugate demonstrates a measurable reduction in potency of at least about 200-fold, at least about 500-fold, at least about 1,000-fold, at least about 2,000-fold, at least about 5,000-fold, at least about 6,500-fold, or at least about 10,000-fold on the high affinity IL-2 receptor (hIL-2R $\alpha\beta\gamma$) relative to a non-modified hIL-2, for example as quantified by a comparison in EC_{50} values in an hIL-2-dependent cell proliferation assay described herein. In some embodiments, the modified hIL-2 protein portion of the immunoconjugates can exhibit a reduction in potency of greater than about 10,000-fold on the high affinity IL-2 receptor (hIL-2R $\alpha\beta\gamma$) relative to a non-modified hIL-2. A greater reduction in hIL-2 potency on the high affinity hIL-2 receptor may be possible and acceptable for the modified hIL-2 proteins described herein, but such a reduction may not be quantifiable with the methods described herein due to limits of the cell proliferation assay conditions;
- The modified hIL-2 protein portion of the immunoconjugate demonstrates a measurable reduction in potency of at least about 200-fold, at least about 500-fold, at least about 1,000-fold, at least about 2,000-fold, at least about 5,000-fold, at least about 6,500-fold, or at least about 10,000-fold on the intermediate affinity IL-2 receptor (hIL-2R $\beta\gamma$) relative to a non-modified hIL-2, for example as quantified by a comparison in EC_{50} values in an hIL-2-dependent cell proliferation assay described herein. In some embodiments, the modified hIL-2 protein portion of the immunoconjugates can exhibit a reduction in potency of greater than about 10,000-fold on the intermediate affinity IL-2 receptor (hIL-2R $\beta\gamma$) relative to a non-modified hIL-2;

- Rescues and expands PD-1-expressing human memory T cell subsets in a GvHD animal model; and
- Has minimal or no impact on body weight, blood chemistry, or hematology parameters after single dose at 1 and 10 mg/kg in cynomolgus monkeys.

[0094] In some embodiments, the immunoconjugate comprises a modified hIL-2 protein comprising a T3A substitution, a R38E substitution, a D20A substitution, and a C125A substitution fused to the C-terminus of the anti-hPD-1 antibody heavy chain comprising a human IgG1 framework with a L235A substitution and a G237A substitution. In some embodiments, the immunoconjugate comprises a light chain comprising the amino acid sequence of SEQ ID NO: 415 and a heavy chain-modified hIL-2 protein fusion comprising the amino acid sequence of SEQ ID NO: 532.

[0095] Suitable antagonistic anti-PD-1 antibodies include nivolumab (OPDIVO®), pembrolizumab (KEYTRUDA®), cemiplimab (LIBTAYO®), dostarlimab (JEMPERLI), or retifanlimab (ZYNYZ™). In some embodiments, the antagonistic anti-PD-1 antibody is nivolumab. In some embodiments, the antagonistic anti-PD-1 antibody is pembrolizumab. References to nivolumab, pembrolizumab, cemiplimab, dostarlimab, or retifanlimab are intended to include any nivolumab-containing, pembrolizumab-containing, cemiplimab-containing, dostarlimab-containing, or retifanlimab-containing product approved by a regulatory authority as a biosimilar of OPDIVO®, KEYTRUDA®, LIBTAYO®, JEMPERLI, or ZYNYZ™ as the case may be.

[0096] The disclosed immunoconjugates can selectively deliver IL-2 signaling to PD-1-expressing T cells. The anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate can be utilized solely to deliver the modified hIL-2 to PD-1-expressing cells and does not block PD-1 receptor function, as do classical anti-PD-1 inhibitor antibodies such as nivolumab (OPDIVO®) and pembrolizumab (KEYTRUDA®). The primary mechanism-of-action of the herein disclosed immunoconjugates is via the T cell selective activity of IL-2. The human PD-1 receptor is primarily expressed on a minor subset of T cells with potent tumor reactivity. Without being bound by theory, it is believed that targeting the modified hIL-2 protein portion of the immunoconjugate to this population of T cells can dramatically amplify anti-tumor immunity while reducing or minimizing off-target systemic IL-2-mediated toxicities mediated by cell populations that lack PD-1 expression.

[0097] The antagonistic anti-PD-1 antibody and the immunoconjugate can be administered to the subject together in a mixture, concurrently as single agents, or sequentially as single agents in any order. In some embodiments, the antagonistic anti-PD-1 antibody and the immunoconjugate are administered to the subject together in a mixture. In some embodiments, the antagonistic anti-PD-1 antibody and the immunoconjugate are administered to the subject concurrently as single agents. In some embodiments, the antagonistic anti-PD-1 antibody and the immunoconjugate are administered to the subject sequentially as single agents in any order. In some embodiments, the methods can comprise administering the immunoconjugate prior to administering the antagonistic anti-PD-1 antibody. In some embodiments, the methods can comprise administering the antagonistic anti-PD-1 antibody prior to administering the immunoconjugate. In some embodiments, the methods can comprise administering the immunoconjugate at substantially the same time as administering the antagonistic anti-PD-1 antibody. The immunoconjugate and the antagonistic anti-PD-1 antibody can be administered such that the second agent is administered while the first agent still shows a biological effect.

[0098] The immunoconjugate may be administered to subjects who are beginning to show signs of relapse/recurrence after a period of antagonistic PD-1 therapy. Thus, in some embodiments, the methods are performed on subjects who are beginning to show signs of relapse/recurrence after or during antagonistic PD-1 therapy.

[0099] Exemplary cancers that can be treated using the disclosed methods include bladder cancer, brain cancer, head and neck cancer, pancreatic cancer, lung cancer, non-small cell lung carcinoma, breast cancer, ovarian cancer, uterine cancer, cervical cancer, endometrial cancer, esophageal cancer, colon cancer, colorectal cancer, rectal cancer, gastric cancer, prostate cancer, blood cancer, skin cancer, melanoma, squamous cell carcinoma, bone cancer, and kidney cancer. In some embodiments, the disclosed methods can be used to treat melanoma, Merkel cell carcinoma, non-small cell lung carcinoma, renal cell carcinoma, triple negative breast cancer, squamous cell carcinoma of the head/neck, hepatocellular carcinoma, or microsatellite instability-high tumors or tumors with deficient DNA mismatch repair.

[00100] Each and every aspect of the disclosed and claimed combination therapies, which are presented herein as methods of treatment, are equally applicable to uses of the immunoconjugates and antagonistic anti-PD-1 antibodies, including, but not limited to, Swiss-

style uses, first medical uses, second/further medical uses, and uses pursuant to EPC2000. Thus, for example, disclosed herein are uses of

(A) an anti-hPD-1 antibody-modified hIL-2 immunoconjugate comprising:

a modified hIL-2 protein comprising a D20A, D20S, D20Q, D20M, D20I, D20V, D20N, D20G, D20T, or D20E substitution at amino acid position 20 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345 and an R38E substitution at amino acid position 38 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345; and

an anti-hPD-1 antibody, or antigen-binding fragment thereof, that immunospecifically binds to hPD-1, wherein the antibody or antigen-binding fragment thereof comprises:

- (i) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 418, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 419, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 420, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 421, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 422, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 423;
- (ii) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 386, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 387, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 388, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 389, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 390, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 391;
- (iii) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 396, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 397, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 398, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 399, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 400, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 401; or
- (iv) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 406, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 407, a heavy

chain CDR3 comprising the amino acid sequence of SEQ ID NO: 408, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 409, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 410, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 411; and
(B) an antagonistic anti-PD-1 antibody that binds PD-1 in the presence of the immunoconjugate
for the treatment of cancer.

Monotherapies

[00101] Disclosed herein methods of treating a renal cell carcinoma, a triple negative breast cancer, a squamous cell carcinoma of the head/neck, a Merkel cell carcinoma, a hepatocellular carcinoma, or a microsatellite instability-high tumor or tumor with deficient DNA mismatch repair in a subject, the methods comprising administering to the subject:

an anti-hPD-1 antibody-modified hIL-2 immunoconjugate comprising:

a modified hIL-2 protein comprising a substitution at amino acid position 20 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345 and a substitution at amino acid position 38 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345; and

an anti-hPD-1 antibody, or antigen-binding fragment thereof, that immunospecifically binds to hPD-1, wherein the antibody or antigen-binding fragment thereof, comprises:

- (i) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 418, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 419, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 420, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 421, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 422, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 423 (referred to herein as “H7-632”);
- (ii) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 386, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 387, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 388, a light

chain CDR1 comprising the amino acid sequence of SEQ ID NO: 389, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 390, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 391 (referred to herein as “2H7”);

- (iii) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 396, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 397, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 398, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 399, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 400, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 401 (referred to herein as “C51E6-5”); or
- (iv) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 406, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 407, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 408, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 409, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 410, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 411 (referred to herein as “A2”).

[0102] Suitable substitutions at amino acid position 20 of the modified hIL-2 portion of the immunoconjugates include, for example, any of a D20A, D20S, D20Q, D20M, D20I, D20V, D20N, D20G, D20T, or D20E substitution relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345.

[0103] Suitable substitutions at amino acid position 38 of the modified hIL-2 portion of the immunoconjugates include, for example, any of an R38E, R38N, R38G, R38H, R38I, R38L, R38M, R38F, R38P, R38S, R38T, R38W, R38Y, R38V, R38A, R38Q, R38D, or a R38K substitution relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345.

[0104] In some embodiments, any one of the D20A, D20S, D20Q, D20M, D20I, D20V, D20N, D20G, D20T, or D20E substitutions can be combined with an R38E substitution.

[0105] Thus, disclosed herein are methods of treating a renal cell carcinoma, a triple negative breast cancer, a squamous cell carcinoma of the head/neck, a Merkel cell carcinoma, a

hepatocellular carcinoma, or a microsatellite instability-high tumor or tumor with deficient DNA mismatch repair in a subject, the methods comprising administering to the subject:

(A) an anti-hPD-1 antibody-modified hIL-2 immunoconjugate comprising:

a modified hIL-2 protein comprising a D20A, D20S, D20Q, D20M, D20I, D20V, D20N, D20G, D20T, or D20E substitution at amino acid position 20 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345 and an R38E substitution at amino acid position 38 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345; and

an anti-hPD-1 antibody, or antigen-binding fragment thereof, that immunospecifically binds to hPD-1, wherein the antibody or antigen-binding fragment thereof comprises:

- (i) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 418, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 419, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 420, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 421, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 422, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 423 (referred to herein as “H7-632”);
- (ii) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 386, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 387, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 388, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 389, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 390, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 391 (referred to herein as “2H7”);
- (iii) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 396, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 397, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 398, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 399, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 400, and a

- light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 401 (referred to herein as "C51E6-5"); or
- (iv) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 406, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 407, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 408, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 409, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 410, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 411 (referred to herein as "A2").

[0106] The modified hIL-2 protein portion of the immunoconjugates can comprise the amino acid sequence of any one of SEQ ID NOs: 134-150, 307, 344, 607-611, 614, 617, or 620. The modified hIL-2 protein portion of the immunoconjugates can comprise the amino acid sequence of any one of SEQ ID NOs: 134-150, 307, 344, 608, 611, 614, or 620. The modified hIL-2 protein portion of the immunoconjugates can comprise the amino acid sequence of any one of SEQ ID NOs: 149, 307, 607-611, 614, 617, or 620. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 134. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 135. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 136. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 137. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 138. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 139. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 140. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 141. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 142. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 143. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 144. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 145. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 146. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 147. In some embodiments, the modified

hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 148. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 149. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 150. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 307. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 344. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 607. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 608. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 609. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 610. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 611. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 614. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 617. In some embodiments, the modified hIL-2 proteins comprise the amino acid sequence of SEQ ID NO: 620. The modified hIL-2 protein of any one of amino acid sequences SEQ ID NOs: 134-150, 307, 344, 607-611, 614, 617, or 620 can further comprise a T3A substitution and/or a C125A substitution. In some embodiments, the modified hIL-2 protein of any one of amino acid sequences SEQ ID NOs: 134-150, 307, 344, 607-611, 614, 617, or 620 further comprises a T3A substitution. In some embodiments, the modified hIL-2 protein of any one of amino acid sequences SEQ ID NOs: 134-150, 307, 344, 607-611, 614, 617, or 620 further comprises a C125A substitution. In some embodiments, the modified hIL-2 protein of any one of amino acid sequences SEQ ID NOs: 134-150, 307, 344, 607-611, 614, 617, or 620 further comprises a T3A substitution and a C125A substitution.

[0107] The modified hIL-2 protein portion of the immunoconjugates can comprise a D20A substitution relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345 and a R38E substitution relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345. Thus, disclosed herein are methods of treating a renal cell carcinoma, a triple negative breast cancer, a squamous cell carcinoma of the head/neck, a Merkel cell carcinoma, a hepatocellular carcinoma, or a microsatellite instability-high tumor or tumor with deficient DNA mismatch repair in a subject, the methods comprising administering to the subject:

(A) an anti-hPD-1 antibody-modified hIL-2 immunoconjugate comprising:

a modified hIL-2 protein comprising a D20A substitution at amino acid position 20 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345 and an R38E substitution at amino acid position 38 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345; and

an anti-hPD-1 antibody, or antigen-binding fragment thereof, that immunospecifically binds to hPD-1, wherein the antibody or antigen-binding fragment thereof comprises:

- (i) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 418, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 419, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 420, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 421, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 422, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 423 (referred to herein as “H7-632”);
- (ii) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 386, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 387, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 388, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 389, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 390, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 391 (referred to herein as “2H7”);
- (iii) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 396, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 397, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 398, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 399, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 400, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 401 (referred to herein as “C51E6-5”); or
- (iv) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 406, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 407, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 408, a

light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 409, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 410, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 411 (referred to herein as “A2”).

[0108] The modified hIL-2 protein portion of the immunoconjugates can further comprise a substitution at amino acid position 3 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345. A suitable substitution includes, for example, a T3A. In some embodiments, the modified hIL-2 protein portion of the immunoconjugates comprise a T3A substitution, a D20A substitution, and a R38E substitution. In some aspects, the modified hIL-2 protein portion of the immunoconjugates comprise the amino acid sequence of SEQ ID NO: 216.

[0109] Alternatively, the modified hIL-2 protein portion of the immunoconjugates can further comprise a deletion of amino acid position 3 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345. In some embodiments, the modified hIL-2 protein portion of the immunoconjugates comprise a deletion of amino acids 1-3, a D20A substitution, and a R38E substitution. In some aspects, the modified hIL-2 protein portion of the immunoconjugates comprise the amino acid sequence of SEQ ID NO: 218.

[0110] The modified hIL-2 protein portion of the immunoconjugates can further comprise a deletion or substitution at amino acid position 125 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345. The substitution at amino acid position 125 can be C125A. In some embodiments, the modified hIL-2 protein portion of the immunoconjugates comprise a D20A substitution, a R38E substitution, and a C125A substitution. In some embodiments, the modified hIL-2 protein portion of the immunoconjugates comprise the amino acid sequence of SEQ ID NO: 215. In some embodiments, the modified hIL-2 protein portion of the immunoconjugates comprise a T3A substitution, a D20A substitution, a R38E substitution, and a C125A substitution. In some embodiments, the modified hIL-2 protein portion of the immunoconjugates comprise the amino acid sequence of SEQ ID NO: 217. In some embodiments, the modified hIL-2 protein portion of the immunoconjugates comprise a deletion of amino acids 1-3, a D20A substitution, a R38E substitution, and a C125A substitution. In some embodiments, the modified hIL-2 protein portion of the immunoconjugates comprise the amino acid sequence of SEQ ID NO: 219.

[0111] The modified hIL-2 protein portion of the immunoconjugates can exhibit a reduction in potency of at least about 200-fold, at least about 500-fold, at least about 1,000-fold, at least about 2,000-fold, at least about 5,000-fold, at least about 6,500-fold, or at least about 10,000-fold on the high affinity IL-2 receptor (hIL-2R $\alpha\beta\gamma$) relative to a non-modified hIL-2, for example as quantified by a comparison in EC₅₀ values in an hIL-2-dependent cell proliferation assay described herein. In some embodiments, the modified hIL-2 protein portion of the immunoconjugates can exhibit a reduction in potency of greater than about 10,000-fold on the high affinity IL-2 receptor (hIL-2R $\alpha\beta\gamma$) relative to a non-modified hIL-2. A greater reduction in hIL-2 potency on the high affinity hIL-2 receptor may be possible and acceptable for the modified hIL-2 proteins described herein, but such a reduction may not be quantifiable with the methods described herein due to limits of the cell proliferation assay conditions.

[0112] In addition, the modified hIL-2 protein portion of the immunoconjugates can exhibit a reduction in potency of at least about 200-fold, at least about 500-fold, at least about 1,000-fold, at least about 2,000-fold, at least about 5,000-fold, at least about 6,500-fold, or at least about 10,000-fold on the intermediate affinity IL-2 receptor (hIL-2R $\beta\gamma$) relative to a non-modified hIL-2, for example as quantified by a comparison in EC₅₀ values in an hIL-2-dependent cell proliferation assay described herein. In some embodiments, the modified hIL-2 protein portion of the immunoconjugates can exhibit a reduction in potency of greater than about 10,000-fold on the intermediate affinity IL-2 receptor (hIL-2R $\beta\gamma$) relative to a non-modified hIL-2.

[0113] The modified hIL-2 protein portion of the immunoconjugates can exhibit a reduction in potency of up to about 10,000-fold on the high affinity IL-2 receptor (hIL-2R $\alpha\beta\gamma$) and a reduction in potency of up to about 10,000-fold on the intermediate affinity IL-2 receptor (hIL-2R $\beta\gamma$) relative to a non-modified hIL-2, for example as quantified by a comparison in EC₅₀ values in an hIL-2-dependent cell proliferation assay described herein. The modified hIL-2 protein portion of the immunoconjugates can exhibit a reduction in potency of greater than about 10,000-fold on the high affinity IL-2 receptor (hIL-2R $\alpha\beta\gamma$) and a reduction in potency of greater than about 10,000-fold on the intermediate affinity IL-2 receptor (hIL-2R $\beta\gamma$) relative to a non-modified hIL-2.

[0114] The modified hIL-2 protein can be fused to the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate at the N-terminus of an antibody light

chain, the C-terminus of an antibody light chain, the N-terminus of an antibody heavy chain, the C-terminus of an antibody heavy chain, the N-terminus of the antigen-binding fragment, or the C-terminus of the antigen-binding fragment. In some embodiments, the modified hIL-2 protein portion of the immunoconjugates is directly fused by a peptide bond to the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate. The modified hIL-2 protein portion of the immunoconjugates can be, for example, directly fused by a peptide bond to the C-terminal amino acid residue of the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate. In some embodiments, the modified hIL-2 protein is fused to the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate through a linker.

[0115] Fusion of the modified hIL-2 proteins to the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate can rescue the modified hIL-2 proteins' ability to activate the intermediate affinity IL-2 receptor. In some embodiments, the immunoconjugate is able to activate the intermediate affinity IL-2 receptor to a degree that is comparable to wild type hIL-2 activation of the intermediate affinity IL-2 receptor.

[0116] In some embodiments, the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugates comprise a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 418, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 419, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 420, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 421, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 422, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 423 (referred to herein as "H7-632").

[0117] In some embodiments, the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugates comprise a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 386, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 387, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 388, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 389, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 390, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 391 (referred to herein as "2H7").

[0118] In some embodiments, the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugates comprise a heavy chain CDR1 comprising the amino

acid sequence of SEQ ID NO: 396, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 397, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 398, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 399, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 400, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 401 (referred to herein as “C51E6-5”).

[0119] In some embodiments, the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugates comprise a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 406, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 407, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 408, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 409, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 410, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 411 (referred to herein as “A2”).

[0120] The anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugates can comprise a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 416 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 417 (referred to herein as “H7-632”).

[0121] The anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugates can comprise a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 384 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 385 (referred to herein as “2H7”).

[0122] The anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugates can comprise a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 394 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 395 (referred to herein as “C51E6-5”).

[0123] The anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugates can comprise a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 404 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 405 (referred to herein as “A2”).

[0124] The anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugates can comprise an IgG1 heavy chain constant region.

[0125] The anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugates can have substitutions or deletions within the constant region to minimize Fc-mediated immune effector function, such as FcγRIIIA-mediated antibody-dependent cell-mediated cytotoxicity (ADCC), FcγRI- and FcγRIIa-dependent antibody-dependent cellular phagocytosis (ADCP), and C1q binding-mediated complement-dependent cytotoxicity (CDC). In some embodiments, the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugates comprises a L235A substitution, wherein the amino acid numbering is according to EU numbering. In some embodiments, the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugates comprises a G237A substitution, wherein the amino acid numbering is according to EU numbering. In some embodiments, the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugates comprises an L235A and a G237A substitution, wherein the amino acid numbering is according to EU numbering.

[0126] The anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate can comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 414 and a light chain comprising the amino acid sequence of SEQ ID NO: 415 (referred to herein as “H7-632-hIgG1-LAGA”).

[0127] The anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate can comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 424 and a light chain comprising the amino acid sequence of SEQ ID NO: 425 (referred to herein as “2H7-hIgG4”).

[0128] The anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate can comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 426 and a light chain comprising the amino acid sequence of SEQ ID NO: 427 (referred to herein as “C51E6-5-hIgG4”).

[0129] The anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate can comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 428 and a light chain comprising the amino acid sequence of SEQ ID NO: 429 (referred to herein as “A2-hIgG4”).

[0130] The immunoconjugates can have one or more of the following properties:

- Binds to PD-1 but does not inhibit PD-L1 binding to PD-1;

- Binds to PD-1 in the presence of standard-of-care anti-PD-1 antibodies used in the clinic (*e.g.*, pembrolizumab (KEYTRUDA[®]) or nivolumab (OPDIVO[®]));
- Is highly selective for PD-1 and does not immunospecifically bind other related B7 family members;
- Binds PD-1 on activated human T cells ($EC_{50} \sim 0.1-0.2$ nM in a flow binding assay);
- The modified hIL-2 protein portion of the immunoconjugate demonstrates a measurable reduction in potency of at least about 200-fold, at least about 500-fold, at least about 1,000-fold, at least about 2,000-fold, at least about 5,000-fold, at least about 6,500-fold, or at least about 10,000-fold on the high affinity IL-2 receptor (hIL-2R $\alpha\beta\gamma$) relative to a non-modified hIL-2, for example as quantified by a comparison in EC_{50} values in an hIL-2-dependent cell proliferation assay described herein. In some embodiments, the modified hIL-2 protein portion of the immunoconjugates can exhibit a reduction in potency of greater than about 10,000-fold on the high affinity IL-2 receptor (hIL-2R $\alpha\beta\gamma$) relative to a non-modified hIL-2. A greater reduction in hIL-2 potency on the high affinity hIL-2 receptor may be possible and acceptable for the modified hIL-2 proteins described herein, but such a reduction may not be quantifiable with the methods described herein due to limits of the cell proliferation assay conditions;
- The modified hIL-2 protein portion of the immunoconjugate demonstrates a measurable reduction in potency of at least about 200-fold, at least about 500-fold, at least about 1,000-fold, at least about 2,000-fold, at least about 5,000-fold, at least about 6,500-fold, or at least about 10,000-fold on the intermediate affinity IL-2 receptor (hIL-2R $\beta\gamma$) relative to a non-modified hIL-2, for example as quantified by a comparison in EC_{50} values in an hIL-2-dependent cell proliferation assay described herein. In some embodiments, the modified hIL-2 protein portion of the immunoconjugates can exhibit a reduction in potency of greater than about 10,000-fold on the intermediate affinity IL-2 receptor (hIL-2R $\beta\gamma$) relative to a non-modified hIL-2;
- Rescues and expands PD-1-expressing human memory T cell subsets in a GvHD animal model; and
- Has minimal or no impact on body weight, blood chemistry, or hematology parameters after single dose at 1 and 10 mg/kg in cynomolgus monkeys.

[0131] In some embodiments, the immunoconjugate comprises a modified hIL-2 protein comprising a T3A substitution, a R38E substitution, a D20A substitution, and a C125A substitution fused to the C-terminus of the anti-hPD-1 antibody heavy chain comprising a human IgG1 framework with a L235A substitution and a G237A substitution. In some embodiments, the immunoconjugate comprises a light chain comprising the amino acid sequence of SEQ ID NO: 415 and a heavy chain-modified hIL-2 protein fusion comprising the amino acid sequence of SEQ ID NO: 532.

[0132] The disclosed immunoconjugates can selectively deliver IL-2 signaling to PD-1-expressing T cells. The anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate can be utilized solely to deliver the modified hIL-2 to PD-1-expressing cells and does not block PD-1 receptor function, as do classical anti-PD-1 inhibitor antibodies such as nivolumab (OPDIVO®) and pembrolizumab (KEYTRUDA®). The primary mechanism-of-action of the herein disclosed immunoconjugates is via the T cell selective activity of IL-2. The human PD-1 receptor is primarily expressed on a minor subset of T cells with potent tumor reactivity. Without being bound by theory, it is believed that targeting the modified hIL-2 protein portion of the immunoconjugate to this population of T cells can dramatically amplify anti-tumor immunity while reducing or minimizing off-target systemic IL-2-mediated toxicities mediated by cell populations that lack PD-1 expression.

[0133] Each and every aspect of the disclosed and claimed monotherapies, which are presented herein as methods of treatment, are equally applicable to uses of the immunoconjugates, including, but not limited to, Swiss-style uses, first medical uses, second/further medical uses, and uses pursuant to EPC2000. Thus, for example, disclosed herein are uses of an anti-hPD-1 antibody-modified hIL-2 immunoconjugate comprising:

a modified hIL-2 protein comprising a D20A, D20S, D20Q, D20M, D20I, D20V, D20N, D20G, D20T, or D20E substitution at amino acid position 20 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345 and an R38E substitution at amino acid position 38 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345; and

an anti-hPD-1 antibody, or antigen-binding fragment thereof, that immunospecifically binds to hPD-1, wherein the antibody or antigen-binding fragment thereof comprises:

- (i) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 418, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 419, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 420, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 421, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 422, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 423;
- (ii) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 386, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 387, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 388, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 389, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 390, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 391;
- (iii) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 396, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 397, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 398, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 399, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 400, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 401; or
- (iv) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 406, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 407, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 408, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 409, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 410, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 411,

for the treatment of a renal cell carcinoma, a triple negative breast cancer, a squamous cell carcinoma of the head/neck, a Merkel cell carcinoma, a hepatocellular carcinoma, or a microsatellite instability-high tumor or tumor with deficient DNA mismatch repair.

EXAMPLES

[0134] The following examples are provided to further describe some of the embodiments disclosed herein. The examples are intended to illustrate, not to limit, the disclosed embodiments.

General Methods

Protocol A. Flow cytometry screen for binding of anti-hPD-1 antibodies or anti-hPD-1 antibody-attenuated hIL-2 fusions to human PD-1

[0135] To test for binding to hPD-1, antibodies and antibody-attenuated hIL-2 fusion proteins were characterized in full titration curves. A Jurkat cell line was transfected with a mammalian vector which encoded amino acids 1-185 of human PD-1 (SEQ ID NO: 346) to stably express the extracellular domain and a portion of the transmembrane domain of human PD-1, and this transfected cell line was used to determine binding of anti-hPD-1 antibodies. Jurkat + hPD-1 cells were washed and added to 96-well plates at 100,000 cells per well in FACS buffer (PBS, 0.2% Heat-inactivated Fetal Bovine Serum). Cells were blocked with 1:50 dilution of human FcR Block (Miltenyi) for 10 minutes at 4 °C and washed with FACS buffer.

[0136] Antibodies or antibody-attenuated hIL-2 immunoconjugates (fusion proteins) were serially diluted six-fold in FACS buffer for an 8-point curve and added to human PD-1 expressing Jurkat cells for 1 hour on ice in 100 µL volume. Cells were washed and re-suspended in FACS buffer containing 1:40 dilution of Allophycocyanin conjugated anti-human IgG Fc monoclonal antibody. Cells were washed once more, re-suspended in FACS buffer containing 1:1000 dilution of Sytox Green (Thermo Fisher) and flow cytometric analysis was conducted on the BD FACS Canto II, BD Celesta or BD Fortessa (BD Biosciences) flow cytometers. The geometric mean fluorescent intensity (gMFI) was calculated using FlowJo software version 10. Half maximal effective concentration (EC₅₀) values were calculated from the gMFI of the Allophycocyanin signal across the titrated concentrations using GraphPad Prism 7 software.

Protocol B. Flow cytometry competition screen for binding of anti-hPD-1 antibodies or anti-hPD-1 antibody-attenuated hIL-2 fusions to human PD-1

[0137] Antibodies and antibody-attenuated hIL-2 fusion proteins were tested for the ability to bind human PD-1 in the presence of a saturating concentration of anti-hPD-1 #1-mIgG2b-N297A (sequence comprising the heavy and light chain variable region sequences of

nivolumab, clone 5C4, as described in U.S. Patent Pub. No. US 2009/0217401A1, formatted onto a murine IgG2b-N297A background) (SEQ ID NOs: 348 and 349) or anti-hPD-1 #2-mIgG2b-N297A (sequence comprising the heavy and light chain variable region sequences of pembrolizumab (clone 109A-H/K09A-L-11) as described in Int'l Pub. No. WO2008/156712A1, formatted onto a murine IgG2b-N297A background) (SEQ ID NOs: 350 and 351).

[0138] Antibodies or antibody-attenuated hIL-2 fusion proteins were serially diluted six-fold for an 8-point titration curve with and without saturating amounts of 10 μ M anti-hPD-1 #1-mIgG2b-N297A or anti-hPD-1 #2-mIgG2b-N297A. Briefly, Jurkat cells stably expressing hPD-1 (as described in Protocol A above) were washed and re-suspended in FACS buffer containing 1:50 dilution of human FcR Blocking reagent. Cells were incubated at 4 °C for 10 minutes and washed. Cells were then re-suspended in 100 μ L volume with anti-hPD-1 #1-mIgG2b-N297A or anti-hPD-1 #2-mIgG2b-N287A diluted in FACS buffer to 10 μ M and incubated at 4 °C for one hour. Cells were washed and incubated with test antibodies or antibody-attenuated hIL-2 fusion proteins serially diluted six-fold for an 8-point curve in 100 μ L volume for one hour at 4 °C. To detect bound test anti-hPD-1 antibodies or anti-hPD-1-attenuated hIL-2 fusion proteins, cells were washed again and incubated with 1:40 dilution of Allophycocyanin-conjugated anti-human IgG Fc monoclonal antibody for 45 minutes on ice. Cells were washed and re-suspended in FACS buffer containing 1:1000 dilution of Sytox Green (Thermo Fisher). To generate a comparison, Jurkat cells stably expressing human PD-1 were incubated with only the titrated test antibodies or antibody-attenuated hIL-2 fusion proteins (without anti-hPD-1 #1-mIgG2b-N297A or anti-hPD-1 #2-mIgG2b-N297A) and subsequently with 1:40 dilution of Allophycocyanin-conjugated anti-human IgG Fc secondary. As a control, the variable regions of anti-hPD-1 #1 and anti-hPD-1 #2 were cloned into hIgG4 frameworks and were assessed with and without the addition of anti-hPD-1 #1-mIgG2b-N297A or anti-hPD-1 #2-mIgG2b-N297A. Flow cytometry was carried out on the BD Canto II, BD Celesta, or BD Fortessa (BD Biosciences) flow cytometers and gMFI was calculated using FlowJo software version 10. EC₅₀ values were calculated from the gMFI of the Allophycocyanin signal across the titrated concentrations using GraphPad Prism 7 software.

Protocol C. Cell-based screen for characterization of non-antagonist anti-hPD-1 antibodies or anti-hPD-1 antibody-attenuated hIL-2 fusions

[0139] Human PD-1 antibodies and anti-hPD-1-attenuated hIL-2 fusion proteins were characterized for the ability to block hPD-1 from binding to ligand hPD-L1 (SEQ ID NO: 584). Anti-hPD-1 antibodies and anti-hPD-1-attenuated hIL-2 fusion proteins were either characterized as an antagonist or non-antagonist using an *in vitro* cell-based human PD-1/PD-L1 blockade bioassay (Promega, Cat# J1255). This co-culture assay utilized two cell lines: FCγR11b artificial Antigen Presenting Cells / Chinese Ovary Hamster K1 (aAPC/CHO-K1) and Jurkat Effector cells. aAPC/CHO K1 cells stably express both human PD-L1 ligand and a cell surface protein to activate cognate T cell receptors (TCRs) while Jurkat Effector cells express hPD-1 and a luciferase reporter under the control of Nuclear Factor of Activated T cells response element (NFAT-RE). When these cells are co-cultured in the presence of a non-antagonistic antibody, hPD-1/hPD-L1 interaction inhibits TCR signaling and no luminescence is detected. In the presence of an antibody that antagonizes hPD-1 interaction with hPD-L1 (SEQ ID NO: 584), the inhibitory signal is disrupted and luminescence is detected.

[0140] The thaw-and-use assay was performed according to manufacturer's instructions. In short, aAPC/CHO-K1 cells were first thawed and plated at 30,000 cells per well in flat-bottom 96-well plates for 18 hours at 37 °C in a 5% CO₂ incubator. After cells had adhered, the media was removed and 200 nM or 1000 nM test antibodies or antibody-attenuated hIL-2 fusion proteins were diluted in 40 µL assay buffer (RPMI 1640 medium + 1% FBS) and added to the aAPC/CHO-K1 cells. A human IgG4 isotype control monoclonal antibody which targeted Keyhole Limpet Hemocyanin (KLH) clone C3 (SEQ ID NOs: 585 and 586) was used as a negative control. Jurkat effector cells expressing hPD-1 were added at 24,000 cells per well in 40 µL volume. The final concentration of fixed antibodies tested was 100 nM or 500 nM. In some examples, a range of concentrations of anti-hPD-1 or anti-hPD-1-attenuated hIL-2 fusion proteins were tested in this co-culture assay, with the top concentration in a five-fold titration series of 500 nM (FIG. 7).

[0141] The co-culture assay was incubated at 37 °C in a 5% CO₂ incubator for an additional 18-20 hours. To read the luminescence signal, plates were allowed to come to room temperature, and 80 µL of the Bio-Glo™ reagent was added to each well. The plates were

incubated for 15 minutes in the dark at room temperature and luminescence was read on a Victor X luminometer (Perkin Elmer). Relative luminescence units (RLU) were averaged for each triplicate and graphed using GraphPad Prism 7 software.

Protocol D. *In vitro* phosphorylated STAT5 assay to test attenuation of hIL-2 variants

[0142] The level of attenuation of hIL-2 receptor activation activity of antibody-attenuated hIL-2 fusion proteins was characterized using a phosphorylated STAT5 assay. Variants were tested in both hIL-2 responsive human natural killer NK-92 cells and engineered human erythroleukemic TF1 cells. The NK-92 cell line naturally expresses the high-affinity hIL-2 receptor (IL-2R $\alpha\beta\gamma$) at physiologic levels, while the TF1 cell line that naturally expresses the IL-2R γ (SEQ ID NO: 352) was engineered to also stably express human CD122 (IL-2R β) (SEQ ID NO: 353) for expression of the intermediate affinity hIL-2 receptor complex (IL-2R $\beta\gamma$). This TF1+IL-2R β stable cell line does not express the IL-2R α (SEQ ID NO: 354). Both NK-92 and TF1+IL-2R β cell lines were used to assess the level of attenuation of IL-2 potency in these cell-based potency assays as fixed concentration screens and full titration curves.

[0143] To perform the fixed concentration screen, 100,000 NK-92 cells or TF1+IL-2R β cells were plated into 96 wells in 50 μ L of fresh growth medium lacking human IL-2 cytokine and incubated overnight at 37 °C in a CO₂ incubator. After 15-16 hours, human IL-2 starved cells were treated with 25.7 nM recombinant hIL-2 (denoted as rhIL-2) (SEQ ID NO: 345) or test antibody-attenuated hIL-2 fusion proteins for the NK-92 cell assay, or with 33.3 nM hIL-2 or test hIL-2 variants for the TF1+IL-2R β cell assay. Cells were incubated at 37 °C, 5% CO₂ for 10 minutes. Cells were fixed with Cytofix Buffer (BD Biosciences) for 10 minutes at 37 °C and then permeabilized after treatment with Perm Buffer III (BD Biosciences) for 30 minutes on ice. hIL-2-dependent Stat5 phosphorylation was detected after staining fixed and permeabilized cells with Alexa Fluor-647 conjugated anti-Stat5 antibody (BD Biosciences) at 0.5 μ L per sample for 45 minutes at room temperature in the dark. Cells were washed and reagents were diluted in BD Pharmingen Buffer (BD Biosciences). Stained cells were acquired on a FACS-Celesta cytometer (BD Biosciences) and analyzed using FlowJo software version 10.7.2. The assays were performed in cohorts but normalized using the rhIL-2 for each plate. The degree of attenuation of selected antibody-attenuated hIL-2 fusion proteins were evaluated in an 8-point, 6-fold serially titrated curve ranging from 1200 nM to 7 pM on both NK-92 and TF1+IL-2R β cell lines. The

procedure for the pStat5 curves was performed in the same manner as the method described above. EC₅₀ values were calculated from the geometric mean fluorescent intensity (gMFI) across the titrated concentrations using GraphPad Prism 7 software. The fold change in activity from rhIL-2 was calculated by dividing the EC₅₀ values for the variants by the EC₅₀ of hIL-2.

Protocol E. *In vitro* cell-based proliferation assay to test attenuation of antibody-attenuated hIL-2 fusion proteins

[0144] The antibody-attenuated hIL-2 fusion proteins were also tested for attenuated hIL-2 activity in hIL-2 dependent cell proliferation assays. 10,000 NK-92 cells (expressing the high affinity receptor hIL-2R $\alpha\beta\gamma$) or TF1+IL-2R β cells (expressing the intermediate affinity receptor hIL-2R $\beta\gamma$) suspended in 50 μ L of fresh growth medium without hIL-2 cytokine were plated per well in 96-well U-bottom cell culture plate. Eight point, 6-fold serial titrations of antibody-attenuated hIL-2 fusion proteins with a highest concentration of 996 nM were diluted in fresh media and overlaid on cells in wells. Cells were incubated at 37 °C in a 5% CO₂ incubator for 3 days for TF1+IL-2R β cells or 4 days for NK-92 cells. To measure proliferation, Cell-Titer-Glo (Promega) was added to wells, incubated for 10 minutes at room temperature and luminescence was read for 0.1 second per well using a VictorX Multilabel Plate Reader (Perkin Elmer). EC₅₀ values were calculated from the relative luminescence units (RLU) across the titrated concentrations using GraphPad Prism 7 software. The fold change in activity from rhIL-2 was calculated by dividing the EC₅₀ values for the variants by the EC₅₀ of hIL-2. The assays were performed in cohorts but normalized using the rhIL-2 EC₅₀ value for each plate.

Example 1: Optimization of antibody-attenuated hIL-2 fusion protein variants and determination of their hIL-2 activity on the intermediate and high-affinity hIL-2 receptor complexes

[0145] In order to determine the optimal structures for an antibody-attenuated hIL-2 fusion protein, non-attenuated hIL-2 was fused to an anti-DNase I antibody (clone 1H3) designated as 1H3-hIgG1 (SEQ ID NO: 379, SEQ ID NO: 374) in the antibody variable region in a variety of ways as illustrated in FIG. 1. Variations included the hIL-2 fused at the N-terminus of the human anti-DNase I antibody (clone 1H3) immunoglobulin hIgG1 heavy chain or human kappa light chain via a direct fusion (df) denoted as hIL-2 Nterm light chain df (SEQ

ID NO: 379, SEQ ID NO: 356), hIL-2 Nterm heavy chain df (SEQ ID NO: 358, SEQ ID NO: 374) or six amino acid linker (L6) (SEQ ID NO: 355) denoted as hIL-2 Nterm light chain L6 fusion (SEQ ID NO: 379, SEQ ID NO: 357) and hIL-2 Nterm heavy chain L6 fusion (SEQ ID NO: 359, SEQ ID NO: 374). Variations in which the hIL-2 moiety was fused to the C-terminus of both the heavy chains and light chains via df or L6 were also created and denoted as hIL-2 Cterm heavy chain df (SEQ ID NO: 360, SEQ ID NO: 374), hIL-2 Cterm heavy chain L6 fusion (SEQ ID NO: 361, SEQ ID NO: 374), hIL-2 Cterm light chain df (SEQ ID NO: 379, SEQ ID NO: 362), hIL-2 Cterm light chain L6 fusion (SEQ ID NO: 379, SEQ ID NO: 363). Further variations were generated in which a CD25/IL-2R α extracellular domain (amino acids 1-164) (SEQ ID NO: 126) was fused to the N-terminus or C-terminus of the heavy chains or the kappa light chains to interfere with the binding of the IL-2 to CD25 of the IL-2 receptor (FIG. 2). In these constructs, human CD25 extracellular domain (amino acids 1-164) (SEQ ID NO: 126) was fused to human IL-2 via a 20 amino acid linker (L20) (SEQ ID NO: 364), which was then directly fused or fused via an L6 linker (SEQ ID NO: 355) to 1H3-hIgG1 heavy chain or light chain at the N terminus: hCD25-L20-hIL-2 Nterm heavy chain df (SEQ ID NO: 365, SEQ ID NO: 374), hCD25-L20-hIL-2 Nterm heavy chain L6 fusion (SEQ ID NO: 366, SEQ ID NO: 374), hCD25-L20-hIL-2 Nterm light chain df (SEQ ID NO: 379, SEQ ID NO: 367), hCD25-L20-hIL-2 Nterm light chain L6 fusion (SEQ ID NO: 379, SEQ ID NO: 368). Lastly, a final set of variants in which the CD25/IL-2R α extracellular domain moiety (SEQ ID NO: 126) fused to the C-terminus of the heavy chain and kappa light chains were created: hCD25-L20-hIL-2 Cterm heavy chain df (SEQ ID NO: 369, SEQ ID NO: 374), hCD25-L20-hIL-2 Cterm heavy chain L6 fusion (SEQ ID NO: 370, SEQ ID NO: 374), hCD25-L20-hIL-2 Cterm light chain df (SEQ ID NO: 379, SEQ ID NO: 371), hCD25-L20-hIL-2 Cterm light chain L6 fusion (SEQ ID NO: 379, SEQ ID NO: 372). These antibody-hIL-2 fusion proteins were produced, expressed, and Protein-A purified using standard techniques. The 16 N- or C-terminus and linker variants described above were evaluated in an *in vitro* cell-based phosphorylated STAT5 assay using an 8-point, 6-fold serial titration, as described in Protocol D.

[0146] Table 1 summarizes the EC₅₀ calculated over the 8-point, 6-fold serially titrated curves using the geometric mean fluorescence intensity (gMFI) calculated by the FlowJo version 10 software. The fold change from rhIL-2 was also calculated for each variant as a measurement of the level of attenuation as compared to the activity of the rhIL-2 positive control. Some EC₅₀

values were unable to be calculated by the GraphPad Prism 7 software and were marked as Not Calculated (NC); however, based on dose-titration curves there was no attenuation for these variants.

[0147] Fusions of the hIL-2 moiety to the N-terminus or C-terminus of the immunoglobulin heavy chain resulted in no reduction in IL-2 activity when compared to rhIL-2 on cell lines expressing the high-affinity hIL-2 receptor (NK-92) or intermediate-affinity hIL-2 receptor (TF1+IL-2R β). The direct fusion (df) of hIL-2 to the antibody component of the fusion protein resulted in no change in IL-2 activity when compared with fusion employing a six amino acid linker (L6) between the IL-2 and antibody components. Similarly, fusions of the IL-2 component to the heavy chain or light chain of the antibody component resulted in no change in IL-2 activity when compared to rhIL-2. All N- or C-terminus and linker fusion protein variants in which the hCD25/hIL-2R α moiety was fused to hIL-2 were predicted to exhibit reduced binding of the fusion protein to the CD25 of the hIL-2 receptor on cells. Experimentally these constructs exhibited strongly attenuated hIL-2 activity (by at least 45-fold) on the high affinity IL-2 receptor (NK-92) and by 18-fold on the intermediate hIL-2 receptor (TF1+IL-2R β).

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Table 1. pSTAT5 EC₅₀ and fold change on fusion protein domain variants

HC or LC Component Of Fusion Protein	HC and LC SEQ ID NOs:	pSTAT5 EC ₅₀ (NK-92)	Fold change from rhIL-2 (NK-92)	Attenuation based on dose- titration curves (NK-92)	pSTAT5 EC ₅₀ (TF1+IL- 2Rβ)	Fold change from rhIL-2 (TF1+IL- 2Rβ)	Attenuation based on dose- titration curves (TF1+IL-2Rβ)
hIL-2 Nterm heavy chain df	358, 374	<0.1 ^a	1 ^a	Not Attenuated	1.11	2	Not Attenuated
hIL-2 Nterm heavy chain L6 fusion	359, 374	NC ^a	NC ^a	Not Attenuated	0.19	0	Not Attenuated
hIL-2 Nterm light chain df	379, 356	<0.1 ^a	1 ^a	Not Attenuated	0.52	1	Not Attenuated
hIL-2 Nterm light chain L6 fusion	379, 357	<0.1 ^a	0 ^a	Not Attenuated	0.13	0	Not Attenuated
hIL-2 Cterm heavy chain df	360, 374	<0.1 ^a	0 ^a	Not Attenuated	<0.1	0	Not Attenuated
hIL-2 Cterm heavy chain L6 fusion	361, 374	NC ^a	NC ^a	Not Attenuated	<0.1	0	Not Attenuated
hIL-2 Cterm light chain df	379, 362	NC ^a	NC ^a	Not Attenuated	1.15	1	Not Attenuated
hIL-2 Cterm light chain L6 fusion	379, 363	<0.1 ^a	0 ^a	Not Attenuated	0.25	0	Not Attenuated
hCD25-L20- hIL-2 Nterm heavy chain df	365, 374	7.42	1052	Attenuated	190.50 ^a	314 ^a	Attenuated
hCD25-L20- hIL-2 Nterm	366, 374	2.24	318	Attenuated	10.70	18	Attenuated

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heavy chain L6 fusion										
hCD25-L20-hIL-2 Nterm light chain df	379, 367	106.80	15149	Attenuated	328.50 ^a	542 ^a		Attenuated		
hCD25-L20-hIL-2 Nterm light chain L6 fusion	379, 368	4.45	631	Attenuated	27.88	46		Attenuated		
hCD25-L20-hIL-2 Cterm heavy chain df	369, 374	1.89	149	Attenuated	93.89 ^a	104 ^a		Attenuated		
hCD25-L20-hIL-2 Cterm heavy chain L6 fusion	370, 374	6.09	479	Attenuated	90.53 ^a	101 ^a		Attenuated		
hCD25-L20-hIL-2 Cterm light chain df	379, 371	0.58	45	Attenuated	156.90 ^a	174 ^a		Attenuated		
hCD25-L20-hIL-2 Cterm light chain L6 fusion	379, 372	1.76	138	Attenuated	221.90 ^a	247 ^a		Attenuated		

NC = Not Calculated, ^a = Fold change is an estimate only since a full four parameter logistic curve was not reached

Example 2: Antibody-attenuated hIL-2 fusion protein variant production and determination of their binding kinetics to Recombinant Human CD25 and/or Human CD122

[0148] Since there was no reduction in hIL-2 activity in the various N-terminus or C-terminus immunoglobulin heavy chain fusion proteins, the hIL-2 Cterm heavy chain L6 fusion (SEQ ID NOs: 361, 374), designated as “1H3-hIgG1-L6-hIL-2”, was used as the base construct for antibody-attenuated-hIL-2 fusion protein variants with substitutions in the hIL-2 moiety. Single, double and/or multiple amino acid substitutions were introduced into selected residues of human IL-2 in order to investigate the role those residues play in the recognition of either human CD25/IL-2R α and/or human CD122/IL-2R β or CD132/IL-2R γ (human IL-2R subunits). Over three hundred antibody-attenuated hIL-2 fusion protein variants with substitutions in the hIL-2 moiety were generated and evaluated in 6 rounds. These variants were first screened using a flow-based phosphorylated STAT5 (pSTAT5) assay at a fixed concentration on IL-2 dependent cell lines (NK-92 and TF1+IL-2R β) as well as in dose-titration curves. Phosphorylated STAT5 is a downstream signal of IL-2 activity and was used as a snapshot measurement of IL-2 potency. IL-2 dependent cell proliferation assays were also performed to measure IL-2 activity over a period of 3-4 days. Criteria for attenuated hIL-2 selection included: (1) reduced IL-2 potency on both NK-92 and TF1+IL-2R β cell lines with greater than 50% agonist activity on both cell lines; and (2) moderate-to-high production yield.

[0149] Human anti-DNase I antibody-hIL-2 fusion proteins were generated by fusing the human IL-2 or the human IL-2 variants (SEQ ID NOs: 1-344, 377, 378, and 575) to the C-terminus of a human anti-DNase I antibody (clone 1H3, having a human IgG1 isotype) heavy chain via the L6 linker, which were combined with the hIgG1 light chain (1H3-hkappa LC; SEQ ID NO: 374) to generate the 1H3-hIgG1-L6-hIL-2 fusion proteins (provided in Table 28). Mouse anti-yellow fever virus antibody-hIL-2 fusion proteins were also generated by fusing human IL-2 variants to the C-terminus of a mouse anti-yellow fever virus antibody (clone 2D12, having a mouse IgG1 isotype) heavy chain with a D265A substitution for decreased immune effector function via the L6 linker, which were combined with the 2D12-mIgG1 light chain (2D12-mKappa LC; SEQ ID NO: 376) to generate the 2D12-mIgG1-D265A-L6-hIL-2 fusion proteins (provided in Table 28). Some of these mouse anti-yellow fever virus antibody-hIL-2 fusion proteins were formatted onto a human IgG1 constant region and were generated in the

same manner as described above using, which was combined with 2D12-hKappa light chain (2D12-hKappa LC; SEQ ID NO: 573). Iterations of IL-2 amino acid substitutions were performed in six rounds, designated Groups 1 to 6. 1H3-hIgG1-L6-hIL-2, 2D12-mIgG1-D265A-L6-hIL-2, and 2D12-hIgG1-L6-hIL-2 fusion proteins were produced, expressed, and Protein-A purified using standard techniques.

[0150] Group 1 contained an initial series of only 2D12-mIgG1-D265A-L6-hIL-2 or 2D12-hIgG1-L6-hIL-2 fusion proteins which comprised a substitution or combination of substitutions in human IL-2 which were predicted to be involved in binding to only one of the IL-2 receptor subunits CD25/IL-2R α , CD122/IL-2R β , or CD132/IL-2R γ . The fusion proteins in this group included the following substitutions to IL-2 predicted to modulate binding to CD25/IL-2R α : F42K (SEQ ID NO: 1), V69A (SEQ ID NO: 2), V69E (SEQ ID NO: 3), V69F (SEQ ID NO: 4), V69G (SEQ ID NO: 5), V69H (SEQ ID NO: 6), V69I (SEQ ID NO: 7), V69K (SEQ ID NO: 8), V69L (SEQ ID NO: 9), V69M (SEQ ID NO: 10), V69Q (SEQ ID NO: 11), V69S (SEQ ID NO: 12), V69T (SEQ ID NO: 13), V69W (SEQ ID NO: 14), V69Y (SEQ ID NO: 15), V69R (SEQ ID NO: 581), (F42K/F44K) (SEQ ID NO: 16), (F44K/Y45R) (SEQ ID NO: 17), (F42K/V69R) (SEQ ID NO: 18), (Y45R/V69R) (SEQ ID NO: 19), (F42K/F44K/Y45R) (SEQ ID NO: 20), (F42A/Y45A/L72G) (SEQ ID NO: 574), (R38A/F42K/Y45R) (SEQ ID NO: 21), (R38E/F42K/Y45R) (SEQ ID NO: 22), (K43E/F42K/Y45R) (SEQ ID NO: 23), (K43T/F42K/Y45R) (SEQ ID NO: 24), (F42K/Y45R/E62A) (SEQ ID NO: 25), (P65R/F42K/Y45R) (SEQ ID NO: 26), (P65S/F42K/Y45R) (SEQ ID NO: 27), (V69A/F42K/Y45R) (SEQ ID NO: 28), (V69D/F42K/Y45R) (SEQ ID NO: 29), or (V69R/F42K/Y45R) (SEQ ID NO: 30). The substitutions in this group included the following substitutions predicted to modulate binding to CD122/IL-2R β : D20A (SEQ ID NO: 31), D20N (SEQ ID NO: 32), D20K (SEQ ID NO: 33), N88A (SEQ ID NO: 34), N88G (SEQ ID NO: 35), N88H (SEQ ID NO: 36), N88K (SEQ ID NO: 37), (D20A/D84A) (SEQ ID NO: 38), (D20A/E15A) (SEQ ID NO: 39), (D20A/E95A) (SEQ ID NO: 40), (D20A/N88A) (SEQ ID NO: 41), (D20A/S87A) (SEQ ID NO: 42), (D84A/N88A) (SEQ ID NO: 43), (E15A/N88A) (SEQ ID NO: 44), or (S87A/N88A) (SEQ ID NO: 45). Group 1 also included the following substitutions to IL-2 predicted to modulate IL-2 binding to CD132/IL-2-R γ : Q126L (SEQ ID NO: 377) or Q126E (SEQ ID NO: 378). The IL-2 substitutions studied in Group 1 were not predicted to modulate binding to more than one of the IL-2 receptor subunits.

[0151] Group 2 contained a series of 1H3-hIgG1-L6-hIL-2 fusion proteins which comprised one or more substitutions in human IL-2 which were predicted to be involved in CD25/IL-2R α binding only. The fusion proteins in this group included the following substitutions to IL-2 predicted to modulate binding to CD25/IL-2R α : R38A (SEQ ID NO: 46), R38D (SEQ ID NO: 47), R38E (SEQ ID NO: 48), R38Q (SEQ ID NO: 49), F42R (SEQ ID NO: 50), F42A (SEQ ID NO: 51), F42D (SEQ ID NO: 52), F42H (SEQ ID NO: 53), K43A (SEQ ID NO: 54), K43E (SEQ ID NO: 55), K43Q (SEQ ID NO: 56), Y45A (SEQ ID NO: 57), Y45K (SEQ ID NO: 58), Y45S (SEQ ID NO: 59), Y45R (SEQ ID NO: 60), E61A (SEQ ID NO: 61), E61R (SEQ ID NO: 62), E61K (SEQ ID NO: 63), E62A (SEQ ID NO: 64), E62R (SEQ ID NO: 65), E62K (SEQ ID NO: 66), E62Y (SEQ ID NO: 67), E68Y (SEQ ID NO: 68), E68A (SEQ ID NO: 69), E68K (SEQ ID NO: 70), E68R (SEQ ID NO: 71), E68L (SEQ ID NO: 72), L72Y (SEQ ID NO: 73), L72R (SEQ ID NO: 74), L72A (SEQ ID NO: 75), L72D (SEQ ID NO: 76), L72H (SEQ ID NO: 77), L72F (SEQ ID NO: 78), (R38D/E61R) (SEQ ID NO: 79), (R38D/E61R/K43E) (SEQ ID NO: 80), or (T3A/F42A/Y45A/L72G/C125A) (SEQ ID NO: 81). The substitution T3A was introduced into the IL-2 amino acid sequence to remove the predicted O-linked glycosylation site on human IL-2 (see for example Int'l Pub. No. WO2012/107417) and the substitution C125A was introduced into the IL-2 amino acid sequence to remove an unpaired cysteine residue (see for example Int'l Pub. No. WO2018/184964). The IL-2 substitutions studied in Group 2 were predicted to not modulate IL-2 binding to CD132/IL-2R γ , nor were these substitutions predicted to modulate binding to more than one of the IL-2 receptor subunits.

[0152] Group 3 contained a series of 1H3-hIgG1-L6-hIL-2 fusion proteins which comprised one or more substitutions in human IL-2 which were predicted to be involved in CD122/IL-2R β binding only. The fusion proteins in this group included the following substitutions to IL-2 predicted to modulate binding to CD122/IL-2R β : E15A (SEQ ID NO: 82), E15R (SEQ ID NO: 83), E15K (SEQ ID NO: 84), H16A (SEQ ID NO: 85), H16Y (SEQ ID NO: 86), H16E (SEQ ID NO: 87), L19A (SEQ ID NO: 88), D20I (SEQ ID NO: 89), D20S (SEQ ID NO: 90), D20H (SEQ ID NO: 91), D20T (SEQ ID NO: 92), D20W (SEQ ID NO: 93), D20Y (SEQ ID NO: 94), D20R (SEQ ID NO: 95), D20F (SEQ ID NO: 96), R81A (SEQ ID NO: 97), D84A (SEQ ID NO: 98), D84R (SEQ ID NO: 99), D84K (SEQ ID NO: 100), S87A (SEQ ID NO: 101), N88Y (SEQ ID NO: 102), N88D (SEQ ID NO: 103), N88R (SEQ ID NO: 104), N88E (SEQ ID NO: 105), N88F (SEQ ID NO: 106), N88I (SEQ ID NO: 107), I92A (SEQ ID NO: 108).

108), I92Y (SEQ ID NO: 109), I92S (SEQ ID NO: 110), I92F (SEQ ID NO: 111), I92R (SEQ ID NO: 112), I92D (SEQ ID NO: 113), I92E (SEQ ID NO: 114), E95A (SEQ ID NO: 115), E95R (SEQ ID NO: 116), E95K (SEQ ID NO: 117), (D20Y/H16E) (SEQ ID NO: 118), (D20Y/H16A) (SEQ ID NO: 119), (D20Y/H16Y) (SEQ ID NO: 120), (D20Y/I92A) (SEQ ID NO: 121), (D20Y/I92S) (SEQ ID NO: 122), (D20Y/I92R) (SEQ ID NO: 123), (D20Y/E95R) (SEQ ID NO: 124), or (D20Y/E95A) (SEQ ID NO: 125).

[0153] Group 4 contained a series of fusion proteins containing the 1H3-hIgG1-L6-hIL-2 HC fused to a CD25/IL-2R α extracellular domain moiety (SEQ ID NO: 126), a 20 amino acid linker (L20) (SEQ ID NO: 364), and human IL-2 variants comprising one or more substitutions to residues predicted to be involved in binding to CD122/IL-2R β . The fusion proteins in this group included the following substitutions to IL-2 predicted to modulate binding to CD122/IL-2R β : E15A (SEQ ID NO: 82), D20I (SEQ ID NO: 89), D20S (SEQ ID NO: 90), D20H (SEQ ID NO: 91), D20W (SEQ ID NO: 93), D20Y (SEQ ID NO: 94), D20R (SEQ ID NO: 95), D20F (SEQ ID NO: 96), D84K (SEQ ID NO: 100), S87A (SEQ ID NO: 101), N88Y (SEQ ID NO: 102), N88D (SEQ ID NO: 103), N88R (SEQ ID NO: 104), N88E (SEQ ID NO: 105), N88F (SEQ ID NO: 106), N88I (SEQ ID NO: 107), I92A (SEQ ID NO: 108), E95A (SEQ ID NO: 115), or E95K (SEQ ID NO: 117). The antibody-attenuated hIL-2 fusion proteins in this group are denoted as 1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2.

[0154] Group 5 contained a series of 1H3-hIgG1-L6-hIL-2 which comprised a combination of substitutions in IL-2 which were predicted to be involved in binding of IL-2 to CD25/IL-2R α and to CD122/IL-2R β or CD132/IL-2R γ . In addition, some variants had a deletion in the first three amino acids at the N-terminus of the hIL-2 moiety (Δ 1-3APT). The fusion proteins in Group 5 included the following substitutions to IL-2 predicted to modulate IL-2 binding to CD25/IL-2R α and to CD122/IL-2R β : (F42D/D20A) (SEQ ID NO: 127), (F42R/D20A) (SEQ ID NO: 128), (F42K/D20A) (SEQ ID NO: 129), (F42A/D20A) (SEQ ID NO: 130), (F42H/D20A) (SEQ ID NO: 131), (Y45R/D20A) (SEQ ID NO: 132), (Y45K/D20A) (SEQ ID NO: 133), (R38N/D20A) (SEQ ID NO: 134), (R38G/D20A) (SEQ ID NO: 135), (R38H/D20A) (SEQ ID NO: 136), (R38I/D20A) (SEQ ID NO: 137), (R38L/D20A) (SEQ ID NO: 138), (R38M/D20A) (SEQ ID NO: 139), (R38F/D20A) (SEQ ID NO: 140), (R38P/D20A) (SEQ ID NO: 141), (R38S/D20A) (SEQ ID NO: 142), (R38T/D20A) (SEQ ID NO: 143), (R38W/D20A) (SEQ ID NO: 144), (R38Y/D20A) (SEQ ID NO: 145), (R38V/D20A) (SEQ ID

NO: 146), (R38A/D20A) (SEQ ID NO: 147), (R38Q/D20A) (SEQ ID NO: 148), (D20A/R38E) (SEQ ID NO: 149), (R38D/D20A) (SEQ ID NO: 150), (K43E/D20A) (SEQ ID NO: 151), (E61A/D20A) (SEQ ID NO: 152), (E62A/D20A) (SEQ ID NO: 153), (E62Y/D20A) (SEQ ID NO: 154), (L72D/D20A) (SEQ ID NO: 155), (L72H/D20A) (SEQ ID NO: 156), (L72R/D20A) (SEQ ID NO: 157), (F42D/I92D) (SEQ ID NO: 158), (F42R/I92D) (SEQ ID NO: 159), (F42H/I92D) (SEQ ID NO: 160), (F42A/I92D) (SEQ ID NO: 161), (H16A/F42A) (SEQ ID NO: 575), (K43E/I92D) (SEQ ID NO: 162), (Y45R/I92D) (SEQ ID NO: 163), (Y45K/I92D) (SEQ ID NO: 164), (E62A/I92D) (SEQ ID NO: 165), (E62Y/I92D) (SEQ ID NO: 166), (L72D/I92D) (SEQ ID NO: 167), (L72H/I92D) (SEQ ID NO: 168), (L72R/I92D) (SEQ ID NO: 169), (R38D/I92D) (SEQ ID NO: 170), (R38E/I92D) (SEQ ID NO: 171), (R38Q/I92D) (SEQ ID NO: 172), (R38A/I92D) (SEQ ID NO: 173), (R38E/N88R) (SEQ ID NO: 174), (R38E/D84R) (SEQ ID NO: 175), (R38E/D84K) (SEQ ID NO: 176), (F42A/Y45R/D20A) (SEQ ID NO: 177), (F42H/Y45R/D20A) (SEQ ID NO: 178), (R38D/E61R/D20A) (SEQ ID NO: 179), (R38E/E61R/D20A) (SEQ ID NO: 180), (R38Q/E61R/D20A) (SEQ ID NO: 181), (R38A/E61R/D20A) (SEQ ID NO: 182), (R38A/D20A/E95A) (SEQ ID NO: 183), (D20A/E95A/R38D) (SEQ ID NO: 184), (D20A/E95A/R38E) (SEQ ID NO: 185), (D20A/E95A/R38Q) (SEQ ID NO: 186), (D20A/E95A/F42R) (SEQ ID NO: 187), (D20A/E95A/F42A) (SEQ ID NO: 188), (D20A/E95A/F42D) (SEQ ID NO: 189), (D20A/E95A/F42H) (SEQ ID NO: 190), (D20A/E95A/F42K) (SEQ ID NO: 191), (D20A/E95A/K43A) (SEQ ID NO: 192), (D20A/E95A/K43E) (SEQ ID NO: 193), (D20A/E95A/K43Q) (SEQ ID NO: 194), (D20A/E95A/Y45A) (SEQ ID NO: 195), (D20A/E95A/Y45K) (SEQ ID NO: 196), (D20A/E95A/Y45S) (SEQ ID NO: 197), (D20A/E95A/Y45R) (SEQ ID NO: 198), (D20A/E95A/E61A) (SEQ ID NO: 199), (D20A/E95A/E62A) (SEQ ID NO: 200), (D20A/E95A/E62R) (SEQ ID NO: 201), (D20A/E95A/E62K) (SEQ ID NO: 202), (D20A/E95A/E62Y) (SEQ ID NO: 203), (D20A/E95A/E68Y) (SEQ ID NO: 204), (D20A/E95A/E68A) (SEQ ID NO: 205), (D20A/E95A/E68L) (SEQ ID NO: 206), (D20A/E95A/L72Y) (SEQ ID NO: 207), (D20A/E95A/L72R) (SEQ ID NO: 208), (D20A/E95A/L72A) (SEQ ID NO: 209), (D20A/E95A/L72D) (SEQ ID NO: 210), (D20A/E95A/L72H) (SEQ ID NO: 211), (D20A/E95A/L72F) (SEQ ID NO: 212), (F42K/Y45R/D20A/S87A) (SEQ ID NO: 213), (F42K/Y45R/D20A/E95A) (SEQ ID NO: 214), (D20A/R38E/C125A) (SEQ ID NO: 215),

(T3A/D20A/R38E) (SEQ ID NO: 216), (T3A/D20A/R38E/C125A) (SEQ ID NO: 217), (Δ 1-3APT/D20A/R38E) (SEQ ID NO: 218), or (Δ 1-3APT/D20A/R38E/C125A) (SEQ ID NO: 219). The fusion proteins in Group 5 included the following substitutions to IL-2 predicted to modulate IL-2 binding to CD25/IL-2R α and to CD132/IL-2R: (R38E/Q22A) (SEQ ID NO: 220), (R38E/T123A) (SEQ ID NO: 221), (R38E/I129A) (SEQ ID NO: 222), (R38E/S130A) (SEQ ID NO: 223), (R38E/Q126A) (SEQ ID NO: 224), (R38E/Q126D) (SEQ ID NO: 225), (R38E/Q126V) (SEQ ID NO: 226), (R38E/Q22A/S130A) (SEQ ID NO: 227), (F42K/Y45R/Q126D) (SEQ ID NO: 228), or (D20A/E95A/Q126D) (SEQ ID NO: 229). Mutations to the hIL-2 sequence for Group 5 antibody-attenuated hIL-2 fusion proteins in which the numbering is according to IL-2 sequence are listed in SEQ ID NO: 127-229 and 575.

[0155] Group 6 contained a series of 1H3-hIgG1-L6-hIL-2 fusion proteins which comprised a combination of substitutions in human IL-2 which were predicted to be involved in binding of IL-2 to CD25/IL-2R α and to CD122/IL-2R β , but not to CD132/IL-2R γ . The fusion proteins in Group 6 included the following combination of substitutions in IL-2 predicted to modulate IL-2 binding to CD25/IL-2R α and CD122/IL-2R β : (D20A/E61R) (SEQ ID NO: 230), (D20A/E61N) (SEQ ID NO: 231), (D20A/E61D) (SEQ ID NO: 232), (D20A/E61Q) (SEQ ID NO: 233), (D20A/E61G) (SEQ ID NO: 234), (D20A/E61H) (SEQ ID NO: 235), (D20A/E61I) (SEQ ID NO: 236), (D20A/E61L) (SEQ ID NO: 237), (D20A/E61K) (SEQ ID NO: 238), (D20A/E61M) (SEQ ID NO: 239), (D20A/E61F) (SEQ ID NO: 240), (D20A/E61P) (SEQ ID NO: 241), (D20A/E61S) (SEQ ID NO: 242), (D20A/E61T) (SEQ ID NO: 243), (D20A/E61W) (SEQ ID NO: 244), (D20A/E61Y) (SEQ ID NO: 245), (D20A/E61V) (SEQ ID NO: 246), (D20A/F42N) (SEQ ID NO: 247), (D20A/F42Q) (SEQ ID NO: 248), (D20A/F42E) (SEQ ID NO: 249), (D20A/F42G) (SEQ ID NO: 250), (D20A/F42I) (SEQ ID NO: 251), (D20A/F42L) (SEQ ID NO: 252), (D20A/F42M) (SEQ ID NO: 253), (D20A/F42P) (SEQ ID NO: 254), (D20A/F42S) (SEQ ID NO: 255), (D20A/F42T) (SEQ ID NO: 256), (D20A/F42W) (SEQ ID NO: 257), (D20A/F42Y) (SEQ ID NO: 258), (D20A/F42V) (SEQ ID NO: 259), (D20A/Y45A) (SEQ ID NO: 260), (D20A/Y45N) (SEQ ID NO: 261), (D20A/Y45D) (SEQ ID NO: 262), (D20A/Y45Q) (SEQ ID NO: 263), (D20A/Y45E) (SEQ ID NO: 264), (D20A/Y45G) (SEQ ID NO: 265), (D20A/Y45H) (SEQ ID NO: 266), (D20A/Y45I) (SEQ ID NO: 267), (D20A/Y45L) (SEQ ID NO: 268), (D20A/Y45M) (SEQ ID NO: 269), (D20A/Y45F) (SEQ ID NO: 270), (D20A/Y45P) (SEQ ID NO: 271), (D20A/Y45S) (SEQ ID NO: 272), (D20A/Y45T) (SEQ ID NO: 273), (D20A/Y45W)

(SEQ ID NO: 274), (D20A/Y45V) (SEQ ID NO: 275), (I92D/F42N) (SEQ ID NO: 276), (I92D/F42Q) (SEQ ID NO: 277), (I92D/F42E) (SEQ ID NO: 278), (I92D/F42G) (SEQ ID NO: 279), (I92D/F42I) (SEQ ID NO: 280), (I92D/F42L) (SEQ ID NO: 281), (I92D/F42K) (SEQ ID NO: 282), (I92D/F42M) (SEQ ID NO: 283), (I92D/F42P) (SEQ ID NO: 284), (I92D/F42S) (SEQ ID NO: 285), (I92D/F42T) (SEQ ID NO: 286), (I92D/F42W) (SEQ ID NO: 287), (I92D/F42Y) (SEQ ID NO: 288), (I92D/F42V) (SEQ ID NO: 289), (I92D/Y45A) (SEQ ID NO: 290), (I92D/Y45N) (SEQ ID NO: 291), (I92D/Y45D) (SEQ ID NO: 292), (I92D/Y45Q) (SEQ ID NO: 293), (I92D/Y45E) (SEQ ID NO: 294), (I92D/Y45G) (SEQ ID NO: 295), (I92D/Y45H) (SEQ ID NO: 296), (I92D/Y45I) (SEQ ID NO: 297), (I92D/Y45L) (SEQ ID NO: 298), (I92D/Y45M) (SEQ ID NO: 299), (I92D/Y45F) (SEQ ID NO: 300), (I92D/Y45P) (SEQ ID NO: 301), (I92D/Y45S) (SEQ ID NO: 302), (I92D/Y45T) (SEQ ID NO: 303), (I92D/Y45W) (SEQ ID NO: 304), (I92D/Y45V) (SEQ ID NO: 305), (R38E/D20H) (SEQ ID NO: 306), (R38E/D20S) (SEQ ID NO: 307), (F42A/N88R) (SEQ ID NO: 308), (F42A/N88D) (SEQ ID NO: 309), (R38E/D84A) (SEQ ID NO: 310), (R38E/D84N) (SEQ ID NO: 311), (R38E/D84Q) (SEQ ID NO: 312), (R38E/D84E) (SEQ ID NO: 313), (R38E/D84G) (SEQ ID NO: 314), (R38E/D84H) (SEQ ID NO: 315), (R38E/D84I) (SEQ ID NO: 316), (R38E/D84L) (SEQ ID NO: 317), (R38E/D84M) (SEQ ID NO: 318), (R38E/D84F) (SEQ ID NO: 319), (R38E/D84P) (SEQ ID NO: 320), (R38E/D84S) (SEQ ID NO: 321), (R38E/D84T) (SEQ ID NO: 322), (R38E/D84W) (SEQ ID NO: 323), (R38E/D84Y) (SEQ ID NO: 324), (R38E/D84V) (SEQ ID NO: 325), (R38E/I92A) (SEQ ID NO: 326), (R38E/I92R) (SEQ ID NO: 327), (R38E/I92N) (SEQ ID NO: 328), (R38E/I92Q) (SEQ ID NO: 329), (R38E/I92E) (SEQ ID NO: 330), (R38E/I92G) (SEQ ID NO: 331), (R38E/I92H) (SEQ ID NO: 332), (R38E/I92L) (SEQ ID NO: 333), (R38E/I92K) (SEQ ID NO: 334), (R38E/I92M) (SEQ ID NO: 335), (R38E/I92F) (SEQ ID NO: 336), (R38E/I92P) (SEQ ID NO: 337), (R38E/I92S) (SEQ ID NO: 338), (R38E/I92T) (SEQ ID NO: 339), (R38E/I92W) (SEQ ID NO: 340), (R38E/I92Y) (SEQ ID NO: 341), (R38E/I92V) (SEQ ID NO: 342), (R38E/H16E) (SEQ ID NO: 343), or (R38K/D20A) (SEQ ID NO: 344). Mutations to the hIL-2 sequence for Group 6 antibody-attenuated hIL-2 fusion proteins in which the numbering is according to IL-2 sequence is listed in SEQ ID NO: 230-344.

[0156] The binding kinetics of some purified 1H3-hIgG1-L6-hIL-2 variant proteins for individual recombinant human CD25 and human CD122 were determined using bio-layer interferometry (BLI). Briefly, binding experiments were performed using an Octet Red96

instrument (Pall ForteBio) at 25 °C. C-terminal poly-histidine tagged human CD25 and human CD122 extracellular domains were captured onto anti-His2 sensors (Pall ForteBio). Receptor loaded sensors were dipped into a 7-point serial 3-fold dilution of each 1H3-hIgG-L6-hIL-2 variant, starting at a top concentration of 300 nM. 1H3-hIgG1-L6-hIL-2 fusion proteins were diluted into an assay buffer consisting of phosphate buffered saline (PBMS) supplemented with 0.1% BSA, 0.02% Tween-20 (pH 7.2). Loaded sensors were regenerated using 10 mM Glycine buffer (pH 1.7). Kinetic constants were calculated using a monovalent binding model.

[0157] Table 2 documents the association constant (k_{on}), dissociation constant (k_{off}), and equilibrium constant (K_D) of 74 immunoglobulin-hIL-2 fusion protein variants bound to recombinant human CD25 or recombinant human CD122.

Table 2. Binding kinetics of 1H3-hIgG-L6-hIL-2 fusion proteins to recombinant human CD25 or CD122 by Octet BLI

1H3-hIgG1-L6-hIL-2 fusion proteins	SEQ ID NO of hIL-2 variant	Predicted receptor sub-unit targeted by IL-2 substitution	K_D (M)	k_{on} (1/Ms)	k_{off} (1/s)
1H3-hIgG1-L6-hIL-2 WT	345	N/A	3.20E-10	5.90E+05	1.90E-04
1H3-hIgG1-L6-hIL-2 (E15A)	82	CD122	2.04E-09	1.15E+05	2.35E-04
1H3-hIgG1-L6-hIL-2 (E15R)	83	CD122	3.41E-09	9.48E+04	3.23E-04
1H3-hIgG1-L6-hIL-2 (E15K)	84	CD122	1.39E-09	1.71E+05	2.37E-04
1H3-hIgG1-L6-hIL-2 (H16A)	85	CD122	1.68E-09	1.71E+05	2.87E-04
1H3-hIgG1-L6-hIL-2 (H16Y)	86	CD122	1.46E-09	1.50E+05	2.20E-04
1H3-hIgG1-L6-hIL-2 (H16E)	87	CD122	1.40E-09	1.57E+05	2.20E-04
1H3-hIgG1-L6-hIL-2 (L19A)	88	CD122	1.76E-09	2.03E+05	3.57E-04

1H3-hIgG1-L6-hIL-2 (D20I)	89	CD122	1.16E-09	1.70E+05	1.98E-04
1H3-hIgG1-L6-hIL-2 (D20S)	90	CD122	6.24E-10	1.74E+05	1.09E-04
1H3-hIgG1-L6-hIL-2 (D20H)	91	CD122	1.13E-09	1.88E+05	2.12E-04
1H3-hIgG1-L6-hIL-2 (D20W)	93	CD122	1.01E-09	1.87E+05	1.90E-04
1H3-hIgG1-L6-hIL-2 (D20Y)	94	CD122	1.42E-09	1.51E+05	2.14E-04
1H3-hIgG1-L6-hIL-2 (D20R)	95	CD122	1.21E-09	1.44E+05	1.75E-04
1H3-hIgG1-L6-hIL-2 (D20F)	96	CD122	1.57E-09	1.75E+05	2.75E-04
1H3-hIgG1-L6-hIL-2 (R38A)	46	CD25	5.55E-09	1.82E+05	1.01E-03
1H3-hIgG1-L6-hIL-2 (R38D)	47	CD25	1.86E-09	8.84E+05	1.64E-03
1H3-hIgG1-L6-hIL-2 (R38E)	48	CD25	8.74E-09	3.31E+05	2.89E-03
1H3-hIgG1-L6-hIL-2 (R38Q)	49	CD25	6.33E-09	4.83E+05	3.05E-03
1H3-hIgG1-L6-hIL-2 (F42R)	50	CD25	2.63E-09	1.59E+06	4.20E-03
1H3-hIgG1-L6-hIL-2 (F42A)	51	CD25	9.25E-09	9.89E+05	9.15E-03
1H3-hIgG1-L6-hIL-2 (F42D)	52	CD25	4.51E-09	1.70E+06	7.64E-03
1H3-hIgG1-L6-hIL-2 (F42H)	53	CD25	6.84E-09	8.23E+05	5.63E-03
1H3-hIgG1-L6-hIL-2 (K43A)	54	CD25	4.79E-09	2.59E+05	1.24E-03

1H3-hIgG1-L6-hIL-2 (K43E)	55	CD25	5.66E-09	4.52E+05	2.56E-03
1H3-hIgG1-L6-hIL-2 (K43Q)	56	CD25	2.28E-09	4.49E+05	1.02E-03
1H3-hIgG1-L6-hIL-2 (Y45A)	57	CD25	3.66E-09	4.29E+05	1.57E-03
1H3-hIgG1-L6-hIL-2 (Y45K)	58	CD25	9.03E-09	5.22E+05	4.71E-03
1H3-hIgG1-L6-hIL-2 (Y45S)	59	CD25	2.45E-09	5.05E+05	1.24E-03
1H3-hIgG1-L6-hIL-2 (Y45R)	60	CD25	1.96E-09	6.46E+05	1.27E-03
1H3-hIgG1-L6-hIL-2 (E61A)	61	CD25	7.00E-09	3.21E+05	2.25E-03
1H3-hIgG1-L6-hIL-2 (E61R)	62	CD25	8.84E-09	1.22E+06	1.08E-02
1H3-hIgG1-L6-hIL-2 (E61K)	63	CD25	1.56E-08	3.16E+05	4.94E-03
1H3-hIgG1-L6-hIL-2 (E62A)	64	CD25	1.23E-08	3.79E+05	4.67E-03
1H3-hIgG1-L6-hIL-2 (E62R)	65	CD25	No binding observed		
1H3-hIgG1-L6-hIL-2 (E62K)	66	CD25	No binding observed		
1H3-hIgG1-L6-hIL-2 (E62Y)	67	CD25	1.55E-08	2.91E+05	4.50E-03
1H3-hIgG1-L6-hIL-2 (E68Y)	68	CD25	8.18E-09	1.80E+05	1.47E-03
1H3-hIgG1-L6-hIL-2 (E68A)	69	CD25	4.49E-09	1.45E+05	6.52E-04
1H3-hIgG1-L6-hIL-2 (E68K)	70	CD25	9.63E-09	2.54E+05	2.44E-03

1H3-hIgG1-L6-hIL-2 (E68R)	71	CD25	1.16E-08	2.54E+05	2.96E-03
1H3-hIgG1-L6-hIL-2 (E68L)	72	CD25	8.62E-09	1.02E+05	8.82E-04
1H3-hIgG1-L6-hIL-2 (I92R)	112	CD122	2.54E-09	1.08E+05	2.76E-04
1H3-hIgG1-L6-hIL-2 (I92D)	113	CD122	7.94E-09	4.95E+04	3.93E-04
1H3-hIgG1-L6-hIL-2 (I92E)	114	CD122	2.41E-09	8.54E+04	2.06E-04
1H3-hIgG1-L6-hIL-2 (E95A)	115	CD122	3.11E-09	1.47E+05	4.58E-04
1H3-hIgG1-L6-hIL-2 (E95R)	116	CD122	2.29E-09	1.14E+05	2.61E-04
1H3-hIgG1-L6-hIL-2 (E95K)	117	CD122	3.25E-09	1.25E+05	4.07E-04
1H3-hIgG1-L6-hIL-2 (F42K/Y45R/D20A/S87A)	213	CD25+CD122	3.25E-08	1.24E+05	4.05E-03
1H3-hIgG1-L6-hIL-2 (F42K/Y45R/D20A/E95A)	214	CD25+CD122	No binding observed		
1H3-hIgG1-L6-hIL-2 (F42K/Y45R/Q126D)	228	CD25+CD132	No binding observed		
1H3-hIgG1-L6-hIL-2 (D20A/E95A/Q126D)	229	CD122+CD132	3.34E-09	4.87E+04	1.62E-04
1H3-hIgG1-L6-hIL-2 (R38D/E61R)	79	CD25	No binding observed		
1H3-hIgG1-L6-hIL-2 (R38D/E61R/K43E)	80	CD25	No binding observed		

[0158] Table 3 documents the association (k_{on}) constants, dissociation (k_{off}) constants, and equilibrium constants (K_D) of 74 1H3-hIgG1-L6-hIL-2 fusion proteins bound to recombinant human CD122.

Table 3. Binding kinetics of 1H3-hIgG-L6-hIL-2 fusion proteins to recombinant human CD122 by Octet BLI

1H3-hIgG-L6-hIL-2 fusion proteins	SEQ ID NO of hIL-2 variant	Predicted receptor sub-unit targeted by IL-2 substitution	K _D (M)	k _{on} (1/Ms)	k _{off} (1/s)
1H3-hIgG1-L6-hIL-2 WT	345 ^a	N/A	5.60E-09	7.00E+05	3.90E-03
1H3-hIgG1-L6-hIL-2 (E15A)	82 ^b	CD122	8.89E-09	1.75E+05	1.56E-03
1H3-hIgG1-L6-hIL-2 (E15R)	83	CD122	3.69E-09	1.46E+05	5.38E-04
1H3-hIgG1-L6-hIL-2 (E15K)	84	CD122	3.56E-09	2.42E+05	8.62E-04
1H3-hIgG1-L6-hIL-2 (H16A)	85	CD122	1.78E-09	1.55E+06	2.76E-03
1H3-hIgG1-L6-hIL-2 (H16Y)	86	CD122	4.36E-09	9.97E+05	4.35E-03
1H3-hIgG1-L6-hIL-2 (H16E)	87	CD122	No binding observed		
1H3-hIgG1-L6-hIL-2 (L19A)	88	CD122	1.03E-08	4.72E+05	4.87E-03
1H3-hIgG1-L6-hIL-2 (D20I)	89	CD122	No binding observed		
1H3-hIgG1-L6-hIL-2 (D20S)	90	CD122	No binding observed		

1H3-hIgG1-L6-hIL-2 (D20H)	91	CD122	No binding observed		
1H3-hIgG1-L6-hIL-2 (D20W)	93	CD122	No binding observed		
1H3-hIgG1-L6-hIL-2 (D20Y)	94	CD122	No binding observed		
1H3-hIgG1-L6-hIL-2 (D20R)	95	CD122	No binding observed		
1H3-hIgG1-L6-hIL-2 (D20F)	96	CD122	No binding observed		
1H3-hIgG1-L6-hIL-2 (R38A)	46	CD25	1.38E-08	2.08E+05	2.87E-03
1H3-hIgG1-L6-hIL-2 (R38D)	47	CD25	2.20E-09	4.28E+05	9.42E-04
1H3-hIgG1-L6-hIL-2 (R38E)	48	CD25	5.81E-09	4.64E+05	2.69E-03
1H3-hIgG1-L6-hIL-2 (R38Q)	49	CD25	1.01E-09	2.81E+05	2.84E-04
1H3-hIgG1-L6-hIL-2 (F42R)	50	CD25	5.47E-09	5.42E+05	2.96E-03
1H3-hIgG1-L6-hIL-2 (F42A)	51	CD25	5.97E-09	4.19E+05	2.50E-03
1H3-hIgG1-L6-hIL-2 (F42D)	52	CD25	1.04E-08	2.38E+05	2.46E-03

1H3-hlgG1-L6-hIL-2 (F42H)	53	CD25	6.33E-09	4.45E+05	2.81E-03
1H3-hlgG1-L6-hIL-2 (K43A)	54	CD25	1.03E-08	2.85E+05	2.94E-03
1H3-hlgG1-L6-hIL-2 (K43E)	55	CD25	5.47E-09	3.65E+05	2.00E-03
1H3-hlgG1-L6-hIL-2 (K43Q)	56	CD25	4.21E-09	5.14E+05	2.17E-03
1H3-hlgG1-L6-hIL-2 (Y45A)	57	CD25	4.93E-09	4.51E+05	2.22E-03
1H3-hlgG1-L6-hIL-2 (Y45K)	58	CD25	6.56E-09	3.55E+05	2.33E-03
1H3-hlgG1-L6-hIL-2 (Y45S)	59	CD25	6.96E-09	5.07E+05	3.53E-03
1H3-hlgG1-L6-hIL-2 (Y45R)	60	CD25	7.58E-09	4.36E+05	3.31E-03
1H3-hlgG1-L6-hIL-2 (E61A)	61	CD25	1.34E-08	3.13E+05	4.18E-03
1H3-hlgG1-L6-hIL-2 (E61R)	62	CD25	1.30E-08	4.56E+05	5.91E-03
1H3-hlgG1-L6-hIL-2 (E61K)	63	CD25	1.56E-08	3.16E+05	4.94E-03
1H3-hlgG1-L6-hIL-2 (E62A)	64	CD25	1.23E-08	3.79E+05	4.67E-03

1H3-hIgG1-L6-hIL-2 (E62R)	65	CD25	No binding observed		
1H3-hIgG1-L6-hIL-2 (E62K)	66	CD25	No binding observed		
1H3-hIgG1-L6-hIL-2 (E62Y)	67	CD25	1.55E-08	2.91E+05	4.50E-03
1H3-hIgG1-L6-hIL-2 (E68Y)	68	CD25	8.18E-09	1.80E+05	1.47E-03
1H3-hIgG1-L6-hIL-2 (E68A)	69	CD25	4.49E-09	1.45E+05	6.52E-04
1H3-hIgG1-L6-hIL-2 (E68K)	70	CD25	1.05E-08	2.02E+05	2.12E-03
1H3-hIgG1-L6-hIL-2 (E68R)	71	CD25	8.51E-09	2.27E+05	1.93E-03
1H3-hIgG1-L6-hIL-2 (E68L)	72	CD25	2.72E-09	7.79E+04	2.12E-04
1H3-hIgG1-L6-hIL-2 (L72Y)	73	CD25	6.39E-09	1.94E+05	1.24E-03
1H3-hIgG1-L6-hIL-2 (L72R)	74	CD25	1.96E-08	3.07E+04	6.01E-04
1H3-hIgG1-L6-hIL-2 (L72A)	75	CD25	9.08E-09	1.47E+05	1.34E-03
1H3-hIgG1-L6-hIL-2 (L72D)	76	CD25	9.52E-09	1.57E+05	1.50E-03

1H3-hIgG1-L6-hIL-2 (L72H)	77	CD25	9.03E-09	1.65E+05	1.49E-03
1H3-hIgG1-L6-hIL-2 (L72F)	78	CD25	5.04E-09	2.28E+05	1.15E-03
1H3-hIgG1-L6-hIL-2 (R81A)	97	CD122	7.08E-09	2.20E+05	1.56E-03
1H3-hIgG1-L6-hIL-2 (D84A)	98	CD122	No binding observed		
1H3-hIgG1-L6-hIL-2 (D84R)	99	CD122	1.88E-08	4.73E+05	8.88E-03
1H3-hIgG1-L6-hIL-2 (S87A)	101	CD122	7.09E-09	3.31E+05	2.34E-03
1H3-hIgG1-L6-hIL-2 (N88Y)	102	CD122	No binding observed		
1H3-hIgG1-L6-hIL-2 (N88D)	103	CD122	No binding observed		
1H3-hIgG1-L6-hIL-2 (N88R)	104	CD122	No binding observed		
1H3-hIgG1-L6-hIL-2 (N88E)	105	CD122	No binding observed		
1H3-hIgG1-L6-hIL-2 (N88F)	106	CD122	No binding observed		
1H3-hIgG1-L6-hIL-2 (N88I)	107	CD122	No binding observed		

1H3-hlgG1-L6-hIL-2 (I92A)	108	CD122	3.38E-09	1.95E+06	6.58E-03
1H3-hlgG1-L6-hIL-2 (I92Y)	109	CD122	1.23E-08	4.53E+05	5.57E-03
1H3-hlgG1-L6-hIL-2 (I92S)	110	CD122	No binding observed		
1H3-hlgG1-L6-hIL-2 (I92F)	111	CD122	5.45E-09	1.03E+05	5.59E-04
1H3-hlgG1-L6-hIL-2 (I92R)	112	CD122	No binding observed		
1H3-hlgG1-L6-hIL-2 (I92D)	113	CD122	No binding observed		
1H3-hlgG1-L6-hIL-2 (I92E)	114	CD122	1.62E-09	9.33E+05	1.51E-03
1H3-hlgG1-L6-hIL-2 (E95A)	115	CD122	8.17E-09	2.87E+05	2.35E-03
1H3-hlgG1-L6-hIL-2 (E95R)	116	CD122	No binding observed		
1H3-hlgG1-L6-hIL-2 (E95K)	117	CD122	3.81E-09	6.58E+05	2.51E-03
1H3-hlgG1-L6-hIL-2 (F42K/Y45R/D20A/S87A)	213	CD25+CD122	No binding observed		
1H3-hlgG1-L6-hIL-2 (F42K/Y45R/D20A/E95A)	214	CD25+CD122	No binding observed		

1H3-hIgG1-L6-hIL-2 (F42K/Y45R/Q126D)	228	CD25+CD132	9.16E-09	3.75E+05	3.44E-03
1H3-hIgG1-L6-hIL-2 (D20A/E95A/Q126D)	229	CD122+CD132	No binding observed		
1H3-hIgG1-L6-hIL-2 (R38D/E61R)	79	CD25	1.29E-08	3.68E+05	4.73E-03
1H3-hIgG1-L6-hIL-2 (R38D/E61R/K43E)	80	CD25	7.47E-09	4.52E+05	3.38E-03

^a SEQ ID NO: 345 corresponds to wild type hIL-2.

^b SEQ ID NO: 57 is attenuated IL-2 sequence only.

Example 3: Testing for attenuation for the high-affinity and intermediate-affinity hIL-2 receptor with a fixed concentration cell-based potency pSTAT5 screen

[0159] The attenuation of antibody-attenuated hIL-2 fusion proteins described in Example 2 was tested in a fixed concentration pSTAT5 screen using the NK-92 (expressing the high affinity hIL-2 receptor) and TF1+IL-2R β (expressing the intermediate affinity hIL-2 receptor) cell lines as described in Protocol D. Tables 4-8 list the fold change of geometric mean fluorescent intensity (gMFI) of antibody-attenuated hIL-2 fusion proteins from free cytokine wild-type rhIL-2, a measurement of reduction of IL-2 activity. For the fixed concentration screen, the fold change was calculated by dividing the gMFI of the rhIL-2 by the gMFI of the variants. For experiments with full titration curves, fold change from rhIL-2 was calculated by dividing the EC₅₀ values for the rhIL-2 by the EC₅₀ of variants. Fold change was rounded to the nearest whole number. A reduced gMFI in both NK-92 and TF1+IL-2R β cell lines when compared to the gMFI resulting from rhIL-2 was indicative of attenuation of IL-2 activity at both the high- and intermediate-affinity receptors. Group 1 variants described in Example 2 were not tested in the fixed concentration cell-based potency pSTAT5 screen.

[0160] Each variant tested was also assessed for IL-2 agonistic activity and characterized either as a full or partial IL-2 agonist, or having no IL-2 activity (inactive). 1H3-hIgG1-L6-hIL-2 fusion protein dose-titration curves that reached the maximal gMFI level exhibited by the rhIL-2 positive control were considered to be antibody-attenuated hIL-2 fusion protein with full agonist activity. Partial agonist activity was calculated as a percentage of full activity using rhIL-2 maximal gMFI as 100%. Antibody-attenuated hIL-2 fusion protein with less than 10% of the rhIL-2 maximal gMFI at the highest concentration of 1200 nM were considered to have no agonist activity (inactive). Some EC₅₀ values and level of attenuation could not be accurately calculated using the GraphPad Prism 7 software since activity did not reach a maximum and accordingly these values are an estimate.

[0161] pSTAT5 fixed concentration results demonstrated that while some single residue substitutions attenuated IL-2 activity on the high-affinity cell line (NK-92), a combination of substitutions which modulated binding to both the alpha chain and the beta chain or both the alpha chain and gamma chain were required to substantially attenuate IL-2 activity on the high affinity IL-2 receptor (more than 20-fold attenuation from recombinant hIL-2).

Table 4. Fold change from rhIL-2 in a fixed concentration pSTAT5 screen on 1H3-hIgG1-L6-hIL-2 fusion proteins from Group 2

Variants	SEQ ID NO of hIL-2 variant	Fold change from hIL-2 (NK-92)	Fold change from hIL-2 (TF1+IL-2R β)
1H3-hIgG1-L6-hIL-2 (R38D)	47	7	1
1H3-hIgG1-L6-hIL-2 (R38E)	48	12	1
1H3-hIgG1-L6-hIL-2 (R38Q)	49	1	1
1H3-hIgG1-L6-hIL-2 (F42R)	50	7	1
1H3-hIgG1-L6-hIL-2 (F42A)	51	1	1
1H3-hIgG1-L6-hIL-2 (F42H)	53	1	1
1H3-hIgG1-L6-hIL-2 (K43E)	55	1	1
1H3-hIgG1-L6-hIL-2 (K43Q)	56	1	1
1H3-hIgG1-L6-hIL-2 (Y45A)	57	1	1
1H3-hIgG1-L6-hIL-2 (Y45K)	58	1	1
1H3-hIgG1-L6-hIL-2 (Y45S)	59	1	1
1H3-hIgG1-L6-hIL-2 (Y45R)	60	10	1
1H3-hIgG1-L6-hIL-2 (E68Y)	68	1	1
1H3-hIgG1-L6-hIL-2 (E68A)	69	1	1
1H3-hIgG1-L6-hIL-2 (E68L)	72	2	1
1H3-hIgG1-L6-hIL-2 (L72Y)	73	1	1
1H3-hIgG1-L6-hIL-2 (L72A)	75	1	1
1H3-hIgG1-L6-hIL-2 (L72F)	78	1	1
1H3-hIgG1-L6-hIL-2 (R38D/E61R)	79	NT-1	1
1H3-hIgG1-L6-hIL-2 (R38D/E61R/K43E)	80	NT-1	1
1H3-hIgG1-L6-hIL-2 (T3A/F42A/Y45A/L72G/C125A)	81	10	1

NT-1 = Already tested in pSTAT5 full titration first, no data for fixed concentration assay.

Table 5. Fold change from rhIL-2 in a fixed concentration pSTAT5 screen on 1H3-hIgG1-L6-hIL-2 fusion proteins from Group 3

Variants	SEQ ID NO of hIL-2 variant	Fold change from hIL-2 (NK-92)	Fold change from hIL-2 (TF1+IL-2R β)
1H3-hIgG1-L6-hIL-2 (E15A)	82	1	1
1H3-hIgG1-L6-hIL-2 (E15R)	83	1	1
1H3-hIgG1-L6-hIL-2 (E15K)	84	1	1
1H3-hIgG1-L6-hIL-2 (H16A)	85	1	1

1H3-hIgG1-L6-hIL-2 (H16Y)	86	1	1
1H3-hIgG1-L6-hIL-2 (H16E)	87	1	NT-1
1H3-hIgG1-L6-hIL-2 (L19A)	88	1	NT-1
1H3-hIgG1-L6-hIL-2 (D20I)	89	12	NT-1
1H3-hIgG1-L6-hIL-2 (D20S)	90	4	NT-1
1H3-hIgG1-L6-hIL-2 (D20H)	91	10	NT-1
1H3-hIgG1-L6-hIL-2 (D20W)	93	16	NT-1
1H3-hIgG1-L6-hIL-2 (D20Y)	94	17	NT-1
1H3-hIgG1-L6-hIL-2 (D20R)	95	19	NT-1
1H3-hIgG1-L6-hIL-2 (D20F)	96	17	NT-1
1H3-hIgG1-L6-hIL-2 (R81A)	97	1	1
1H3-hIgG1-L6-hIL-2 (D84A)	98	1	NT-1
1H3-hIgG1-L6-hIL-2 (D84R)	99	3	NT-1
1H3-hIgG1-L6-hIL-2 (D84K)	100	2	NT-1
1H3-hIgG1-L6-hIL-2 (S87A)	101	1	1
1H3-hIgG1-L6-hIL-2 (N88Y)	102	22	NT-1
1H3-hIgG1-L6-hIL-2 (N88D)	103	2	NT-1
1H3-hIgG1-L6-hIL-2 (N88R)	104	3	NT-1
1H3-hIgG1-L6-hIL-2 (N88E)	105	10	NT-1
1H3-hIgG1-L6-hIL-2 (N88F)	106	19	NT-1
1H3-hIgG1-L6-hIL-2 (N88I)	107	9	NT-1
1H3-hIgG1-L6-hIL-2 (I92A)	108	1	1
1H3-hIgG1-L6-hIL-2 (I92Y)	109	1	NT-1
1H3-hIgG1-L6-hIL-2 (I92S)	110	1	NT-1
1H3-hIgG1-L6-hIL-2 (I92F)	111	1	1
1H3-hIgG1-L6-hIL-2 (I92R)	112	1	NT-1
1H3-hIgG1-L6-hIL-2 (I92D)	113	3	NT-1
1H3-hIgG1-L6-hIL-2 (I92E)	114	1	1
1H3-hIgG1-L6-hIL-2 (E95A)	115	1	1
1H3-hIgG1-L6-hIL-2 (E95R)	116	1	NT-1
1H3-hIgG1-L6-hIL-2 (E95K)	117	1	1
1H3-hIgG1-L6-hIL-2 (D20T)	92	3	2
1H3-hIgG1-L6-hIL-2 (D20A)	31	7	2
1H3-hIgG1-L6-hIL-2 (D20Y/H16E)	118	6	4
1H3-hIgG1-L6-hIL-2 (D20Y/H16A)	119	10	3
1H3-hIgG1-L6-hIL-2 (D20Y/H16Y)	120	10	4
1H3-hIgG1-L6-hIL-2 (D20Y/I92A)	121	11	4
1H3-hIgG1-L6-hIL-2 (D20Y/I92S)	122	11	4
1H3-hIgG1-L6-hIL-2 (D20Y/I92R)	123	12	5

1H3-hIgG1-L6-hIL-2 (D20Y/E95R)	124	12	5
1H3-hIgG1-L6-hIL-2 (D20Y/E95A)	125	11	5

NT-1 = Already tested in pSTAT5 full titration first, no data for fixed concentration assay.

Table 6. Fold change from rhIL-2 in a fixed concentration pSTAT5 screen on 1H3-hIgG1-L6-hIL-2 fusion proteins from Group 4

Variants	SEQ ID NO of hIL-2 variant	Fold change from hIL-2 (NK-92)	Fold change from hIL-2 (TF1+IL-2Rβ)
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (E15A)	82	17	1
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20I)	89	21	15
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20S)	90	2	14
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20H)	91	22	15
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20W)	93	23	15
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20Y)	94	23	16
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20R)	95	23	16
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20F)	96	23	18
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D84K)	100	23	17
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (S87A)	101	17	2
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (N88Y)	102	23	18
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (N88D)	103	23	17
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (N88R)	104	24	17
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (N88E)	105	25	18
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (N88F)	106	25	18
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (N88I)	107	25	20

1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (I92A)	108	15	3
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (E95A)	115	14	1
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (E95K)	117	25	8

Table 7. Fold change from rhIL-2 in a fixed concentration pSTAT5 screen on 1H3-hIgG1-L6-hIL-2 fusion proteins from Group 5

Variants	SEQ ID NO of hIL- 2 variant	Fold change from hIL-2 (NK-92)	Fold change from hIL-2 (TF1+IL-2R β)
1H3-hIgG1-L6-hIL-2 (F42D/D20A)	127	11	3
1H3-hIgG1-L6-hIL-2 (F42R/D20A)	128	10	2
1H3-hIgG1-L6-hIL-2 (F42K/D20A)	129	10	4
1H3-hIgG1-L6-hIL-2 (F42A/D20A)	130	11	3
1H3-hIgG1-L6-hIL-2 (F42H/D20A)	131	12	2
1H3-hIgG1-L6-hIL-2 (Y45R/D20A)	132	11	1
1H3-hIgG1-L6-hIL-2 (Y45K/D20A)	133	11	2
1H3-hIgG1-L6-hIL-2 (R38N/D20A)	134	14	3
1H3-hIgG1-L6-hIL-2 (R38G/D20A)	135	13	2
1H3-hIgG1-L6-hIL-2 (R38H/D20A)	136	12	3
1H3-hIgG1-L6-hIL-2 (R38I/D20A)	137	11	3
1H3-hIgG1-L6-hIL-2 (R38L/D20A)	138	11	4
1H3-hIgG1-L6-hIL-2 (R38M/D20A)	139	11	3
1H3-hIgG1-L6-hIL-2 (R38F/D20A)	140	12	3
1H3-hIgG1-L6-hIL-2 (R38P/D20A)	141	13	3
1H3-hIgG1-L6-hIL-2 (R38S/D20A)	142	15	2
1H3-hIgG1-L6-hIL-2 (R38T/D20A)	143	13	3
1H3-hIgG1-L6-hIL-2 (R38W/D20A)	144	14	2
1H3-hIgG1-L6-hIL-2 (R38Y/D20A)	145	14	3
1H3-hIgG1-L6-hIL-2 (R38V/D20A)	146	12	3
1H3-hIgG1-L6-hIL-2 (R38A/D20A)	147	13	3
1H3-hIgG1-L6-hIL-2 (R38Q/D20A)	148	14	3
1H3-hIgG1-L6-hIL-2 (R38E/D20A)	149	15	3
1H3-hIgG1-L6-hIL-2 (R38D/D20A)	150	15	3
1H3-hIgG1-L6-hIL-2 (K43E/D20A)	151	13	2
1H3-hIgG1-L6-hIL-2 (E61A/D20A)	152	14	2
1H3-hIgG1-L6-hIL-2 (E62A/D20A)	153	14	2
1H3-hIgG1-L6-hIL-2 (E62Y/D20A)	154	14	3

1H3-hIgG1-L6-hIL-2 (L72D/D20A)	155	14	2
1H3-hIgG1-L6-hIL-2 (L72H/D20A)	156	14	3
1H3-hIgG1-L6-hIL-2 (L72R/D20A)	157	10	3
1H3-hIgG1-L6-hIL-2 (F42D/I92D)	158	12	5
1H3-hIgG1-L6-hIL-2 (F42R/I92D)	159	12	3
1H3-hIgG1-L6-hIL-2 (F42H/I92D)	160	12	2
1H3-hIgG1-L6-hIL-2 (F42A/I92D)	161	12	3
1H3-hIgG1-L6-hIL-2 (K43E/I92D)	162	13	4
1H3-hIgG1-L6-hIL-2 (Y45R/I92D)	163	13	1
1H3-hIgG1-L6-hIL-2 (Y45K/I92D)	164	13	1
1H3-hIgG1-L6-hIL-2 (E62A/I92D)	165	13	3
1H3-hIgG1-L6-hIL-2 (E62Y/I92D)	166	14	5
1H3-hIgG1-L6-hIL-2 (L72D/I92D)	167	14	5
1H3-hIgG1-L6-hIL-2 (L72H/I92D)	168	14	5
1H3-hIgG1-L6-hIL-2 (L72R/I92D)	169	14	5
1H3-hIgG1-L6-hIL-2 (R38D/I92D)	170	15	2
1H3-hIgG1-L6-hIL-2 (R38E/I92D)	171	15	2
1H3-hIgG1-L6-hIL-2 (R38Q/I92D)	172	14	2
1H3-hIgG1-L6-hIL-2 (R38A/I92D)	173	13	4
1H3-hIgG1-L6-hIL-2 (R38E/N88R)	174	16	1
1H3-hIgG1-L6-hIL-2 (R38E/D84R)	175	14	2
1H3-hIgG1-L6-hIL-2 (R38E/D84K)	176	14	2
1H3-hIgG1-L6-hIL-2 (F42A/Y45R/D20A)	177	11	2
1H3-hIgG1-L6-hIL-2 (F42H/Y45R/D20A)	178	12	2
1H3-hIgG1-L6-hIL-2 (R38D/E61R/D20A)	179	12	3
1H3-hIgG1-L6-hIL-2 (R38E/E61R/D20A)	180	11	3
1H3-hIgG1-L6-hIL-2 (R38Q/E61R/D20A)	181	12	3
1H3-hIgG1-L6-hIL-2 (R38A/E61R/D20A)	182	13	3
1H3-hIgG1-L6-hIL-2 (D20A/E95A/R38A)	183	6	5
1H3-hIgG1-L6-hIL-2 (D20A/E95A/R38D)	184	21	6
1H3-hIgG1-L6-hIL-2 (D20A/E95A/R38E)	185	21	5
1H3-hIgG1-L6-hIL-2 (D20A/E95A/R38Q)	186	19	6
1H3-hIgG1-L6-hIL-2 (D20A/E95A/F42R)	187	21	4
1H3-hIgG1-L6-hIL-2 (D20A/E95A/F42A)	188	21	5
1H3-hIgG1-L6-hIL-2 (D20A/E95A/F42D)	189	22	12
1H3-hIgG1-L6-hIL-2 (D20A/E95A/F42H)	190	22	4
1H3-hIgG1-L6-hIL-2 (D20A/E95A/F42K)	191	21	4
1H3-hIgG1-L6-hIL-2 (D20A/E95A/K43A)	192	5	7
1H3-hIgG1-L6-hIL-2 (D20A/E95A/K43E)	193	13	6
1H3-hIgG1-L6-hIL-2 (D20A/E95A/K43Q)	194	5	6
1H3-hIgG1-L6-hIL-2 (D20A/E95A/Y45A)	195	4	5

1H3-hIgG1-L6-hIL-2 (D20A/E95A/Y45K)	196	22	6
1H3-hIgG1-L6-hIL-2 (D20A/E95A/Y45S)	197	5	6
1H3-hIgG1-L6-hIL-2 (D20A/E95A/Y45R)	198	25	6
1H3-hIgG1-L6-hIL-2 (D20A/E95A/E61A)	199	10	6
1H3-hIgG1-L6-hIL-2 (D20A/E95A/E62A)	200	23	6
1H3-hIgG1-L6-hIL-2 (D20A/E95A/E62R)	201	25	17
1H3-hIgG1-L6-hIL-2 (D20A/E95A/E62K)	202	25	15
1H3-hIgG1-L6-hIL-2 (D20A/E95A/E62Y)	203	25	10
1H3-hIgG1-L6-hIL-2 (D20A/E95A/E68Y)	204	8	5
1H3-hIgG1-L6-hIL-2 (D20A/E95A/E68A)	205	5	8
1H3-hIgG1-L6-hIL-2 (D20A/E95A/E68L)	206	7	9
1H3-hIgG1-L6-hIL-2 (D20A/E95A/L72Y)	207	1	5
1H3-hIgG1-L6-hIL-2 (D20A/E95A/L72R)	208	12	9
1H3-hIgG1-L6-hIL-2 (D20A/E95A/L72A)	209	2	6
1H3-hIgG1-L6-hIL-2 (D20A/E95A/L72D)	210	21	6
1H3-hIgG1-L6-hIL-2 (D20A/E95A/L72H)	211	14	6
1H3-hIgG1-L6-hIL-2 (D20A/E95A/L72F)	212	2	6
1H3-hIgG1-L6-hIL-2 (D20A/E95A/F42K/Y45R)	214	21	5
1H3-hIgG1-L6-hIL-2 (D20A/R38E/C125A)	215	16	3
1H3-hIgG1-L6-hIL-2 (T3A/D20A/R38E)	216	18	2
1H3-hIgG1-L6-hIL-2 (T3A/D20A/R38E/C125A)	217	18	3
1H3-hIgG1-L6-hIL-2 (Δ 1- 3APT/D20A/R38E)	218	13	1
1H3-hIgG1-L6-hIL-2 (Δ 1- 3APT/D20A/R38E/C125A)	219	15	4
1H3-hIgG1-L6-hIL-2 (R38E/Q22A)	220	12	0
1H3-hIgG1-L6-hIL-2 (R38E/T123A)	221	12	0
1H3-hIgG1-L6-hIL-2 (R38E/I129A)	222	13	1
1H3-hIgG1-L6-hIL-2 (R38E/S130A)	223	12	0
1H3-hIgG1-L6-hIL-2 (R38E/Q126A)	224	13	1
1H3-hIgG1-L6-hIL-2 (R38E/Q126D)	225	15	4
1H3-hIgG1-L6-hIL-2 (R38E/Q126V)	226	14	1
1H3-hIgG1-L6-hIL-2 (R38E/Q22A/S130A)	227	13	1

Table 8. Fold change from rhIL-2 in a fixed concentration pSTAT5 screen on 1H3-hIgG1-L6-hIL-2 fusion proteins from Group 6

Variants	SEQ ID NO of hIL-2 variant	Fold change from hIL-2 (NK-92)	Fold change from hIL-2 (TF1+IL-2R β)
1H3-hIgG1-L6-hIL-2 (D20A/E61R)	230	25	4
1H3-hIgG1-L6-hIL-2 (D20A/E61N)	231	15	1
1H3-hIgG1-L6-hIL-2 (D20A/E61D)	232	11	0
1H3-hIgG1-L6-hIL-2 (D20A/E61Q)	233	16	2
1H3-hIgG1-L6-hIL-2 (D20A/E61G)	234	15	2
1H3-hIgG1-L6-hIL-2 (D20A/E61H)	235	15	2
1H3-hIgG1-L6-hIL-2 (D20A/E61I)	236	16	1
1H3-hIgG1-L6-hIL-2 (D20A/E61L)	237	16	1
1H3-hIgG1-L6-hIL-2 (D20A/E61K)	238	17	2
1H3-hIgG1-L6-hIL-2 (D20A/E61M)	239	15	2
1H3-hIgG1-L6-hIL-2 (D20A/E61F)	240	14	0
1H3-hIgG1-L6-hIL-2 (D20A/E61P)	241	15	1
1H3-hIgG1-L6-hIL-2 (D20A/E61S)	242	16	1
1H3-hIgG1-L6-hIL-2 (D20A/E61T)	243	16	2
1H3-hIgG1-L6-hIL-2 (D20A/E61W)	244	15	2
1H3-hIgG1-L6-hIL-2 (D20A/E61Y)	245	15	2
1H3-hIgG1-L6-hIL-2 (D20A/E61V)	246	17	3
1H3-hIgG1-L6-hIL-2 (D20A/F42N)	247	15	2
1H3-hIgG1-L6-hIL-2 (D20A/F42Q)	248	15	2
1H3-hIgG1-L6-hIL-2 (D20A/F42E)	249	16	1
1H3-hIgG1-L6-hIL-2 (D20A/F42G)	250	17	2
1H3-hIgG1-L6-hIL-2 (D20A/F42I)	251	17	2
1H3-hIgG1-L6-hIL-2 (D20A/F42L)	252	14	2

1H3-hIgG1-L6-hIL-2 (D20A/F42M)	253	15	2
1H3-hIgG1-L6-hIL-2 (D20A/F42P)	254	17	2
1H3-hIgG1-L6-hIL-2 (D20A/F42S)	255	15	2
1H3-hIgG1-L6-hIL-2 (D20A/F42T)	256	16	2
1H3-hIgG1-L6-hIL-2 (D20A/F42W)	257	16	2
1H3-hIgG1-L6-hIL-2 (D20A/F42Y)	258	17	2
1H3-hIgG1-L6-hIL-2 (D20A/F42V)	259	18	2
1H3-hIgG1-L6-hIL-2 (D20A/Y45A)	260	15	2
1H3-hIgG1-L6-hIL-2 (D20A/Y45N)	261	14	2
1H3-hIgG1-L6-hIL-2 (D20A/Y45D)	262	18	3
1H3-hIgG1-L6-hIL-2 (D20A/Y45Q)	263	17	3
1H3-hIgG1-L6-hIL-2 (D20A/Y45E)	264	18	3
1H3-hIgG1-L6-hIL-2 (D20A/Y45G)	265	18	2
1H3-hIgG1-L6-hIL-2 (D20A/Y45H)	266	16	2
1H3-hIgG1-L6-hIL-2 (D20A/Y45I)	267	13	2
1H3-hIgG1-L6-hIL-2 (D20A/Y45L)	268	13	2
1H3-hIgG1-L6-hIL-2 (D20A/Y45M)	269	16	3
1H3-hIgG1-L6-hIL-2 (D20A/Y45F)	270	13	2
1H3-hIgG1-L6-hIL-2 (D20A/Y45P)	271	25	4
1H3-hIgG1-L6-hIL-2 (D20A/Y45S)	272	14	3
1H3-hIgG1-L6-hIL-2 (D20A/Y45T)	273	24	3
1H3-hIgG1-L6-hIL-2 (D20A/Y45W)	274	19	3
1H3-hIgG1-L6-hIL-2 (D20A/Y45V)	275	21	3
1H3-hIgG1-L6-hIL-2 (I92D/F42N)	276	29	5
1H3-hIgG1-L6-hIL-2 (I92D/F42Q)	277	29	4
1H3-hIgG1-L6-hIL-2 (I92D/F42E)	278	30	5

1H3-hIgG1-L6-hIL-2 (I92D/F42G)	279	32	5
1H3-hIgG1-L6-hIL-2 (I92D/F42I)	280	31	4
1H3-hIgG1-L6-hIL-2 (I92D/F42L)	281	31	5
1H3-hIgG1-L6-hIL-2 (I92D/F42K)	282	26	4
1H3-hIgG1-L6-hIL-2 (I92D/F42M)	283	28	5
1H3-hIgG1-L6-hIL-2 (I92D/F42P)	284	29	4
1H3-hIgG1-L6-hIL-2 (I92D/F42S)	285	30	5
1H3-hIgG1-L6-hIL-2 (I92D/F42T)	286	28	3
1H3-hIgG1-L6-hIL-2 (I92D/F42W)	287	18	4
1H3-hIgG1-L6-hIL-2 (I92D/F42Y)	288	22	3
1H3-hIgG1-L6-hIL-2 (I92D/F42V)	289	30	3
1H3-hIgG1-L6-hIL-2 (I92D/Y45A)	290	11	3
1H3-hIgG1-L6-hIL-2 (I92D/Y45N)	291	4	3
1H3-hIgG1-L6-hIL-2 (I92D/Y45D)	292	29	5
1H3-hIgG1-L6-hIL-2 (I92D/Y45Q)	293	25	3
1H3-hIgG1-L6-hIL-2 (I92D/Y45E)	294	27	4
1H3-hIgG1-L6-hIL-2 (I92D/Y45G)	295	20	3
1H3-hIgG1-L6-hIL-2 (I92D/Y45H)	296	7	3
1H3-hIgG1-L6-hIL-2 (I92D/Y45I)	297	20	4
1H3-hIgG1-L6-hIL-2 (I92D/Y45L)	298	5	3
1H3-hIgG1-L6-hIL-2 (I92D/Y45M)	299	14	3
1H3-hIgG1-L6-hIL-2 (I92D/Y45F)	300	10	3
1H3-hIgG1-L6-hIL-2 (I92D/Y45P)	301	28	4
1H3-hIgG1-L6-hIL-2 (I92D/Y45S)	302	11	3
1H3-hIgG1-L6-hIL-2 (I92D/Y45T)	303	28	4
1H3-hIgG1-L6-hIL-2 (I92D/Y45W)	304	27	4
1H3-hIgG1-L6-hIL-2 (I92D/Y45V)	305	28	5
1H3-hIgG1-L6-hIL-2 (R38E/D20H)	306	17	5
1H3-hIgG1-L6-hIL-2 (R38E/D20S)	307	17	3
1H3-hIgG1-L6-hIL-2 (F42A/N88R)	308	18	3
1H3-hIgG1-L6-hIL-2 (F42A/N88D)	309	18	3
1H3-hIgG1-L6-hIL-2 (R38E/D84A)	310	18	1
1H3-hIgG1-L6-hIL-2 (R38E/D84N)	311	18	1
1H3-hIgG1-L6-hIL-2 (R38E/D84Q)	312	18	1
1H3-hIgG1-L6-hIL-2 (R38E/D84E)	313	16	1

1H3-hIgG1-L6-hIL-2 (R38E/D84G)	314	18	1
1H3-hIgG1-L6-hIL-2 (R38E/D84H)	315	19	2
1H3-hIgG1-L6-hIL-2 (R38E/D84I)	316	20	1
1H3-hIgG1-L6-hIL-2 (R38E/D84L)	317	19	1
1H3-hIgG1-L6-hIL-2 (R38E/D84M)	318	20	2
1H3-hIgG1-L6-hIL-2 (R38E/D84F)	319	20	2
1H3-hIgG1-L6-hIL-2 (R38E/D84P)	320	20	1
1H3-hIgG1-L6-hIL-2 (R38E/D84S)	321	21	1
1H3-hIgG1-L6-hIL-2 (R38E/D84T)	322	20	1
1H3-hIgG1-L6-hIL-2 (R38E/D84W)	323	21	1
1H3-hIgG1-L6-hIL-2 (R38E/D84Y)	324	21	1
1H3-hIgG1-L6-hIL-2 (R38E/D84V)	325	22	1
1H3-hIgG1-L6-hIL-2 (R38E/I92A)	326	22	1
1H3-hIgG1-L6-hIL-2 (R38E/I92R)	327	22	2
1H3-hIgG1-L6-hIL-2 (R38E/I92N)	328	22	1
1H3-hIgG1-L6-hIL-2 (R38E/I92Q)	329	22	1
1H3-hIgG1-L6-hIL-2 (R38E/I92E)	330	22	2
1H3-hIgG1-L6-hIL-2 (R38E/I92G)	331	22	1
1H3-hIgG1-L6-hIL-2 (R38E/I92H)	332	21	1
1H3-hIgG1-L6-hIL-2 (R38E/I92L)	333	17	1
1H3-hIgG1-L6-hIL-2 (R38E/I92K)	334	24	3
1H3-hIgG1-L6-hIL-2 (R38E/I92M)	335	20	1
1H3-hIgG1-L6-hIL-2 (R38E/I92F)	336	16	1
1H3-hIgG1-L6-hIL-2 (R38E/I92P)	337	24	5
1H3-hIgG1-L6-hIL-2 (R38E/I92S)	338	22	2
1H3-hIgG1-L6-hIL-2 (R38E/I92T)	339	22	1
1H3-hIgG1-L6-hIL-2 (R38E/I92W)	340	23	1
1H3-hIgG1-L6-hIL-2 (R38E/I92Y)	341	21	1
1H3-hIgG1-L6-hIL-2 (R38E/I92V)	342	21	1
1H3-hIgG1-L6-hIL-2 (R38E/H16E)	343	25	3
1H3-hIgG1-L6-hIL-2 (R38K/D20A)	344	17	3

Example 4: Testing for attenuation of IL-2 fusion proteins for each of the high-affinity and intermediate-affinity hIL-2 receptors with a cell-based potency pSTAT5 dose-titration screen

[0162] The attenuation of selected antibody-attenuated hIL-2 fusion proteins described in Example 2 (1H3-hIgG1-L6-hIL-2 fusion protein from Groups 2-6) were tested in pSTAT5 titration curves using the NK-92 and TF1+IL-2R β cell lines as described in Protocol D.

[0163] The gMFI of the Alexa Fluor 647 pSTAT5-positive signal was used to generate four parameter logistic curves and GraphPad Prism 7 software was then used to calculate EC₅₀ values. These values were compared to recombinant hIL-2 (rhIL-2) control as a measurement of attenuation. Tables 9-13 summarize the fold change in activity from rhIL-2 calculated using the gMFI of the Alexa Fluor 647 signal.

[0164] An increase in the fold change from rhIL-2 was indicative of the degree of attenuation of hIL-2 activity. Each antibody-attenuated hIL-2 fusion protein tested in the pSTAT5 titration curve was also assessed for agonistic activity and characterized as either full, partial, or no activity (inactive). Antibody-attenuated hIL-2 fusion protein dose-titration curves that reached the maximal gMFI level as the rhIL-2 were considered to be variants with full agonist activity. Partial agonist activity was calculated as described in Example 3. Inactive antibody-attenuated hIL-2 fusion proteins were classified as having less than 10% activity in comparison to rhIL-2. Some fold changes from rhIL-2 could not be accurately calculated (denoted as Not Calculated or “NC”) using the GraphPad Prism 7 software since a full four parameter logistic curve was not generated and accordingly these values are an estimate (annotated as ^a in Tables 9-13). However, these variants had greater than 10,000-fold attenuation from rhIL-2 on graphs (data not shown). This is denoted on Tables 9-13 as “>10,000 on graph; NC”.

[0165] Full titration pSTAT5 curves demonstrated similar findings as presented in Example 3 in which substitutions that modulated binding to both the alpha chain and the beta chain substantially attenuated IL-2 activity on the high affinity IL-2 receptor in comparison to single substitutions for binding to the alpha or beta chain only. The full titration pSTAT5 assay was additionally able to differentiate between variants with substitutions that caused inactivity versus highly attenuated variants. Finally, comparison of dose-titration curves illustrated more accurate of levels of attenuation over a fixed concentration assay.

Table 9. Fold change from rhIL-2 and agonistic activity on 1H3-hIgG1-L6-hIL-2 fusion proteins from Group 2

Variants	SEQ ID NO of hIL-2 variant	Fold change from rhIL-2 (NK-92)	Agonistic Activity (NK-92)	Fold change from rhIL-2 (TF1+IL-2R β)	Agonistic Activity (TF1+IL-2R β)
1H3-hIgG1-L6-hIL-2 (R38A)	46	2	Full	0	Full
1H3-hIgG1-L6-hIL-2 (R38D)	47	55	Full	1	Full
1H3-hIgG1-L6-hIL-2 (R38E)	48	99-136	Full	0	Full
1H3-hIgG1-L6-hIL-2 (F42R)	50	65	Full	0	Full
1H3-hIgG1-L6-hIL-2 (F42D)	52	193	Full	0	Full
1H3-hIgG1-L6-hIL-2 (K43A)	54	3 ^a	Full	0	Full
1H3-hIgG1-L6-hIL-2 (Y45R)	57	81 ^a	Full	0	Full
1H3-hIgG1-L6-hIL-2 (E61A)	61	3 ^a	Full	0	Full
1H3-hIgG1-L6-hIL-2 (E61R)	62	22 ^a	Full	0	Full
1H3-hIgG1-L6-hIL-2 (E61K)	63	14 ^a	Full	0	Full
1H3-hIgG1-L6-hIL-2 (E62A)	64	6 ^a	Full	0	Full
1H3-hIgG1-L6-hIL-2 (E62R)	65	>10,000	Partial, 80%	38	Full
1H3-hIgG1-L6-hIL-2 (E62K)	66	2048	Full	10	Full
1H3-hIgG1-L6-hIL-2 (E62Y)	67	18	Full	0	Full
1H3-hIgG1-L6-hIL-2 (E68K)	70	2 ^a	Full	0	Full
1H3-hIgG1-L6-hIL-2 (E68R)	71	3 ^a	Full	0	Full
1H3-hIgG1-L6-hIL-2 (L72R)	74	2 ^a	Full	1	Full
1H3-hIgG1-L6-hIL-2 (L72D)	76	4 ^a	Full	0	Full
1H3-hIgG1-L6-hIL-2 (L72H)	77	1 ^a	Partial, 80%	0	Full
1H3-hIgG1-L6-hIL-2 (R38D/E61R)	79	479	Partial, 80%	NT	NT
1H3-hIgG1-L6-hIL-2 (R38D/E61R/K43E)	80	598	Full	NT	NT
1H3-hIgG1-L6-hIL-2 (T3A/F42A/Y45A/L72G/C125A)	81	360 - 1426	Full	0	Full

NT = not tested

^a = Fold change is an estimate only since a full four parameter logistic curve was not reached

Table 10. Fold change from rhIL-2 and agonistic activity on 1H3-hIgG1-L6-hIL-2 fusion proteins variants from Group 3

Variants	SEQ ID NO of	Fold change from	Agonistic Activity (NK-92)	Fold change from	Agonistic Activity
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	hIL-2 variant	rhIL-2 (NK-92)		rhIL-2 (TF1+IL- 2Rβ)	(TF1+IL- 2Rβ)
1H3-hIgG1-L6-hIL-2 (H16E)	87	63	Full	63	Full
1H3-hIgG1-L6-hIL-2 (L19A)	88	0	Full	0	Full
1H3-hIgG1-L6-hIL-2 (D20I)	89	NT	NT	>10,000 on graph, NC ^a	Inactive
1H3-hIgG1-L6-hIL-2 (D20S)	90	28	Partial, 80%	277 ^a	Partial, 80%
1H3-hIgG1-L6-hIL-2 (D20H)	91	>10,000 ^a	Partial, 90%	2767 ^a	Partial, 50%
1H3-hIgG1-L6-hIL-2 (D20W)	93	NT	NT	>10,000 on graph, NC ^a	Inactive
1H3-hIgG1-L6-hIL-2 (D20Y)	94	>10,000 ^a	Partial, 50 - 70%	84 - 143 ^a	Partial, 80%
1H3-hIgG1-L6-hIL-2 (D20R)	95	NT	NT	>10,000 on graph, NC ^a	Inactive
1H3-hIgG1-L6-hIL-2 (D20F)	96	NT	NT	>10,000 on graph, NC ^a	Inactive
1H3-hIgG1-L6-hIL-2 (D84A)	98	NT	NT	14	Full
1H3-hIgG1-L6-hIL-2 (D84R)	99	16	Full	244 ^a	Partial, 70%
1H3-hIgG1-L6-hIL-2 (D84K)	100	14	Partial, 90%	195 ^a	Full
1H3-hIgG1-L6-hIL-2 (N88Y)	102	NT	NT	>10,000 on graph, NC ^a	Inactive
1H3-hIgG1-L6-hIL-2 (N88D)	103	21	Partial, 90%	130	Full
1H3-hIgG1-L6-hIL-2 (N88R)	104	5- 27	Partial, 80% - Full	289 - 556	Partial, 40%
1H3-hIgG1-L6-hIL-2 (N88E)	105	NT	NT	>10,000 on graph, NC ^a	Partial, 40%
1H3-hIgG1-L6-hIL-2 (N88F)	106	NT	NT	>10,000 on graph, NC ^a	Inactive

1H3-hIgG1-L6-hIL-2 (N88I)	107	NT	NT	>10,000 on graph, NC ^a	Inactive
1H3-hIgG1-L6-hIL-2 (I92Y)	109	NT	NT	1	Full
1H3-hIgG1-L6-hIL-2 (I92S)	110	NT	NT	8	Full
1H3-hIgG1-L6-hIL-2 (I92R)	112	NT	NT	31	Full
1H3-hIgG1-L6-hIL-2 (I92D)	113	8 - 20	Full	68 - 365 ^a	Partial, 70 - 90%
1H3-hIgG1-L6-hIL-2 (E95R)	116	NT	NT	5	Full
1H3-hIgG1-L6-hIL-2 (D20T)	92	8	Full	167 ^a	Partial, 80%
1H3-hIgG1-L6-hIL-2 (D20A)	31	21	Partial, 80%	117 ^a	Partial, 80%
1H3-hIgG1-L6-hIL-2 (D20Y/H16E)	94	52 ^a	Partial, 80%	2159 ^a	Partial, 30%
1H3-hIgG1-L6-hIL-2 (D20Y/H16A)	119	>10,000 ^a	Partial, 40%	30 ^a	Partial, 20%
1H3-hIgG1-L6-hIL-2 (D20Y/H16Y)	120	>10,000 ^a	Partial, 40%	343 ^a	Partial, 20%
1H3-hIgG1-L6-hIL-2 (D20Y/I92A)	121	>10,000 ^a	Partial, 20%	4 ^a	Partial, 10%
1H3-hIgG1-L6-hIL-2 (D20Y/I92S)	122	>10,000 ^a	Partial, 10%	12 ^a	Partial, 10%

NT = Not Tested; NC = Not Calculated by GraphPad Prism 7

^a = Fold change is an estimate only since a full four parameter logistic curve was not reached

Table 11. Fold change from rhIL-2 and agonistic activity on 1H3-hIgG1-L6-hIL-2 fusion proteins from Group 4

Variants	SEQ ID NO of hIL-2 variant	Fold change from rhIL-2 (NK-92)	Agonistic Activity (NK-92)	Fold change from rhIL-2 (TF1+IL-2Rβ)	Agonistic Activity (TF1+IL-2Rβ)
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (E15A)	82	184	Full	20	Full
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20I)	89	>10,000 ^a	Partial, 80%	>10,000 on graph, NC ^a	Inactive
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20S)	90	2403	Full	>10,000 on graph, NC ^a	Inactive
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20H)	91	>10,000 ^a	Partial, 80%	>10,000 on graph, NC ^a	Inactive
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20W)	93	>10,000 ^a	Partial, 60%	>10,000 on graph, NC ^a	Inactive
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20Y)	94	>10,000 ^a	Partial, 90%	>10,000 on graph, NC ^a	Inactive
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20R)	95	>10,000 ^a	Partial, 80%	>10,000 on graph, NC ^a	Inactive
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20F)	96	>10,000 ^a	Partial, 70%	>10,000 on graph, NC ^a	Inactive
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D84K)	100	>10,000	Full	>10,000 on graph, NC ^a	Inactive
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (S87A)	101	305	Full	44	Full
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (N88Y)	102	>10,000 ^a	Partial, 50%	>10,000 on graph, NC ^a	Inactive
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (N88D)	103	393	Full	>10,000 on graph, NC ^a	Inactive
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (N88R)	104	274	Full	>10,000 on graph, NC ^a	Inactive
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (N88E)	105	>10,000 ^a	Full	>10,000 on graph, NC ^a	Inactive

1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (N88F)	106	>10,000 ^a	Partial, 80%	>10,000 on graph, NC ^a	Inactive
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (N88I)	107	7780	Full	>10,000 on graph, NC ^a	Inactive
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (I92A)	108	26	Full	95	Full
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (E95A)	115	30	Full	16	Full
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (E95K)	117	792	Full	434 ^a	Partial, 60%

NC = Not Calculated by GraphPad Prism 7
^a = Fold change is an estimate only since a full four parameter logistic curve was not reached

Table 12. Fold change from rhIL-2 and agonistic activity on 1H3-hIgG1-L6-hIL-2 fusion proteins from Group 5

Variants	SEQ ID NO of hIL-2 variant	Fold change from rhIL-2 (NK-92)	Agonistic Activity (NK-92)	Fold change from rhIL-2 (TF1+IL-2Rβ)	Agonistic Activity (TF1+IL-2Rβ)
1H3-hIgG1-L6-hIL-2 (F42K/D20A)	129	>10,000 ^a	Partial, 30%	219 ^a	Partial, 50%
1H3-hIgG1-L6-hIL-2 (F42A/D20A)	130	>10,000 ^a	Partial, 70%	96 ^a	Partial, 70%
1H3-hIgG1-L6-hIL-2 (R38N/D20A)	134	4497	Partial, 70%	121 ^a	Partial, 70%
1H3-hIgG1-L6-hIL-2 (R38G/D20A)	135	2811	Partial, 70%	139 ^a	Partial, 70%
1H3-hIgG1-L6-hIL-2 (R38H/D20A)	136	1752	Partial, 80%	107 ^a	Partial, 70%
1H3-hIgG1-L6-hIL-2 (R38I/D20A)	137	658	Partial, 70%	107 ^a	Partial, 60%
1H3-hIgG1-L6-hIL-2 (R38L/D20A)	138	532	Partial, 80%	125 ^a	Partial, 70%
1H3-hIgG1-L6-hIL-2 (R38M/D20A)	139	786	Partial, 90%	85 ^a	Partial, 90%
1H3-hIgG1-L6-hIL-2 (R38F/D20A)	140	1072	Partial, 80%	124 ^a	Partial, 90%
1H3-hIgG1-L6-hIL-2 (R38P/D20A)	141	337	Partial, 70%	337 ^a	Partial, 80%
1H3-hIgG1-L6-hIL-2 (R38S/D20A)	142	571	Partial, 70%	571 ^a	Partial, 90%
1H3-hIgG1-L6-hIL-2 (R38V/D20A)	146	765	Partial, 70%	765 ^a	Partial, 90%
1H3-hIgG1-L6-hIL-2 (R38A/D20A)	147	619	Partial, 80%	70 ^a	Partial, 70%

1H3-hlgG1-L6-hIL-2 (R38Q/D20A)	148	4700	Partial, 80%	91 ^a	Partial, 70%
1H3-hlgG1-L6-hIL-2 (D20A/R38E)	149	>10,000 ^a	Partial, 60% - Full	409 ^a	Partial, 50%
1H3-hlgG1-L6-hIL-2 (R38D/D20A)	150	>10,000 ^a	Partial, 70%	172 ^a	Partial, 70%
1H3-hlgG1-L6-hIL-2 (K43E/D20A)	151	584	Partial, 90%	231 ^a	Partial, 70%
1H3-hlgG1-L6-hIL-2 (F42R/I92D)	159	801 ^a	Partial, 40%	52 ^a	Partial, 80%
1H3-hlgG1-L6-hIL-2 (F42H/I92D)	160	194	Full	801 ^a	Partial, 80%
1H3-hlgG1-L6-hIL-2 (F42A/I92D)	161	338 ^a	Partial, 70%	194 ^a	Full
1H3-hlgG1-L6-hIL-2 (R38D/I92D)	170	>10,000 ^a	Partial, 80%	338 ^a	Partial, 80%
1H3-hlgG1-L6-hIL-2 (R38E/I92D)	171	>10,000 ^a	Partial, 70%	51 ^a	Partial, 80%
1H3-hlgG1-L6-hIL-2 (R38Q/I92D)	172	561	Full	48 ^a	Partial, 90%
1H3-hlgG1-L6-hIL-2 (R38E/D84R)	175	>10,000 ^a	Partial, 60%	50 ^a	Partial, 80%
1H3-hlgG1-L6-hIL-2 (R38E/D84K)	176	>10,000 ^a	Partial, 40%	45 ^a	Partial, 80%
1H3-hlgG1-L6-hIL-2 (R38D/E61R/D20A)	179	>10,000 on graph, NC ^a	Partial, 40%	62 ^a	Partial, 70%
1H3-hlgG1-L6-hIL-2 (R38E/E61R/D20A)	180	>10,000 ^a	Partial, 90%	181 ^a	Partial, 60%
1H3-hlgG1-L6-hIL-2 (R38Q/E61R/D20A)	181	>10,000 ^a	Partial, 40%	115 ^a	Partial, 80%
1H3-hlgG1-L6-hIL-2 (R38A/E61R/D20A)	182	>10,000 ^a	Partial, 40%	130 ^a	Partial, 60%
1H3-hlgG1-L6-hIL-2 (D20A/E95A/R38A)	183	149 - 199	Partial, 70 - 80%	157 ^a	Partial, 70%
1H3-hlgG1-L6-hIL-2 (D20A/E95A/R38D)	184	>10,000	Partial, 60 - 70%	84 - 508 ^a	Full
1H3-hlgG1-L6-hIL-2 (D20A/E95A/R38E)	185	>10,000 ^a	Partial, 70 - 90%	188 - 427 ^a	Partial, 70% - Full
1H3-hlgG1-L6-hIL-2 (D20A/E95A/R38Q)	186	3725	Partial, 70%	124 - 413 ^a	Partial, 80% - Full
1H3-hlgG1-L6-hIL-2 (D20A/E95A/F42R)	187	>10,000 ^a	Partial, 70%	87 ^a	Partial, 60%
1H3-hlgG1-L6-hIL-2 (D20A/E95A/F42A)	188	3000 - 5718 ^a	Partial, 90%	45 - 244 ^a	Partial, 70% - Full
1H3-hlgG1-L6-hIL-2 (D20A/E95A/F42D)	189	>10,000 ^a	Partial, 10%	1451 ^a	Partial, 30%
1H3-hlgG1-L6-hIL-2 (D20A/E95A/F42H)	190	3579	Partial, 80%	411 ^a	Full

1H3-hlgG1-L6-hIL-2 (D20A/E95A/F42K)	191	>10,000 ^a	Partial, 50%	82 ^a	Partial, 60%
1H3-hlgG1-L6-hIL-2 (D20A/E95A/K43E)	193	386 – 553	Partial, 80 - 90%	46- 142 ^a	Partial, 50 - 80%
1H3-hlgG1-L6-hIL-2 (D20A/E95A/Y45A)	195	62	Partial, 90%	300 ^a	Partial, 70%
1H3-hlgG1-L6-hIL-2 (D20A/E95A/Y45K)	196	7951 ^a	Partial, 70%	205 ^a	Partial, 60%
1H3-hlgG1-L6-hIL-2 (D20A/E95A/Y45R)	198	>10,000 ^a	Partial, 80%	293 ^a	Partial, 60%
1H3-hlgG1-L6-hIL-2 (D20A/E95A/E61A)	199	367	Partial, 80%	195 ^a	Partial, 60%
1H3-hlgG1-L6-hIL-2 (D20A/E95A/E62A)	200	3265 ^a	Partial, 70%	230 ^a	Partial, 50%
1H3-hlgG1-L6-hIL-2 (D20A/E95A/E62R)	201	>10,000 ^a	Inactive, 5%	>10,000 on graph, NC ^a	Partial, 10%
1H3-hlgG1-L6-hIL-2 (D20A/E95A/E62K)	202	>10,000 ^a	Inactive, 10%	>10,000 on graph, NC ^a	Partial, 10%
1H3-hlgG1-L6-hIL-2 (D20A/E95A/E62Y)	203	>10,000 ^a	Partial, 70%	265 ^a	Partial, 40%
1H3-hlgG1-L6-hIL-2 (D20A/E95A/E68Y)	204	131	Partial, 80%	61 ^a	Partial, 50%
1H3-hlgG1-L6-hIL-2 (D20A/E95A/E68A)	205	45	Partial, 60%	620 ^a	Partial, 60%
1H3-hlgG1-L6-hIL-2 (D20A/E95A/E68L)	206	187	Partial, 80%	172 ^a	Partial, 40%
1H3-hlgG1-L6-hIL-2 (D20A/E95A/L72R)	208	1178	Full	499 ^a	Partial, 70%
1H3-hlgG1-L6-hIL-2 (D20A/E95A/L72D)	210	>10,000 ^a	Partial, 70%	456 - 504 ^a	Partial, 60 - 70%
1H3-hlgG1-L6-hIL-2 (D20A/E95A/L72H)	211	798	Partial, 70%	117 ^a	Partial, 70%
1H3-hlgG1-L6-hIL-2 (D20A/E95A/F42K/Y45R)	214	>10,000 ^a	Partial, 60 - 70%	155 185 ^a	Partial, 70%
1H3-hlgG1-L6-hIL-2 (F42K/Y45R/D20A/S87A)	213	840 ^a	Partial, 70%	155 ^a	Partial, 70%
1H3-hlgG1-L6-hIL-2 (D20A/R38E/C125A)	215	>10,000 on graph, NC ^a	Partial, 50%	183 - 584 ^a	Partial, 50 - 70%
hlgG1-L6-hIL-2 (T3A/D20A/R38E)	216	>10,000 ^a	Partial, 60 - 90%	77 - 484 ^a	Partial, 60%
1H3-hlgG1-L6-hIL-2 (T3A/D20A/R38E/C125A)	217	>10,000 ^a	Partial, 90%	218-512 ^a	Partial, 50 - 60%
1H3-hlgG1-L6-hIL-2 (Δ 1-3APT/D20A/R38E)	218	24 - 69	Full	6	Full

1H3-hIgG1-L6-hIL-2 (Δ1-3APT/D20A/R38E/C125A)	219	49 - 619	Partial, 30 - 70%	165 - 619 ^a	Partial, 40 - 50%
1H3-hIgG1-L6-hIL-2 (R38E/Q126D)	225	>10,000 on graph, NC ^a	Partial, 60%	>10,000 on graph, NC ^a	Partial, 40%
1H3-hIgG1-L6-hIL-2 (F42K/Y45R/Q126D)	228	>10,000 ^a	Partial, 60%	226 ^a	Partial, 50%
1H3-hIgG1-L6-hIL-2 (D20A/E95A/Q126D)	229	>10,000 on graph, NC ^a	Inactive	>10,000 on graph, NC ^a	Inactive

NC = Not Calculated by GraphPad Prism 7
^a = Fold change is an estimate only since a full four parameter logistic curve was not reached

Table 13. Fold change from rhIL-2 and agonistic activity on 1H3-hIgG1-L6-hIL-2 fusion proteins from Group 6

Variants	SEQ ID NO of hIL-2 variant	Fold change from rhIL-2 (NK-92)	Agonistic Activity (NK-92)	Fold change from rhIL-2 (TF1+IL-2Rβ)	Agonistic Activity (TF1+IL-2Rβ)
1H3-hIgG1-L6-hIL-2 (D20A/F42N)	247	>10,000 ^a	Partial, 60%	>10,000 on graph, NC ^a	Partial, 80%
1H3-hIgG1-L6-hIL-2 (D20A/F42Q)	248	>10,000 ^a	Partial, 50%	16 ^a	Partial, 70%
1H3-hIgG1-L6-hIL-2 (D20A/F42P)	254	>10,000 ^a	Partial, 60%	13 ^a	Partial, 80%
1H3-hIgG1-L6-hIL-2 (D20A/F42S)	255	>10,000 ^a	Partial, 60%	17 ^a	Partial, 40%
1H3-hIgG1-L6-hIL-2 (D20A/Y45E)	264	4717	Partial, 80%	32 ^a	Partial, 50%
1H3-hIgG1-L6-hIL-2 (I92D/F42Q)	277	>10,000 ^a	Partial, 50%	24 ^a	Partial, 70%
1H3-hIgG1-L6-hIL-2 (I92D/F42I)	280	>10,000 ^a	Partial, 30%	117 ^a	Partial, 20%
1H3-hIgG1-L6-hIL-2 (I92D/F42K)	282	>10,000 ^a	Partial, 50%	58 ^a	Partial, 90%

1H3-hlgG1-L6-hIL-2 (I92D/F42T)	286	>10,000 ^a	Partial, 60%	>10,000 on graph, NC ^a	Partial, 80%
1H3-hlgG1-L6-hIL-2 (R38E/D20S)	307	>10,000 ^a	Partial, 50%	25 ^a	Partial, 40%
1H3-hlgG1-L6-hIL-2 (F42A/N88R)	308	>10,000 ^a	Partial, 70%	34 ^a	Partial, 30%

NC = Not Calculated by GraphPad Prism
^a = Fold change is an estimate only since a full four parameter logistic curve was not reached

Example 5: Testing for attenuation for the high-affinity and intermediate-affinity hIL-2 receptor with cell-based proliferation assays

[0166] The attenuation of IL-2 activity of antibody-attenuated hIL-2 fusion proteins from Groups 1-6 in Example 2 (2D12-mIgG1-D265A-L6-hIL-2, 2D12-hIgG1-L6-hIL-2, and 1H3-hIgG1-L6-hIL-2 fusion proteins) were tested in proliferation assays in both the NK-92 and TF1+IL-2R β cell lines as described in Protocol E. The results of the assays are provided in Tables 14-19.

[0167] Selected 1H3-hIgG1-L6-hIL-2 fusion proteins with substantial attenuation in the pSTAT5 titration curves from Example 4 were tested in this cell-based proliferation assay. pSTAT5 is a downstream read-out of IL-2 activity and assays require only 10 minutes of stimulation which may be a small snapshot of IL-2 dependent activity. For proliferation assays, cells were incubated with 2D12-mIgG1-D265A-L6-hIL-2, 2D12-hIgG1-L6-hIL-2, 1H3-hIgG1-L6-hIL-2 fusion proteins, or recombinant hIL-2 control for 3-4 days, providing a more physiological relevant read-out of IL-2 dependent activity *in vivo*. Other 2D12-mIgG1-D265A-L6-hIL-2 and 2D12-hIgG1-L6-hIL-2 fusion proteins that were generated but not tested in a pSTAT5 assay were assayed for IL-2 dependent activity using this proliferation assay.

[0168] Similar to cell-based pSTAT5 dose-titration experiments, the calculated EC₅₀ as determined from relative luminescence units (RLU) instead of gMFI and analysis of the results were performed identically to Example 4 once EC₅₀ was calculated. Similar to results identified in Example 4, proliferation curves demonstrated that some substitutions that modulated binding to both the alpha chain and beta chain substantially attenuated IL-2 activity on the high affinity receptor in comparison to single substitutions for binding to the alpha or beta chain only. These selected 1H3-hIgG1-L6-hIL-2 fusion proteins were also tested for proliferation on the TF1+IL-2R β cell line and demonstrated that some of these same substitutions substantially attenuated IL-2 activity on the intermediate affinity receptor.

Table 14. Fold change from rhIL-2 and agonistic activity on 2D12-mIgG1-D265A-L6-hIL-2 or 2D12-hIgG1-L6-hIL-2 fusion proteins from Group 1 in a cell-based proliferation assay

Variants	SEQ ID NO of hIL-2 variant	Fold change from rhIL-2 (NK-92)	Agonistic Activity (NK-92)	Fold change from rhIL-2 (TF1+IL- 2Rβ)	Agonistic Activity (TF1+IL-2Rβ)
2D12-mIgG1-D265A-L6-hIL-2 (F42K)	1	2	Full	0	Full
2D12-mIgG1-D265A-L6-hIL-2 (Y45R)	60	3	Full	2	Full
2D12-hIgG1-L6-hIL-2 (V69A)	2	0	Full	0	Full
2D12-hIgG1-L6-hIL-2 (V69E)	3	13	Partial, 60%	83	Full
2D12-hIgG1-L6-hIL-2 (V69H)	6	41	Partial, 60%	544	Full
2D12-hIgG1-L6-hIL-2 (V69K)	8	>10,000 on graph, NC ^a	Inactive	3033	Partial, 40%
2D12-hIgG1-L6-hIL-2 (V69L)	9	1	Full	1	Full
2D12-hIgG1-L6-hIL-2 (V69F)	4	0	Full	1	Full
2D12-hIgG1-L6-hIL-2 (V69G)	5	108	Full	396	Full
2D12-hIgG1-L6-hIL-2 (V69I)	7	1	Full	1	Full
2D12-hIgG1-L6-hIL-2 (V69M)	10	2	Full	3	Full
2D12-hIgG1-L6-hIL-2 (V69Q)	11	7	Full	16	Full
2D12-mIgG1-D265A-L6-hIL-2 (V69R)	581	2392	Partial, 70%	2973	Partial, 50%
2D12-hIgG1-L6-hIL-2 (V69S)	12	6	Full	13	Full
2D12-hIgG1-L6-hIL-2 (V69T)	13	3	Full	3	Full
2D12-hIgG1-L6-hIL-2 (V69W)	14	0	Full	1	Full
2D12-hIgG1-L6-hIL-2 (V69Y)	15	1	Full	1	Full

2D12-mIgG1-D265A-L6-hIL-2 (D20A)	31	1	Full	>10,000 ^a	Full
2D12-mIgG1-D265A-L6-hIL-2 (D20N)	32	0	Full	>10,000 ^a	Full
2D12-mIgG1-D265A-L6-hIL-2 (D20K)	33	4	Full	>10,000 on graph, NC ^a	Inactive
2D12-mIgG1-D265A-L6-hIL-2 (N88A)	34	0	Full	2289	Full
2D12-mIgG1-D265A-L6-hIL-2 (N88G)	35	0	Full	2978	Full
2D12-mIgG1-D265A-L6-hIL-2 (N88H)	36	1-3	Full	>10,000 on graph, NC ^a	Inactive
2D12-mIgG1-D265A-L6-hIL-2 (N88K)	37	564-9557	Partial, 40%	>10,000 on graph, NC ^a	Inactive
2D12-mIgG1-D265A-L6-hIL-2 (Q126L)	375	0-12	Full	118	Full
2D12-mIgG1-D265A-L6-hIL-2 (Q126E)	376	0-3	Full	40	Full
2D12-mIgG1-D265A-L6-hIL-2 (F42K/F44K)	16	44	Full	>10,000 on graph, NC ^a	Inactive
2D12-mIgG1-D265A-L6-hIL-2 (F42K/Y45R)	17	1-2	Full	0-3	Full
2D12-mIgG1-D265A-L6-hIL-2 (F42K/V69R)	18	1500	Partial, 80%	841	Partial, 80%
2D12-mIgG1-D265A-L6-hIL-2 (Y45R/V69R)	19	1	Full	3	Full
2D12-mIgG1-D265A-L6-hIL-2 (D20A/D84A)	38	1	Full	>10,000 on graph, NC ^a	Inactive
2D12-mIgG1-D265A-L6-hIL-2 (D20A/E15A)	39	0	Full	>10,000 on graph, NC ^a	Partial, 40%
2D12-mIgG1-D265A-L6-hIL-2 (D20A/E95A)	40	0	Full	>10,000 ^a	Full

2D12-mIgG1-D265A-L6-hIL-2 (D20A/N88A)	41	6	Partial, 60%	>10,000 on graph, NC ^a	Inactive
2D12-mIgG1-D265A-L6-hIL-2 (D20A/S87A)	42	0	Full	>10,000 ^a	Full
2D12-mIgG1-D265A-L6-hIL-2 (D84A/N88A)	43	0	Full	>10,000 on graph, NC ^a	Inactive
2D12-mIgG1-D265A-L6-hIL-2 (E15A/N88A)	44	0	Full	4201	Partial, 80%
2D12-mIgG1-D265A-L6-hIL-2 (S87A/N88A)	45	0	Full	1521	Full
2D12-mIgG1-D265A-L6-hIL-2 (F42K/F44K/Y45R)	20	NT	NT	0	Full
2D12-mIgG1-D265A-L6-hIL-2 (F42A/Y45A/L72G)	574	0-1	Full	0-3	Full
2D12-mIgG1-D265A-L6-hIL-2 (R38A/F42K/Y45R)	21	1	Full	0	Full
2D12-mIgG1-D265A-L6-hIL-2 (R38E/F42K/Y45R)	22	1-3	Full	0	Full
2D12-mIgG1-D265A-L6-hIL-2 (K43E/F42K/Y45R)	23	0	Full	3	Full
2D12-mIgG1-D265A-L6-hIL-2 (K43T/F42K/Y45R)	24	0	Full	3	Full
2D12-mIgG1-D265A-L6-hIL-2 (F42K/Y45R/E62A)	25	1	Full	0-3	Full
2D12-mIgG1-D265A-L6-hIL-2 (P65R/F42K/Y45R)	26	1	Full	0-2	Full
2D12-mIgG1-D265A-L6-hIL-2 (P65S/F42K/Y45R)	27	1	Full	0-2	Full
2D12-mIgG1-D265A-L6-hIL-2 (V69A/F42K/Y45R)	28	1	Full	0-4	Full
2D12-mIgG1-D265A-L6-hIL-2 (V69D/F42K/Y45R)	29	1	Full	0-5	Full

2D12-mIgG1-D265A-L6-hIL-2 (V69R/F42K/Y45R)	30	1-4	Full	0-6	Full
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NT = Not Tested
NC = Not Calculated by GraphPad Prism 7
a = Fold change is an estimate only since a full four parameter logistic curve was not reached

Table 15. Fold change from rhIL-2 and agonistic activity on 1H3-hIgG1-L6-hIL-2 fusion proteins from Group 2 in a cell-based proliferation assay

Variants	SEQ ID NO of hIL-2 variant	Fold change from rhIL-2 (NK-92)	Agonistic Activity (NK-92)	Fold change from rhIL-2 (TF1+IL- 2Rβ)	Agonistic Activity (TF1+IL-2Rβ)
1H3-hIgG1-L6-hIL-2 (R38A)	46	0	Full	1	Full
1H3-hIgG1-L6-hIL-2 (R38D)	47	3	Full	0	Full
1H3-hIgG1-L6-hIL-2 (R38E)	48	7	Full	1 ^a	Full
1H3-hIgG1-L6-hIL-2 (F42R)	50	6	Full	0 ^a	Full
1H3-hIgG1-L6-hIL-2 (F42D)	52	10	Full	2	Full
1H3-hIgG1-L6-hIL-2 (K43A)	54	1 ^a	Full	2	Full
1H3-hIgG1-L6-hIL-2 (Y45R)	60	4	Full	0 ^a	Full
1H3-hIgG1-L6-hIL-2 (E61A)	61	0 ^a	Full	1	Full
1H3-hIgG1-L6-hIL-2 (E61R)	62	1	Full	1	Full
1H3-hIgG1-L6-hIL-2 (E61K)	63	1	Full	1	Full
1H3-hIgG1-L6-hIL-2 (E62A)	64	1	Full	1	Full
1H3-hIgG1-L6-hIL-2 (E62R)	65	>10,000 on graph, NC ^a	Inactive	209	Partial, 60%
1H3-hIgG1-L6-hIL-2 (E62K)	66	>10,000 ^a	Partial, 40 - 70%	67 - 99	Partial, 60%
1H3-hIgG1-L6-hIL-2 (E62Y)	67	1	Full	1	Full
1H3-hIgG1-L6-hIL-2 (E68K)	70	0	Full	1	Full

1H3-hlgG1-L6-hIL-2 (E68R)	71	1	Full	1	Full
1H3-hlgG1-L6-hIL-2 (L72R)	74	3	Full	3	Full
1H3-hlgG1-L6-hIL-2 (L72D)	76	2	Full	0	Full
1H3-hlgG1-L6-hIL-2 (L72H)	77	1	Full	1	Full
1H3-hlgG1-L6-hIL-2 (R38D/E61R)	79	36	Full	2	Full
1H3-hlgG1-L6-hIL-2 (R38D/E61R/K43E)	80	27	Full	1	Full
1H3-hlgG1-L6-hIL-2 (T3A/F42A/Y45A/L72G/C125A)	81	142	Full	1 - 2	Partial, 40% - Full

NT = Not Tested
NC = Not Calculated by GraphPad Prism 7
^a = Fold change is an estimate only since a full four parameter logistic curve was not reached

Table 16. Fold change from rhIL-2 and agonistic activity on 1H3-hlgG1-L6-hIL-2 fusion proteins from Group 3 in a cell-based proliferation assay

Variants	SEQ ID NO of hIL-2 variant	Fold change from rhIL-2 (NK-92)	Agonistic Activity (NK-92)	Fold change from rhIL-2 (TF1+IL-2Rβ)	Agonistic Activity (TF1+IL-2Rβ)
1H3-hlgG1-L6-hIL-2 (H16E)	87	0	Full	34	Full
1H3-hlgG1-L6-hIL-2 (L19A)	88	NT	NT	1	Full
1H3-hlgG1-L6-hIL-2 (D20I)	89	NT	NT	8 ^a	Partial, 50%
1H3-hlgG1-L6-hIL-2 (D20S)	90	1	Full	201 - 304	Partial, 80% - Full
1H3-hlgG1-L6-hIL-2 (D20H)	91	239	Full	986 - 6461 ^a	Partial, 50 - 70%
1H3-hlgG1-L6-hIL-2 (D20W)	93	NT	NT	>10,000 on graph, NC ^a	Inactive
1H3-hlgG1-L6-hIL-2 (D20Y)	94	880 - 2097 ^a	Full	383	Full
1H3-hlgG1-L6-hIL-2 (D20R)	95	NT	NT	262 - 275	Full

1H3-hIgG1-L6-hIL-2 (D20F)	96	NT	NT	NT	>10,000 on graph, NC ^a	Inactive
1H3-hIgG1-L6-hIL-2 (D84A)	98	NT	NT	NT	21	Full
1H3-hIgG1-L6-hIL-2 (D84R)	99	9	Full	Full	269 - 455	Partial, 80 - 90%
1H3-hIgG1-L6-hIL-2 (D84K)	100	4	Full	Full	354 - 385	Partial, 70% - Full
1H3-hIgG1-L6-hIL-2 (N88Y)	102	NT	NT	NT	>10,000 on graph, NC ^a	Inactive
1H3-hIgG1-L6-hIL-2 (N88D)	103	0	Full	Full	115 - 137	Partial, 70% - Full
1H3-hIgG1-L6-hIL-2 (N88R)	104	1 - 5	Partial, 80% - Full	Partial, 80%	959	Partial, 80%
1H3-hIgG1-L6-hIL-2 (N88E)	105	NT	NT	NT	1162	Partial, 50%
1H3-hIgG1-L6-hIL-2 (N88F)	106	NT	NT	NT	>10,000 on graph, NC ^a	Inactive
1H3-hIgG1-L6-hIL-2 (N88I)	107	NT	NT	NT	>10,000 on graph, NC ^a	Inactive
1H3-hIgG1-L6-hIL-2 (I92Y)	109	NT	NT	NT	1	Full
1H3-hIgG1-L6-hIL-2 (I92S)	110	NT	NT	NT	10	Full
1H3-hIgG1-L6-hIL-2 (I92R)	112	NT	NT	NT	13	Full
1H3-hIgG1-L6-hIL-2 (I92D)	113	15 - 20	Full	Full	609 - 1006	Partial, 90% - Full
1H3-hIgG1-L6-hIL-2 (E95R)	116	NT	NT	NT	8	Full
1H3-hIgG1-L6-hIL-2 (D20T)	92	2	Full	Full	124 - 149	Full
1H3-hIgG1-L6-hIL-2 (D20Y/HI16E)	118	5	Full	Full	8076 ^a	Partial, 80%

NT = Not Tested

NC = Not Calculated by GraphPad Prism 7

^a = Fold change is an estimate only since a full four parameter logistic curve was not reached

Table 17. Fold change from rhIL-2 and agonistic activity on 1H3-hIgG1-L6-hIL-2 fusion proteins from Group 4 in a cell-based proliferation assay

Variants	SEQ ID NO of hIL-2 variant	Fold change from rhIL-2 (NK-92)	Agonistic Activity (NK-92)	Fold change from rhIL-2 (TF1+IL-2Rβ)	Agonistic Activity (TF1+IL-2Rβ)
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (E15A)	82	14	Partial, 90%	13	Partial, 70%
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20S)	90	127	Full	8709 ^a	Partial, 50%
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20W)	93	>10,000 on graph, NC ^a	Inactive	>10,000 on graph, NC ^a	Inactive
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D20Y)	94	>10,000 on graph, NC ^a	Partial, 50%	>10,000 on graph, NC ^a	Inactive
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (D84K)	100	783	Partial, 90%	2051 ^a	Partial, 30%
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (S87A)	101	19	Partial, 90%	20	Partial, 90%
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (N88D)	103	50	Full	3284 ^a	Partial, 90%
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (N88R)	104	42	Full	6864 ^a	Partial, 50%
1H3-hIgG1-L6-hCD25(1-164)-L20-hIL-2 (E95K)	117	51	Full	164	Partial, 80%

NC = Not Calculated by GraphPad Prism 7
^a = Fold change is an estimate only since a full four parameter logistic curve was not reached

Table 18. Fold change from rhIL-2 and agonistic activity on 1H3-hIgG1-L6-hIL-2 fusion proteins from Group 5 in a cell-based proliferation assay

Variants	SEQ ID NO of hIL-2 variant	Fold change from rhIL-2 (NK-92)	Agonistic Activity (NK-92)	Fold change from rhIL-2 (TF1+IL-2Rβ)	Agonistic Activity (TF1+IL-2Rβ)

1H3-hlgG1-L6-hIL-2 (F42K/D20A)	129	>10,000 on graph, NC ^a	Partial, 20%	3060 ^a	Full
1H3-hlgG1-L6-hIL-2 (F42A/D20A)	130	>10,000 on graph, NC ^a	Full	2081 ^a	Full
1H3-hlgG1-L6-hIL-2 (R38P/D20A)	141	86	Full	761	Full
1H3-hlgG1-L6-hIL-2 (R38S/D20A)	142	140	Full	662	Full
1H3-hlgG1-L6-hIL-2 (R38V/D20A)	146	11	Full	843	Full
1H3-hlgG1-L6-hIL-2 (D20A/R38E)	149	1183 - 2016	Partial, 70% - Full	>10,000 ^a	Partial, 80% - Full
1H3-hlgG1-L6-hIL-2 (R38D/D20A)	150	2262 ^a	Full	680	Full
1H3-hlgG1-L6-hIL-2 (F42R/I92D)	159	>10,000 on graph, NC ^a	Partial, 30%	1210	Full
1H3-hlgG1-L6-hIL-2 (F42H/I92D)	160	288 ^a	Full	242 ^a	Full
1H3-hlgG1-L6-hIL-2 (F42A/I92D)	161	>10,000 on graph, NC ^a	Partial, 60%	2275	Partial, 80%
1H3-hlgG1-L6-hIL-2 (R38D/I92D)	170	746 ^a	Partial, 90%	172	Full
1H3-hlgG1-L6-hIL-2 (R38E/I92D)	171	1611 ^a	Full	116	Full
1H3-hlgG1-L6-hIL-2 (R38E/D84R)	175	>10,000 on graph, NC ^a	Full	147	Full
1H3-hlgG1-L6-hIL-2 (R38E/D84K)	176	>10,000 on graph, NC ^a	Partial, 70%	315	Full
1H3-hlgG1-L6-hIL-2 (R38D/E61R/D20A)	179	>10,000 on graph, NC ^a	Partial, 50%	984	Full
1H3-hlgG1-L6-hIL-2 (R38E/E61R/D20A)	180	>10,000 on graph, NC ^a	Full	417	Full
1H3-hlgG1-L6-hIL-2 (R38Q/E61R/D20A)	181	>10,000 on graph, NC ^a	Partial, 80%	803	Full
1H3-hlgG1-L6-hIL-2 (R38A/E61R/D20A)	182	>10,000 on graph, NC ^a	Partial, 60%	1031	Full
1H3-hlgG1-L6-hIL-2 (D20A/E95A/R38A)	183	42	Partial, 70%	537	Partial, 80%
1H3-hlgG1-L6-hIL-2 (D20A/E95A/R38D)	184	5315 ^a	Partial, 50%	492	Partial, 80%

1H3-hlgG1-L6-hIL-2 (D20A/E95A/R38E)	185	>10,000 on graph, NC ^a	Full	439	Partial, 90%
1H3-hlgG1-L6-hIL-2 (D20A/E95A/R38Q)	186	572	Full	859	Partial, 80%
1H3-hlgG1-L6-hIL-2 (D20A/E95A/F42R)	187	2096	Partial, 70%	356	Partial, 70%
1H3-hlgG1-L6-hIL-2 (D20A/E95A/F42A)	188	369	Partial, 70%	73	Partial, 90%
1H3-hlgG1-L6-hIL-2 (D20A/E95A/F42D)	189	>10,000 on graph, NC ^a	Inactive	>10,000 on graph, NC ^a	Inactive
1H3-hlgG1-L6-hIL-2 (D20A/E95A/F42H)	190	641	Partial, 90%	320	Full
1H3-hlgG1-L6-hIL-2 (D20A/E95A/F42K)	191	>10,000 on graph, NC ^a	Inactive	272	Partial, 80%
1H3-hlgG1-L6-hIL-2 (D20A/E95A/K43E)	193	80	Partial, 90%	1876 ^a	Partial, 70%
1H3-hlgG1-L6-hIL-2 (D20A/E95A/Y45A)	195	25	Full	82	Partial, 90%
1H3-hlgG1-L6-hIL-2 (D20A/E95A/Y45K)	196	>10,000 on graph, NC ^a	Partial, 20%	383	Partial, 60%
1H3-hlgG1-L6-hIL-2 (D20A/E95A/Y45R)	198	>10,000 on graph, NC ^a	Inactive	57	Partial, 50%
1H3-hlgG1-L6-hIL-2 (D20A/E95A/E61A)	199	306 ^a	Partial, 80%	702	Partial, 80%
1H3-hlgG1-L6-hIL-2 (D20A/E95A/E62A)	200	>10,000 on graph, NC ^a	Partial, 20%	661	Partial, 60%
1H3-hlgG1-L6-hIL-2 (D20A/E95A/E62R)	201	>10,000 on graph, NC ^a	Inactive	>10,000 on graph, NC ^a	Inactive
1H3-hlgG1-L6-hIL-2 (D20A/E95A/E62K)	202	>10,000 on graph, NC ^a	Inactive	>10,000 on graph, NC ^a	Inactive
1H3-hlgG1-L6-hIL-2 (D20A/E95A/E62Y)	203	721	Partial, 40%	982 ^a	Partial, 30%
1H3-hlgG1-L6-hIL-2 (D20A/E95A/E68Y)	204	11	Full	469	Full
1H3-hlgG1-L6-hIL-2 (D20A/E95A/E68A)	205	6	Partial, 50%	535	Partial, 80%
1H3-hlgG1-L6-hIL-2 (D20A/E95A/E68L)	206	15	Full	972	Partial, 60%
1H3-hlgG1-L6-hIL-2 (D20A/E95A/L72R)	208	655 ^a	Partial, 50%	316	Partial, 40%
1H3-hlgG1-L6-hIL-2 (D20A/E95A/L72D)	210	5415	Inactive	125	Partial, 90%
1H3-hlgG1-L6-hIL-2 (D20A/E95A/L72H)	211	583 ^a	Partial, 60%	135	Partial, 80%

1H3-hlgG1-L6-hIL-2 (D20A/E95A/F42K/Y45R)	214	>10,000 on graph, NC ^a	Inactive	58 - 209	Partial, 40 - 80%
1H3-hlgG1-L6-hIL-2 (F42K/Y45R/D20A/S87A)	213	123	Full	0	Full
1H3-hlgG1-L6-hIL-2 (D20A/R38E/C125A)	215	>10,000 ^a	Partial, 30 - 90%	2102 ^a	Partial, 80%
1H3-hlgG1-L6-hIL-2 (T3A/D20A/R38E)	216	2338 - 5870	Partial, 80% - Full	353 - 571	Full
1H3-hlgG1-L6-hIL-2 (T3A/D20A/R38E/C125A)	217	>10,000 ^a	Full	1086 ^a	Partial, 80% - Full
1H3-hlgG1-L6-hIL-2 (Δ1-3APT/D20A/R38E)	218	4 - 16	Full	32	Partial, 90%
1H3-hlgG1-L6-hIL-2 (Δ1- 3APT/D20A/R38E/C125A)	219	>10,000 ^a	Inactive - Partial, 50%	993 ^a	Partial, 60%
1H3-hlgG1-L6-hIL-2 (F42K/Y45R/Q126D)	228	>10,000 ^a	Partial, 50%	597	Partial, 80%
1H3-hlgG1-L6-hIL-2 (D20A/E95A/Q126D)	229	106 ^a	Inactive	>10,000 on graph, NC ^a	Inactive

NC = Not Calculated by GraphPad Prism 7
^a = Fold change is an estimate only since a full four parameter logistic curve was not reached

Table 19. Fold change from rhIL-2 and agonistic activity on 1H3-hlgG1-L6-hIL-2 fusion proteins from Group 6 in a cell-based proliferation assay

Variants	SEQ ID NO of hIL-2 variant	Fold change from rhIL-2 (NK-92)	Agonistic Activity (NK-92)	Fold change from rhIL-2 (TF1+IL- 2Rβ)	Agonistic Activity (TF1+IL-2Rβ)
1H3-hlgG1-L6-hIL-2 (D20A/E61R)	230	3950 ^a	Partial, 10%	278	Partial, 50%
1H3-hlgG1-L6-hIL-2 (D20A/F42N)	247	>10,000 ^a	Partial, 50%	662	Partial, 80%
1H3-hlgG1-L6-hIL-2 (D20A/F42Q)	248	>10,000 on graph, NC ^a	Partial, 30%	630	Partial, 80%
1H3-hlgG1-L6-hIL-2 (D20A/F42I)	251	1307 ^a	Partial, 20%	494	Partial, 60%
1H3-hlgG1-L6-hIL-2 (D20A/F42L)	252	68	Full	533	Partial, 60%
1H3-hlgG1-L6-hIL-2 (D20A/F42M)	253	53	Full	370	Partial, 50%

1H3-hlgG1-L6-hIL-2 (D20A/F42P)	254	9374 ^a	Partial, 80%	702	Partial, 80%
1H3-hlgG1-L6-hIL-2 (D20A/F42S)	255	1286	Partial, 70%	687	Partial, 70%
1H3-hlgG1-L6-hIL-2 (D20A/F42T)	256	1474 ^a	Partial, 10%	622	Partial, 80%
1H3-hlgG1-L6-hIL-2 (D20A/F42W)	257	414 ^a	Partial, 70%	400	Partial, 70%
1H3-hlgG1-L6-hIL-2 (D20A/F42Y)	258	322	Partial, 70%	545	Partial, 70%
1H3-hlgG1-L6-hIL-2 (D20A, F42V)	259	5796 ^a	Partial, 30%	579	Partial, 80%
1H3-hlgG1-L6-hIL-2 (D20A/Y45A)	260	61	Partial, 80%	554	Partial, 80%
1H3-hlgG1-L6-hIL-2 (D20A/Y45N)	261	31	Full	390	Partial, 70%
1H3-hlgG1-L6-hIL-2 (D20A/Y45D)	262	363	Partial, 60%	729	Partial, 70%
1H3-hlgG1-L6-hIL-2 (D20A/Y45Q)	263	730 ^a	Partial, 70%	348	Partial, 70%
1H3-hlgG1-L6-hIL-2 (D20A/Y45E)	264	1414 ^a	Partial, 60%	486	Partial, 70%
1H3-hlgG1-L6-hIL-2 (D20A/Y45G)	265	613 ^a	Partial, 80%	392	Partial, 60%
1H3-hlgG1-L6-hIL-2 (D20A/Y45H)	266	420 ^a	Partial, 70%	427	Partial, 60%
1H3-hlgG1-L6-hIL-2 (D20A/Y45I)	267	39	Partial, 70%	137	Partial, 30%
1H3-hlgG1-L6-hIL-2 (D20A/Y45L)	268	11	Full	426	Partial, 70%
1H3-hlgG1-L6-hIL-2 (D20A/Y45M)	269	107	Full	449	Partial, 60%
1H3-hlgG1-L6-hIL-2 (D20A/Y45F)	270	25	Partial, 90%	272	Partial, 50%
1H3-hlgG1-L6-hIL-2 (D20A/Y45P)	271	577 ^a	Full	710	Full
1H3-hlgG1-L6-hIL-2 (I92D/F42Q)	277	7227 ^a	Partial, 30%	872	Full
1H3-hlgG1-L6-hIL-2 (I92D/F42I)	280	4587 ^a	Partial, 10%	3644 ^a	Full
1H3-hlgG1-L6-hIL-2 (I92D/F42K)	282	>10,000 ^a	Partial, 20%	848 ^a	Full
1H3-hlgG1-L6-hIL-2 (I92D/F42T)	286	>10,000 ^a	Partial, 40%	1068 ^a	Full
1H3-hlgG1-L6-hIL-2 (I92D/F42W)	287	405 ^a	Full	3954 ^a	Full
1H3-hlgG1-L6-hIL-2 (I92D/F42Y)	288	58	Full	106	Full
1H3-hlgG1-L6-hIL-2 (I92D/F42V)	289	1075 ^a	Partial, 60%	343	Full
1H3-hlgG1-L6-hIL-2 (I92D/Y45A)	290	15	Full	285	Full
1H3-hlgG1-L6-hIL-2 (I92D/Y45Q)	293	53	Full	80	Full

1H3-hIgG1-L6-hIL-2 (I92D/Y45G)	295	41	Full	91	Full
1H3-hIgG1-L6-hIL-2 (I92D/Y45M)	299	7	Full	146	Full
1H3-hIgG1-L6-hIL-2 (I92D/Y45F)	300	33	Full	1650 ^a	Full
1H3-hIgG1-L6-hIL-2 (I92D/Y45S)	302	20	Full	306	Full
1H3-hIgG1-L6-hIL-2 (R38E/D20H)	306	13	Inactive	2945	Partial, 40%
1H3-hIgG1-L6-hIL-2 (R38E/D20S)	307	>10,000 on graph, NC ^a	Partial, 50%	626	Full
1H3-hIgG1-L6-hIL-2 (F42A/N88R)	308	8351 ^a	Partial, 70%	1456	Full
1H3-hIgG1-L6-hIL-2 (F42A/N88D)	309	1966 ^a	Full	86	Full
1H3-hIgG1-L6-hIL-2 (R38E/I92K)	334	>10,000 ^a	Partial, 70%	239	Full
1H3-hIgG1-L6-hIL-2 (R38E/I92P)	337	>10,000 on graph, NC ^a	Inactive	>10,000 on graph, NC ^a	Inactive
1H3-hIgG1-L6-hIL-2 (R38E/H16E)	343	658 ^a	Full	58	Full
1H3-hIgG1-L6-hIL-2 (R38K/D20A)	344	66	Full	369	Partial, 70%

NC = Not Calculated by GraphPad Prism 7
^a = Fold change is an estimate only since a full four parameter logistic curve was not reached

Example 6: Generation of anti-hPD-1 antibodies

[0169] Several approaches were used to generate a variety of different anti-hPD-1 antibodies with desired properties.

[0170] In one approach, anti-hPD-1 human monoclonal antibodies were generated using transgenic chickens (OmniChicken™) that express human antibody genes (human light chain (VLCL or VKCK) and human VH) and the chicken constant regions of the heavy chain (Ching *et al.*, mAbs 2018). Transgenic chickens were immunized with 100 µg of Fc-tagged human PD-1 protein (huPD-1-Fc) (SEQ ID NO: 380) every 14 days for 14 weeks. In another approach, transgenic chickens were genetically immunized six times with DNA encoding human PD-1 (SEQ ID NO: 347) followed by a final boost with 100 µg huPD-1-Fc (SEQ ID NO: 380). The serum immune response of each animal was monitored by ELISA against biotinylated human PD-1 on streptavidin coated plates.

[0171] Splenocytes were isolated from each immunized animal, tested for positive antibody clones using the Gel Encapsulated Microenvironment (GEM) assay (as described in Mettler Izquierdo, S., Varela, S., Park, M., Collarini, E. J., Lu, D., Pramanick, S., Rucker, J., Lopalco, L., Etches, R., & Harriman, W. (2016). High-efficiency antibody discovery achieved with multiplexed microscopy. *Microscopy (Oxford, England)*, 65(4), 341–352) and screened against human PD-1 labelled beads. Positive clones were sequenced and variable regions of the heavy and light chains were cloned, assembled into a single chain variable fragment, and fused to the hinge and Fc regions of immunoglobulins (ScFv-Fc). These unique scFv-Fc fusion proteins were transiently expressed in Expi293 cells and supernatants were tested for binding activity by ELISA on plates coated with huPD-1-Fc (SEQ ID NO: 380) or cynomolgous-PD-1-Fc (SEQ ID NO: 381). In total, 102 unique anti-human PD-1 variable heavy and variable light pairings were identified using this method. 2H7-hIgG4 (SEQ ID NOs: 382-391, 424, and 425) and A2-hIgG4 (SEQ ID NOs: 402-411, 428, and 429) were among the antibodies identified in this approach.

[0172] Other approaches led to the identification of an anti-hPD-1 antibody denoted as C51E6-hIgG4, which was germline optimized to become the antibody designated C51E6-5-hIgG4 (SEQ ID NOs: 392-401, 426, 427), and humanized and further sequence optimized to become the antibody designated Abz1mod-hIgG4 (SEQ ID NOs: 449, 450).

[0173] The anti-PD-1 variable region sequences were expressed as human IgG4 kappa antibodies and were evaluated for the ability to bind to PD-1 expressing cells using flow cytometry as described in General Methods Protocol A. Antibodies to be tested were first screened for binding to human PD-1 using a Jurkat cell line expressing recombinant human PD-1 (Jurkat + hPD-1 cell line). Antibodies were serially diluted from a top concentration of 280 nM and Allophycocyanin-conjugated anti-human IgG secondary antibody was then added to cells for detection. Of 92 hits, 79 test anti-PD-1 antibodies had an EC₅₀ binding (by flow cytometry) of <30 nM. 2H7-hIgG4 (SEQ ID NOs: 382-391, 424, and 425), C51E6-5-hIgG4 (SEQ ID NOs: 392-401, 426, and 427), A2-hIgG4 (SEQ ID NOs: 402-411, 428, and 429), OMC.1.B6-hIgG4 (SEQ ID NOs: 438 and 439), OMC.1.D6-hIgG4 (SEQ ID NOs: 442 and 443), OMC.2.C6-hIgG4 (SEQ ID NOs: 440 and 441), 1H9-hIgG4 (SEQ ID NOs: 576 and 525), 1D5-hIgG4 (SEQ ID NOs: 577 and 527), and 2A3.H7-hIgG4 (SEQ ID NOs: 424 and 523) were among a group of antibodies identified as antibodies with medium to high affinity binding to hPD-1 using a Jurkat cell line expressing human PD-1 (SEQ ID NO: 346). The calculated EC₅₀ of binding to Jurkat cells which recombinantly expressed hPD-1 by flow cytometry in multiple experiments was 0.1-0.3 nM for 2H7-hIgG4, 1H9-hIgG4, 1D5-hIgG4, and 2A3.H7-hIgG4. The calculated EC₅₀ of binding to Jurkat cells expressing hPD-1 by flow for C51E6-5-hIgG4 was 2-4 nM, and 3-16 nM for A2-hIgG4, OMC.1.B6-hIgG4, OMC.1.D6-hIgG4, and OMC.2.C6-hIgG4. Binding was specific to hPD-1 since 2H7-hIgG4, C51E6-5-hIgG4, A2-hIgG4, 1H9-hIgG4, 1D5-hIgG4, 2A3.H7-hIgG4, OMC.1.B6-hIgG4, OMC.1.D6-hIgG4, and OMC.2.C6-hIgG4 antibody titrations did not bind the parental Jurkat cell line which did not express hPD-1 (data not shown).

Example 7: Characterization of anti-hPD-1 antibody binding in the presence of anti-hPD-1 #1-mIgG2b-N297A and anti-hPD-1 #2-mIgG2b-N297A antibodies

[0174] 2H7-hIgG4, C51E6-5-hIgG4, and A2-hIgG4 were assessed for binding competition to hPD-1 in the presence of anti-hPD-1 #1-mIgG2b-N297A and anti-hPD-1 #2-mIgG2b-N297A as described in General Methods Protocol B.

[0175] As a control, OPDIVO® (nivolumab) was titrated in the presence of saturating concentrations of 10 µM anti-hPD-1 #1-mIgG2b-N297A (FIG. 4A). The dose-titration curve in the presence of anti-hPD-1 #1-mIgG2b-N297A competitor was greatly reduced (100 to 1000-fold shift of the dose-titration curve to the right of the graph) when compared to the dose-titration

curve of OPDIVO® without anti-hPD-1 #1-mIgG2b-N297A competitor. The addition of anti-hPD-1 #1-mIgG2b-N297A or anti-hPD-1 #2-mIgG2b-N297A at saturating concentrations (10 μ M) prior to exposure with 2H7-hIgG4, C51E6-5-hIgG4, or A2-hIgG4 did not abrogate binding of 2H7-hIgG4, C51E6-5-hIgG4, or A2-hIgG4 to hPD-1 as illustrated by less than 10-fold shift in FIG. 4B-4D, suggesting that 2H7-hIgG4, C51E6-5-hIgG4 and A2-hIgG4 did not compete for binding to PD-1 in the presence of anti-hPD-1 #1-mIgG2b-N297A or anti-hPD-1 #2-mIgG2b-N297A.

Example 8: Characterization of non-antagonist hPD-1 antibodies

[0176] Anti-hPD-1 antibodies 2H7-hIgG4, C51E6-5-hIgG4 and A2-hIgG4 were tested for PD-1 antagonist activity using an *in vitro* cell-based human PD-1/PD-L1 blockade bioassay as described in General Methods Protocol C. All antibodies except A2-hIgG4 were tested at 200 nM final concentration. A2-hIgG4 was tested at 500 nM final concentration.

[0177] None of the anti-hPD-1 antibodies 2H7-hIgG4, C51E6-5-hIgG4, A2-hIgG4, OMC.1.B6-hIgG4, OMC.1.D6-hIgG4, OMC.2.C6-hIgG4, 1H9-hIgG4, 1D5-hIgG4, and 2A3.H7-hIgG4 demonstrated hPD-1 antagonist activity, as all displayed luminescence levels of an average of 3000 relative luminescence units (RLU) and exhibited an RLU similar to the negative control KLH-C3-hIgG4 (data not shown). In contrast, the anti-hPD-1 #1, which is a known hPD-1 antagonist that blocks hPD-L1 (SEQ ID NO: 584) engagement with hPD-1, exhibited luminescence of above 14,000 RLU (data not shown).

Example 9: Anti-hPD-1-attenuated hIL-2 fusion proteins bind Jurkat cells expressing human PD-1

[0178] In order to construct various antibody and antibody-attenuated hIL-2 fusion protein expression vectors, the corresponding polynucleotide encoding sequences of antibody, cytokines, cytokine receptors and linkers were generated and cloned into expression vectors. The antibodies or antibody fusion proteins were transiently expressed in Human Embryonic Kidney (HEK) 293 cells, then purified by affinity chromatography using Protein A- or Protein G-Sepharose. The purified proteins were concentrated and buffer-exchanged to phosphate buffered saline or phosphate buffered saline containing 100 mM L-arginine and 10 mM L-histidine using ultracentrifugal filtration, after which protein concentration was determined.

[0179] In some approaches, 2H7-hIgG4, C51E6-5-hIgG4, and A2-hIgG4 carrying an S228P hinge stabilization mutation were directly fused (df) to hIL-2 or fused to hIL-2 at the C-terminus of the immunoglobulin heavy chain using the L6 linker. An illustration of these anti-PD-1-attenuated hIL-2 fusion proteins is summarized in FIG. 5. Various constructs were generated with the substitutions in hIL-2 that attenuated hIL-2 activity as described in Example 2. Anti-hPD-1-attenuated hIL-2 fusion proteins listed in Table 20 were tested for binding to hPD-1 using the Jurkat cell line expressing hPD-1 as described in General Methods Protocol A. The variable region of 2H7-hIgG4 (SEQ ID NOs: 384 and 385) was further optimized, and the isotype was switched to a human IgG1 with the effector function null substitutions L235A/G237A (LAGA, as described in WO1998/006248) to become H7-632-hIgG1-LAGA (SEQ ID NOs: 414 and 415). The optimized H7-632-hIgG1-LAGA was also directly fused (df) to a variant of hIL-2 with attenuated hIL-2 activity (hIL-2 T3A/D20A/R38E/C125A; SEQ ID NO: 217) to become H7-767 (SEQ ID NOs: 412-413, 415-423, 532) and both H7-632-hIgG1-LAGA and H7-767 were tested for binding to hPD-1 (Table 20). EC_{50} values were calculated from the geometric mean fluorescent intensity (gMFI) across the titrated concentrations using GraphPad Prism 7 software.

[0180] The generation of anti-hPD-1-attenuated hIL-2 fusion proteins did not reduce binding to hPD-1, and the anti-hPD-1-attenuated hIL-2 fusion proteins were still able to bind to Jurkat cells expressing human PD-1. The calculated EC_{50} of tested anti-hPD-1-attenuated hIL-2 fusion proteins in comparison to respective anti-hPD-1 antibody without the attenuated hIL-2 moiety is summarized in Table 20.

Table 20. Anti-hPD-1-attenuated hIL-2 fusion protein binding (EC₅₀) to hPD-1 expressing Jurkat cell line by flow cytometry

Anti-hPD-1 Antibody	EC ₅₀ (nM)	Corresponding Anti-hPD-1-hIL-2 Fusion Protein	EC ₅₀ (nM)
Anti-hPD-1 #1	0.3586	Anti-hPD-1 #1-hIgG4-L6-hIL-2 (D20A/R38E)	0.5318
C51E6-5-hIgG4	2.048	C51E6-5-hIgG4-L6-hIL-2 (D20A/R38E)	1.587
OMC.1.B6-hIgG4	7.422	OMC.1.B6-hIgG4-L6-hIL-2 (D20A/R38E)	5.635
OMC.2.C6-hIgG4	11.52	OMC.2.C6-hIgG4-L6-hIL-2 (D20A/R38E)	16.32
OMC.1.D6-hIgG4	15.96	OMC.1.D6-hIgG4-L6-hIL-2 (D20A/R38E)	8.87
A2-hIgG4	5.968	A2-hIgG4-df-hIL-2 (D20A/R38E)	10.67
D12-hIgG4	9.674	D12-hIgG4-df-hIL-2 (D20A/R38E)	17.09
G12-hIgG4	5.36	G12-hIgG4-df-hIL-2 (D20A/R38E)	7.578
2H7-hIgG4	0.2769	2H7-hIgG4-df-hIL-2 (D20A/R38E)	0.1946
H7-632-hIgG1-LAGA	0.115	H7-767	0.218

[0181] The addition of the attenuated hIL-2 moiety on anti-hPD-1 antibodies did not abrogate binding to human PD-1 as demonstrated by a less than 2-fold increase in EC₅₀ binding of anti-hPD-1-hIL-2 fusion proteins to Jurkat + hPD-1 cells in comparison to the anti-hPD-1 antibody without the attenuated hIL-2 moiety.

Example 10: Anti-hPD-1-attenuated hIL-2 fusion proteins bind hPD-1 in the presence of anti-hPD-1 #1 and anti-hPD-1 #2 antibodies

[0182] Anti-hPD-1-attenuated hIL-2 fusion proteins were tested for binding to the hPD-1 receptor in the presence of anti-hPD-1 #1 and anti-hPD-1 #2 as described in General Methods Protocol B and Example 7. The converse experiment was also performed in which anti-hPD-1 #1-mIgG2b-N297A or anti-hPD-1 #2-mIgG2b-N297A was examined for binding to hPD-1 in the presence of saturating concentrations of test antibody-attenuated hIL-2 fusion proteins. In this format, Jurkat cells expressing hPD-1 were plated at 100,000 cells per well in FACS buffer, blocked with anti-human FcγR Blocking Reagent (Miltenyi) for 10 minutes at 4 °C and washed. Test antibody-attenuated hIL-2 fusion proteins 2H7-hIgG4-df-hIL-2 (D20A/R38E), C51E6-5-hIgG4-L6-hIL-2 (D20A/R38E), A2-hIgG4-df-hIL-2 (D20A/R38E), H7-767, and isotype control anti-DNase 1H3-hIgG4-df-hIL-2 (D20A/R38E) were diluted to 280 nM final concentration in 100 μL FACS buffer and incubated with Jurkat cells expressing hPD-1 cells for 1 hour on ice. Cells were washed and re-suspended in FACS buffer containing six-fold serial titrations of anti-hPD-1 #1-mIgG2b-N297A or anti-hPD-1 #2-mIgG2b-N297A starting at a maximum concentration of 50 nM for 1 hour on ice. Cells were washed and re-suspended in 1:100 dilution of Phycoerythrin-conjugated anti-mouse IgG light chain kappa monoclonal antibody for 45 minutes on ice. Cells were again washed and re-suspended in FACS buffer with 1:1000 dilution of Sytox Green (Thermo Fisher). Flow cytometry analysis was performed using the BD FACS Canto II (BD Biosciences) and gMFI calculated using FlowJo software version 10. EC₅₀ values were calculated from the gMFI of the Phycoerythrin signal across the titrated concentrations using GraphPad Prism 7 software.

[0183] The addition of the attenuated hIL-2 to anti-hPD-1 antibodies 2H7-hIgG4, C51E6-5-hIgG4, and A2-hIgG4 did not diminish the ability of the anti-hPD-1 proteins to bind to human PD-1 in the presence of anti-hPD-1 #1-mIgG2b-N297A or anti-hPD-1 #2-mIgG2b-N297A, similar to the results described in Example 7 (FIG. 16B-16D). H7-767 was also tested in

this competition assay and FIG. 13B illustrates that H7-767 continues to bind to the hPD-1 receptor in the presence of anti-hPD-1-#1-mIgG2b-N297A or anti-hPD-1 #2-mIgG2b-N297A. In contrast, the binding of the positive control anti-hPD-1 #1 was substantially decreased in the presence of anti-hPD-1 #1-mIgG2b-N297A or anti-hPD-1 #2-mIgG2b-N297A (FIG. 16A, 13A).

[0184] FIG. 6A and FIG. 6B show that for the converse competition assay, anti-hPD-1 #1-mIgG2b-N297A (FIG. 6A) and anti-hPD-1 #2-mIgG2b-N297A (FIG. 6B) were still able to bind to hPD-1 on Jurkat cells in the presence of saturating (280 nM) anti-hPD-1-attenuated hIL-2 fusion proteins 2H7-hIgG4-df-hIL-2 (D20A/R38E), C51E6-5-hIgG4-df-hIL-2 (D20A/R38E) or A2-hIgG4-df-hIL-2 (D20A/R38E). These binding curves with saturating anti-hPD-1-attenuated hIL-2 fusion proteins prior to exposure with anti-hPD-1 fusion proteins overlapped with binding curves of anti-hPD-1 #1-mIgG2b-N297A (no competition) or anti-hPD-1 #2-mIgG2b-N297A (no competition). The binding curves also overlapped with a saturating negative control fusion protein, 1H3-hIgG4-df-hIL-2 (D20A/R38E) that did not bind to hPD-1.

Example 11: Anti-hPD-1-attenuated hIL-2 fusion proteins bind recombinantly-expressed cynomolgus PD-1

[0185] Anti-hPD-1-attenuated hIL-2 fusion proteins were tested in flow cytometry for binding to cynomolgus PD-1 using a human Embryonic Kidney 293 cell line expressing the SV40 large T cell antigen (HEK-293T) that was transiently transfected to recombinantly express cynomolgus PD-1. For each transfection reaction, 2 million HEK-293T cells were transfected with 2µg of pCMV6-hygro-HA-cyno-PD-1 (1-185) (SEQ ID NO: 448), a mammalian vector comprising the cynomolgus PD-1 extracellular domain tagged with a human influenza hemagglutinin and the sequence encoding for hygromycin resistance. Transfection was performed by electroporation. Transfected cells were blocked with human FcγR blocking reagent and stained with titrating amounts of anti-hPD-1-attenuated hIL-2 fusion proteins. Additionally, Phycoerythrin conjugated anti-hemagglutinin clone 15B12 was added to cells to stain for transfected cells and Allophycocyanin-conjugated anti-human IgG Fc secondary clone HP6017 (BioLegend Cat# 409306) was added to cells to stain bound antibody. The cells were analyzed on the BD Canto II and FlowJo software version 10 was used to gate on live, transfected (hemagglutinin-positive) cells and to calculate gMFI of the Allophycocyanin signal. EC₅₀ values

were calculated from the gMFI across the titrated concentrations using GraphPad Prism 7 software.

[0186] Anti-hPD-1-attenuated hIL-2 fusion proteins bound to cynomolgus PD-1-expressing HEK-293T cells in a similar fashion to the binding profile seen on Jurkat T cells expressing human PD-1 (FIG. 17). The EC₅₀ for binding to cynomolgus PD-1 expressing HEK-293T cells was 5 nM for 2H7-hIgG4-df-hIL-2 (D20A/R38E), 6 nM for C51E6-5-hIgG4-df-hIL-2 (D20A/R38E), and 11 nM for A2-hIgG4-df-hIL-2 (D20A/R38E). Anti-hPD-1 #1 and anti-hPD-1 #2 which were formatted as comparator anti-hPD-1-attenuated hIL-2 fusion proteins also bound to cynomolgus PD-1 with EC₅₀ values of 9 nM and 2 nM, respectively, suggesting that the addition of the attenuated hIL-2 moiety on the anti-hPD-1 antibodies did not abrogate binding to cynomolgus PD-1.

Example 12: Anti-hPD-1-attenuated hIL-2 fusion proteins bind activated primary human and cynomolgus PD-1

[0187] The binding of anti-hPD-1 antibodies and anti-hPD-1-attenuated hIL-2 fusion proteins on activated primary T cells expressing hPD-1 was examined by flow cytometry. To test if 2H7-hIgG4, C51E6-5-hIgG4, or A2-hIgG4 bound to native hPD-1, cryopreserved human peripheral blood mononuclear cells (PBMCs) were thawed and activated with 50ng/mL phorbol 12-myristate 13-acetate (PMA) and 1μg/mL ionomycin to up-regulate the hPD-1 receptor. Activated PBMCs were collected, blocked with 1:50 dilution of Human FcγR Blocking Reagent (Miltenyi) for 10 minutes at 4 °C, and stained with titrated concentrations of anti-hPD-1 antibodies 2H7-hIgG4, C51E6-5-hIgG4, A2-hIgG4, anti-hPD-1 #1, and isotype control. Cells were then stained with 1:20 dilution of Allophycocyanin-conjugated anti-human IgG Fc to detect bound antibody. To delineate immune subsets, a cocktail of surface markers included anti-human CD3, anti-CD4, and anti-CD8 antibodies was used. In addition, a sample fraction was examined for cellular expression of hPD-1, hCD25, hCD122, and hCD132. Cells were analyzed on the BD Fortessa (BD Biosciences), FlowJo software version 10 was used to gate on T cell subsets then calculate gMFI of the allophycocyanin signal. EC₅₀ values were calculated from the gMFI across the titrated concentrations using GraphPad Prism 7 software. To test the binding of anti-hPD-1-hIL-2 fusion proteins, cryopreserved CD3⁺ T cells were activated with PMA/ionomycin and flow cytometry binding was performed identically as described above.

[0188] Human PD-1 antibody-attenuated hIL-2 fusion proteins were also tested for binding to activated cynomolgus T cells using flow cytometry. Cynomolgus PBMCs were activated with a mixture of 0.081 μ M PMA and 1.34 μ M ionomycin. 24 hours later, cells were stained using the same procedure as binding to human PD-1 primary cells described above except cynomolgus cross-reactive markers were used. FlowJo software version 10 was used to gate on live, CD3⁺CD4⁺ or CD3⁺CD8⁺ T cells and then to calculate gMFI of the Allophycocyanin signal. EC₅₀ values were calculated from the gMFI across the titrated concentrations of anti-hPD-1 antibodies or hPD-1 antibody-attenuated hIL-2 fusion proteins using GraphPad Prism 7 software.

[0189] In some variants tested, the attenuated hIL-2 also included the substitutions T3A and C125A, which remove a site for O-linked glycosylation and substitute away a free cysteine residue, respectively.

[0190] 40-50% of CD4⁺ T cells were PD-1⁺ while 30-40% of CD8⁺ T cells were PD-1⁺ after PMA and ionomycin activation (data not shown). The calculated EC₅₀ for binding to activated human CD3⁺CD4⁺ T cells by flow cytometry was 0.1-0.7 nM for 2H7-hIgG4, 12 nM for C51E6-5-hIgG4, 30 nM for A2-hIgG4, and 0.04 nM for 2H7-hIgG4-df-hIL-2 (T3A/D20A/R38E/C125A). The EC₅₀ for binding to activated human CD3⁺CD8⁺ T cells was 0.1-0.8 nM for 2H7-hIgG4, 16 nM for C51E6-5-hIgG4, 22 nM for A2-hIgG4, and 0.03 nM for 2H7-hIgG4-df-hIL-2 (T3A/D20A/R38E/C125A). The EC₅₀ for binding to activated human CD3⁺CD4⁺ T cells was 0.19 nM and activated human CD3⁺CD8⁺ T cells was 0.12 nM for H7-767. The EC₅₀ for binding to activated cynomolgus CD3⁺CD4⁺ T cells was 0.09 nM for 2H7-hIgG4 and 0.04 nM for 2H7-hIgG4-df-hIL-2 (T3A/D20A/R38E/C125A). EC₅₀ for binding to activated cynomolgus CD3⁺CD8⁺ T cells was 0.08 nM for 2H7-hIgG4 and 0.03 nM for 2H7-hIgG4-df-hIL-2 (T3A/D20A/R38E/C125A). The EC₅₀ for binding to activated cynomolgus CD3⁺CD4⁺ T cells was 0.26 nM and activated cynomolgus CD3⁺CD8⁺ T cells was 0.24 nM for H7-767. This data demonstrated that when the hPD-1 antibodies were converted to anti-hPD-1-attenuated hIL-2 fusion proteins, the calculated EC₅₀ value for binding to activated hPD-1 remained similar to the calculated EC₅₀ value of hPD-1 naked antibody binding to hPD-1.

[0191] H7-767 and H7-632-hIgG1-LAGA anti-PD-1 naked antibody were tested for binding on primary non-activated human CD4⁺ and CD8⁺ T cells by flow cytometry. Frozen human CD3⁺ T were thawed and flow cytometry performed as described above. Both H7-767

and H7-632-hIgG1-LAGA anti-PD-1 naked antibody did not bind non-activated human CD4⁺ and CD8⁺ T cells (data not shown).

Example 13: Quantification of binding of anti-hPD-1 antibodies and anti-hPD-1-attenuated hIL-2 fusion proteins to recombinant human or cynomolgus PD-1 by surface plasmon resonance (SPR)

[0192] Surface plasmon resonance binding analysis was performed using a high-throughput SPR Carterra® LSA™ to determine binding affinities of anti-hPD-1 antibodies and anti-hPD-1-attenuated hIL-2 fusion proteins. Proteins were diluted to 2 or 10 µg/mL in 10 mM sodium acetate pH 4.5 containing 0.01% Tween-20 and coupled to a HC30M (Carterra Bio) chip using sulfo-N-hydroxysuccinimide / 1-ethyl-3-(3-dimethylamino) propyl carbodiimide (sulpho-NHS/EDC) coupling chemistry and blocked with ethanolamine. A non-regenerative kinetic coupling process was used to determine binding kinetics to commercially sourced recombinant His-tagged human PD-1 and His-tagged cynomolgus PD-1 (Acro Biosystems).

[0193] Anti-hPD-1 antibodies and anti-hPD-1-attenuated hIL-2 fusion proteins were expressed with either a modified human IgG1 or a modified IgG4 isotype with a kappa light chain framework. Additional substitutions L235E, or L235A/G237A (LAGA, as described in Int'l Pub. No. WO1998/006248) (numbering based upon the EU numbering system) were introduced to the Fc region to abrogate effector functions of the immunoglobulin component.

[0194] The association constants (k_a), dissociation constants (k_d), and equilibrium constants (K_D) of various anti-hPD-1 antibodies and anti-hPD-1 antibody-attenuated hIL-2 fusion proteins binding to recombinant human or cynomolgus PD-1 proteins was determined from the titration curves and the Carterra Kinetics software. The maximal feasible SPR signal generated (R_{max}) and residual standard deviation (Res SD) was also calculated. The results from the kinetics screen are summarized in Table 21, and demonstrated that the addition of the attenuated hIL-2 moiety on anti-hPD-1 antibodies did not modulate PD-1 antibody binding to the human PD-1 or cynomolgus PD-1 antigens. In a separate experiment, H7-632-hIgG1-LAGA (SEQ ID NOs: 414 and 415) was measured by SPR and had a steady state equilibrium dissociation constant (K_D) of 1.23×10^{-9} M and H7-767 had a $K_D = 1.93 \times 10^{-9}$ M.

Table 21. Binding kinetics of anti-hPD-1 and anti-hPD-1-hIL-2 fusion proteins to recombinant human PD-1 and cynomolgus PD-1 by high-throughput SPR Carterra® LSA™

	Kinetics Summary										
	Human PD-1						Cyno PD-1				
	Name	k _a (M ⁻¹ s ⁻¹)	k _d (s ⁻¹)	K _D (M)	Rmax	Res SD	k _a (M ⁻¹ s ⁻¹)	k _d (s ⁻¹)	K _D (M)	Rmax	Res SD
Anti-hPD-1 Antibodies	2H7-hlgG4-LE	2.60E+05	8.20E-04	3.10E-09	146	8.5	1.40E+05	1.00E-03	7.10E-09	186	6.5
	2H7-hlgG4-LAGA	1.70E+05	9.10E-04	5.30E-09	258	13	9.10E+04	1.10E-03	1.20E-08	295	11
	Abz1mod-hlgG4	1.40E+05	6.00E-05	4.26E-10	123	8.1	1.70E+05	6.20E-04	3.70E-09	183	10
	A2-hlgG4	3.70E+04	1.30E-03	3.60E-08	341	7.8	6.80E+04	4.00E-02	5.89E-07	238	4.8
	OMC.1.B6-hlgG4	7.70E+04	4.00E-03	5.20E-08	241	6.8	8.80E+04	4.40E-03	5.10E-08	262	5.5
	OMC.2.C6-hlgG4	5.70E+04	6.60E-04	1.20E-08	229	8.7	5.50E+04	7.40E-04	1.30E-08	268	8.9
	OMC.1.D6-hlgG4	4.10E+04	1.70E-03	4.20E-08	263	5.1	5.80E+04	4.00E-02	6.94E-07	182	4
	OMC476pH7-hlgG4	6.00E+04	1.10E-03	1.80E-08	225	8.9	7.80E+04	1.70E-02	2.21E-07	254	2.8
	OMC476pB11-hlgG4	5.00E+04	1.50E-03	3.00E-08	221	7	8.00E+04	2.60E-02	3.21E-07	204	2.7
	OMC476pG10-hlgG4	9.30E+04	4.10E-03	4.40E-08	256	4.9	1.20E+05	6.00E-02	4.87E-07	188	4.9
	OMC476pH10-hlgG4	1.00E+05	6.50E-03	6.40E-08	63	1.8	1.20E+05	5.90E-02	4.80E-07	81	3.8
	OMC476pE4-hlgG4	7.90E+04	8.80E-04	1.10E-08	216	9.6	1.00E+05	3.50E-02	3.31E-07	204	6.3
	D12-hlgG4	5.70E+04	4.60E-04	8.10E-09	234	9.9	5.90E+04	1.60E-02	2.72E-07	297	2.4
	G12-hlgG4	5.30E+04	2.60E-03	5.00E-08	477	8.5	8.60E+04	6.50E-02	7.54E-07	327	7.8
	EH12.2H7-mlgG1*	1.10E+05	2.20E-03	1.90E-08	309	5.2	8.60E+04	7.30E-03	8.50E-08	307	4.2
	J105-mlgG1*	6.20E+04	5.30E-03	8.60E-08	186	2.8	5.00E+04	6.60E-02	1.30E-09	92	1.2
	MIH4-mlgG1*	1.30E+05	1.40E-03	1.00E-08	117	3.8	1.30E+05	1.20E-01	8.91E-07	61	1.8
	J110-hlgG1	1.00E+05	1.00E-03	1.00E-08	346	15	4.10E+04	5.00E-02	1.20E-09	228	8.2
	OPDIVO® (nivolumab)	1.70E+05	1.70E-03	1.00E-08	55	2.6	1.50E+05	9.50E-04	6.40E-09	75	3.2
	KEYTRUDA® (pembrolizumab)	2.90E+05	1.30E-03	4.50E-09	19	2.6	7.00E+05	4.00E-04	5.75E-07	53	3.7

Anti-hPD-1-attenuated hIL-2 Fusion Proteins	2H7-hlgG1-LAGA-hIL-2 (T3A/D20A/R38E/C125A)	1.50E+05	8.30E-04	5.40E-09	420	28	8.80E+04	9.70E-04	1.10E-08	502	21
	2H7-hlgG4-LE-hIL-2 (T3A/D20A/R38E/C125A)	1.90E+05	8.10E-04	4.30E-09	374	17	9.00E+04	1.00E-03	1.10E-08	449	15
	2H7-hlgG4-LAGA-hIL-2 (T3A/D20A/R38E/C125A)	1.70E+05	8.20E-04	4.80E-09	359	22	9.60E+04	9.80E-04	1.00E-08	429	17
	2H7-hlgG1-LAGA-hIL-2 (T3A/R38E/I92K/C125A)	1.80E+05	7.80E-04	4.30E-09	417	25	9.10E+04	9.70E-04	1.10E-08	505	19
	hlgG4-LE-hIL-2 (T3A/R38E/I92K/C125A)	1.90E+05	8.80E-04	4.70E-09	380	19	9.50E+04	1.10E-03	1.20E-08	429	17
	2H7-hlgG4-LAGA-hIL-2 (T3A/R38E/I92K/C125A)	2.20E+05	8.20E-04	3.70E-09	355	17	1.00E+05	1.10E-03	1.10E-08	418	16
	2H7-hlgG1-LAGA-hIL-2 (T3A/R38E/D84K/C125A)	1.30E+05	8.10E-04	6.20E-09	458	29	7.60E+04	1.00E-03	1.30E-08	532	23
	2H7-hlgG4-LE-hIL-2 (T3A/R38E/D84K/C125A)	2.00E+05	9.40E-04	4.70E-09	232	13	1.30E+05	1.10E-03	8.20E-09	262	10
	2H7 hlgG4LAGA-df-hIL-2 (T3A/R38E/D84K/C125A)	1.70E+05	7.30E-04	4.40E-09	400	20	8.10E+04	1.00E-03	1.30E-08	482	20

* Commercially sourced, no sequence available

Example 14: Determining whether anti-hPD-1 antibodies and anti-hPD-1-attenuated hIL-2 fusion proteins compete with anti-hPD-1 #1 and anti-hPD-1 #2 for binding to PD-1 by surface plasmon resonance (SPR)

[0195] Anti-hPD-1 and anti-hPD-1-attenuated hIL-2 fusion proteins were assayed for competition with one another using a sandwich method. Antibodies and corresponding antibody-IL-2 cytokine-fusion proteins were immobilized to HC30M chips using amine coupling chemistry described in Example 13. Following kinetic analysis described in Example 13, 80 nM human PD-1 (Acro Biosystems, Cat # PD-1-H5221-100ug) was injected into the whole array. Competing anti-hPD-1 and anti-hPD-1-attenuated hIL-2 fusion proteins (analyte) were diluted to 30 µg/mL and subsequently injected into the array and binding parameters were assessed using SPR. Assessment of all anti-hPD-1 and anti-hPD-1-hIL-2 fusion proteins was performed in duplicate. Some variants tested had a modified human IgG1 or IgG4 kappa light chain framework with additional L235E or L235A/G237A (LAGA) substitutions to abrogate effector function of the immunoglobulin.

[0196] The screening of pairs of anti-hPD-1 or anti-hPD-1-attenuated hIL-2 fusion proteins allowed the identification of two bins, shown in Table 22. Antibodies and fusion proteins from Group 1 were able to bind hPD-1 in the presence of all antibodies and fusion proteins from Group 2, but competed with all members of the same Group. Antibodies and fusion proteins from Group 2 were able to bind hPD-1 in the presence of all antibodies and fusion proteins from Group 1, but competed with all members of the same Group. None of the anti-hPD-1 listed in Group 1 in Table 22 competed with KEYTRUDA® and OPDIVO®.

Table 22. Groups 1 and 2 from anti-hPD-1 and anti-hPD-1-attenuated hIL-2 fusion protein binning screen by SPR

Group 1	Group 2
Abz1mod-hIgG4	KEYTRUDA®
OMC.1.B6-hIgG4	OPDIVO®
OMC.1.D6-hIgG4	Anti-hPD-1 clone
OMC.2.C6-hIgG4	EH12.2H7-
OMC476pE4-hIgG4	mIgG1*
OMC476pH7-hIgG4	Anti-hPD-1 clone
OMC476pB11-hIgG4	J105-mIgG1*
OMC476pH10-hIgG4	
OMC476pG10-hIgG4	
A2-hIgG4	
D12-hIgG4	

G12-hIgG4 2H7-hIgG4-LE 2H7-hIgG4-LE-df-hIL-2 (T3A/D20A/R38E/C125A) 2H7-hIgG4-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) 2H7-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) 2H7-hIgG4-LE-df-hIL-2 (T3A/R38E/I92K/C125A) 2H7-hIgG4-LAGA-df-hIL-2 (T3A/R38E/I92K/C125A) 2H7-hIgG1-LAGA-df-hIL-2 (T3A/R38E/I92K/C125A) 2H7-hIgG4-LE-df-hIL-2 (T3A/R38E/D84K/C125A) 2H7-hIgG4-LAGA-df-hIL-2 (T3A/R38E/D84K/C125A) 2H7-hIgG1-LAGA-df-hIL-2 (T3A/R38E/D84K/C125A) Anti-PD-1 clone MIH4 mIgG1 Anti-PD-1 clone J110 hIgG1	
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* Commercially sourced, no sequence available

Example 15: Antagonism of anti-hPD-1-attenuated hIL-2 fusion proteins to hPD-1 in the presence of anti-hPD-1 #1 and anti-hPD-1 #2

[0197] Anti-hPD-1-attenuated hIL-2 fusion proteins were tested for antagonism of hPD-1. Characterization of anti-hPD-1-attenuated hIL-2 fusion proteins was performed according to General Methods Protocol C. FIG. 7 illustrates these results. When compared to the PD-1 antagonists KEYTRUDA® or OPDIVO®, 2H7-hIgG4-df-hIL-2 (D20A/R38E), C51E6-5-hIgG4-L6-hIL-2 (D20A/R38E), and A2-hIgG4-df-hIL-2 (D20A/R38E) were non-antagonistic to human PD-1, as demonstrated by the low level of detectable luminescence. H7-632-hIgG1-LAGA and H7-767 were also tested for antagonist activity as described in General Protocol C. FIG. 15 illustrates that H7-632-hIgG1-LAGA and H7-767 do not block hPD-L1 (SEQ ID NO: 584) from interacting with the hPD-1 receptor.

[0198] For competition assays using the cell-based co-culture assay described in General protocol C, a few modifications were performed. Samples of the anti-hPD-1-attenuated hIL-2 fusion proteins were diluted to a fixed concentration of 400 nM and 20 µL was added to 20 µL of titrated anti-hPD-1 #1 or anti-hPD-1 #2. The 40 µL mixture was added to CHO cells. Forty (40) µL of Jurkat PD-1 effector cells were overlayed on the mixture of CHO cells and anti-hPD-1-attenuated hIL-2 fusion proteins. In this competition assay, a final concentration of saturating

100 nM anti-hPD-1-attenuated hIL-2 fusion proteins was tested in combination with titrated anti-hPD-1 #1 or anti-hPD-1 #2. The rest of the assay was performed as described in General Protocol C. FIG. 18A and FIG. 18B demonstrate that the addition of 100 nM anti-hPD-1-attenuated hIL-2 fusion proteins did not compete with the blocking of titrated anti-hPD-1 #1 binding to hPD-L1 (SEQ ID NO: 584). Dose-titration curves of anti-hPD-1 #1 remained unchanged from curves without competitor antibody, suggesting that the presence of anti-hPD-1-attenuated hIL-2 fusion proteins did not compete with anti-hPD-1 #1 function even at high concentrations. In the presence of 100 nM 2H7-hIgG4-df-hIL-2 (D20A/R38E) and 100 nM C51E6-5-hIgG4-L6-hIL-2 (D20A/R38E), anti-hPD-1 #2 exhibited a 35% reduction in luminescence (RLU) at higher concentrations of anti-hPD-1 #2 (FIG. 18B) but it is unclear if this reduction was significant due to the extent of the standard deviation.

[0199] In the converse experiment, either anti-hPD-1 #1 or anti-hPD-1 #2 were diluted to a concentration of 400 nM and 20 μ L was combined with 20 μ L of titrated anti-hPD-1-attenuated hIL-2 fusion proteins. Anti-hPD-1-attenuated hIL-2 fusion proteins were serially titrated and the 40 μ L mixture was added to CHO cells, then overlaid with 40 μ L of Jurkat PD-1 Effector cells. The rest of the assay was performed as described in General Protocol C. FIG. 18C and FIG. 18D demonstrate that the addition of 100 nM anti-hPD-1 #1 (FIG. 18C) or 100 nM anti-hPD-1 #2 (FIG. 18D) do not impair the ability of the anti-hPD-1-attenuated hIL-2 fusion proteins to be antagonists. The observed flat curve above 18,000 relative luminescent units (RLU) indicated that there was no competition for antagonist activity and the anti-hPD-1-attenuated hIL-2 fusion proteins tested remained able to exhibit antagonist function even in the presence of anti-hPD-1 #1 or anti-hPD-1 #2.

Example 16: Testing anti-hPD-1-attenuated hIL-2 fusion proteins for attenuation on the high-affinity and intermediate-affinity hIL-2 receptors with cell-based proliferation assays

[0200] Anti-hPD-1-attenuated hIL-2 fusion proteins were evaluated for the level of attenuation of hIL-2 activity using the cell proliferation assays on NK-92 and TF1+IL-2R β cell lines as described in General Protocol E. Control fusion proteins included fusion proteins incorporating an anti-DNase I antibody (designated 1H3) with a human IgG4 or human IgG1 backbone directly fused to hIL-2 or with a linker (SEQ ID NO: 355) to demonstrate the effects of non-targeting attenuated hIL-2 fusion proteins. The hIL-2 sequence of these constructs contained

substitutions for attenuated hIL-2 activity as described in Example 2. Full, partial, or no agonistic IL-2 activity (inactive) was also assessed similarly to Example 3. Some of the variants tested were expressed on a modified human IgG1 or IgG4 isotype with a kappa light chain, with additional L235E or L235A/G237A (LAGA) substitutions in the Fc region to abrogate immunoglobulin effector function. In some antibody-cytokine fusion proteins, the hIL-2 cytokine was fused to the C-terminus of the light chain (LC fusion).

[0201] The calculated EC₅₀ of each antibody-cytokine fusion protein was determined from relative luminescence units (RLU), and fold change EC₅₀ was calculated when compared with recombinant human IL-2 (rhIL-2). The fold change from rhIL-2 and agonistic activity is summarized in Table 23. Agonistic activity was measured as full, partial, or inactive as determined by the maximal luminescence of antibody-attenuated hIL-2 fusion proteins in comparison to the maximal luminescence of rhIL-2. Antibody-attenuated hIL-2 fusion proteins dose-titration curves that reached the maximal luminescence as the rhIL-2 were considered to be variants with full activity. Partial activity was calculated as a percentage of full activity using rhIL-2 maximal luminescence as 100%. Maximal RLU of antibody-attenuated hIL-2 fusion proteins with less than 10% of the rhIL-2 maximal RLU at the highest concentration of 1200 nM were considered to have no agonist activity or inactive. For some variants EC₅₀ values were estimated only since maximal luminescence was not reached, as annotated by an ^a in Table 23.

Table 23. Fold change from rhIL-2 and agonistic activity of antibody-attenuated hIL-2 fusion proteins on NK-92 (high-affinity IL-2R) and TF1+IL-2R β (intermediate-affinity IL-2R) cell lines.

Non-Targeted Antibody-Attenuated hIL-2 Fusion Proteins	Variants	Fold change from rhIL-2 (NK-92)	Agonistic Activity (NK-92)	Fold change from rhIL-2 (TF1+IL-2R β)	Agonistic Activity (TF1+IL-2R β)
	1H3-hlgG4-df-hIL-2 (WT)	0 ^a	Full	0 - 1	Full
	1H3-hlgG4-L6-hIL-2 (WT)	0 ^a	Full	0 - 1	Full
	1H3-hlgG4-df-hIL-2 (WT) LC fusion	0 ^a	Full	24	Full
	1H3-hlgG4-L6-hIL-2 (WT) LC fusion	0 ^a	Full	2	Full
	1H3-hlgG4-L6-hIL-2 (D20Y)	>10,000 on graph, NC ^a	Inactive	>10,000 on graph, NC ^a	Inactive
	1H3-hlgG4-df-hIL-2 (D20Y)	>10,000 on graph, NC ^a	Partial, 60%	>10,000 on graph, NC ^a	Inactive
	1H3-hlgG1-df-hIL-2 (D20Y)	8539 ^a	Partial, 90%	>10,000 on graph, NC ^a	Inactive
	1H3-hlgG4-L6-hIL-2 (D20A/R38P)	>10,000 ^a	Partial, 80%	4132 ^a	Full
	1H3-hlgG4-L6-hIL-2 (D20A/R38S)	>10,000 on graph, NC ^a	Partial, 90%	9225 ^a	Full
	1H3-hlgG4-L6-hIL-2 (D20A/R38D)	118 ^a	Partial, 90%	8591 ^a	Partial, 90%
	1H3-hlgG4-L6-hIL-2 (D20A/R38Q/E95A)	153	Full	5738 ^a	Full
	1H3-hlgG4-L6-hIL-2 (D20A/F42H/E95A)	>10,000 ^a	Full	1368 ^a	Full
	1H3-hlgG4-L6-hIL-2 (R38D/I92D)	190	Full	437	Full
	1H3-hlgG4-L6-hIL-2 (R38E/I92D)	377 ^a	Full	296	Full
	1H3-hlgG4-L6-hIL-2 (F42H/I92D)	794 ^a	Full	393	Full
	1H3-hlgG4-df-hIL-2 (D20A/R38E)	868 ^a	Partial, 90% - Full	>10,000 ^a	Partial, 70% - Full
	1H3-hlgG4-L6-hIL-2 (D20A/R38E)	177 ^a	Partial, 60 - 80%	>10,000 ^a	Partial, 70% - Full

Anti-hPD-1-Attenuated hIL-2 Fusion Proteins	IH3-hlgG4-L6-hIL-2 (T3A/D20A/R38E)	>10,000 on graph, NC ^a	Partial, 40%	>10,000	Partial, 70%
	IH3-hlgG4-L6-hIL-2 (D20A/R38E/C125A)	>10,000 ^a	Partial, 20%	6436	Partial, 40%
	IH3-hlgG4-L6-hIL-2 (T3A/D20A/R38E/C125A)	>10,000 on graph, NC ^a	Partial, 20%	>10,000	Full
	IH3-hlgG1-L6-hIL-2 (D20A/R38E)	NT	NT	250 - 372	Full
	IH3-hlgG1-L6-hIL-2 (T3A/D20A/R38E)	392	Partial, 80%	186	Partial, 60%
	IH3-hlgG1-L6-hIL-2 (D20A/R38E/C125A)	2346 ^a	Partial, 80%	2157 ^a	Partial, 60%
	IH3-hlgG4-df-hIL-2 (D20A/R38E) LC fusion	>10,000 on graph, NC ^a	Inactive	>10,000 on graph, NC ^a	Inactive
	IH3-hlgG4-L6-hIL-2 (D20A/R38E) LC fusion	>10,000 on graph, NC ^a	Inactive	2155 ^a	Partial, 30%
	IH3-hlgG1-L6-hIL2 (H16A)	0	Full	0 ^a	Full
	IH3-hlgG1-L6-hIL2 (F42A)	0	Full	0 ^a	Full
	IH3-hlgG1-L6-hIL2 (H16A/F42A)	1	Full	0 ^a	Full
	A2-hlgG4-df-hIL-2 (D20A/R38E)	811 ^a	Partial, 20 - 90%	>10,000 ^a	Partial, 60 - 80%
	D12-hlgG4-df-hIL-2 (D20A/R38E)	>10,000 on graph, NC ^a	Partial, 20%	>10,000 ^a	Partial, 40%
	G12-hlgG4-df-hIL-2 (D20A/R38E)	>10,000 ^a	Partial, 20%	>10,000 ^a	Partial, 50%
	OMC476pB11-hlgG4-df-hIL-2 (D20A/R38E)	>10,000 on graph, NC ^a	Partial, 70%	36	Full
	OMC476pE4-hlgG4-df-hIL-2 (D20A/R38E)	>10,000 on graph, NC ^a	Partial, 70%	1619	Full
	OMC476pG10-hlgG4-df-hIL-2 (D20A/R38E)	>10,000 ^a	Partial, 70%	NC ^a	Inactive
	OMC476pH10-hlgG4-df-hIL-2 (D20A/R38E)	>10,000 on graph, NC ^a	Partial, 70%	3563 ^a	Partial, 80%
	A2-hlgG4-df-hIL-2 (D20A/F42A)	284	Full	4323 ^a	Partial, 80%
	A2-hlgG4-df-hIL-2 (D20A/F42S)	3542	Full	4052 ^a	Partial, 90%

A2-hlgG4-df-hIL-2 (D20S/R38E)	NT	NT	NT	7035 ^a	Full
A2-hlgG4-df-hIL-2 (F42A/N88R)	6423		Full	3757 ^a	Partial, 90%
A2-hlgG4-df-hIL-2 (F42I/I92D)	9543		Full	5611 ^a	Partial, 90%
A2-hlgG4-df-hIL-2 (F42Q/I92D)	8572		Full	3363 ^a	Full
A2-hlgG4-df-hIL-2 (F42T/I92D)	2175		Full	5649 ^a	Full
A2-hlgG4-df-hIL-2 (F42W/I92D)	1239		Full	4409 ^a	Partial, 50%
A2-hlgG4-df-hIL-2 (R38E/D84K)	160 - 1503		Full	1158 - 1716	Partial, 90%
A2-hlgG4-df-hIL-2 (R38E/I92K)	252 - 977		Full	864 - 1655	Partial, 80% - Full
C51E6-5-hlgG4-df-hIL-2 (D20A/R38E)	4317		Partial, 70%	>10,000 ^a	Partial, 60%
C51E6-5-hlgG4-L6-hIL-2 (D20A/R38E)	NT		NT	>10,000 ^a	Partial, 80%
C51E6-5-hlgG4-LE-df-hIL-2 (T3A/D20A/R38E/C125A)	4326		Partial, 80%	>10,000 ^a	Partial, 70%
C51E6-5-hlgG4-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A)	4336		Partial, 60%	>10,000 on graph, NC ^a	Partial, 60%
OMC.1.B6-hlgG4-L6-hIL-2 (D20A/R38E)	NT		NT	8460 ^a	Partial, 70%
OMC.1.D6-hlgG4-L6-hIL-2 (D20A/R38E)	NT		NT	>10,000 ^a	Partial, 70%
OMC.2.C6-hlgG4-L6-hIL-2 (D20A/R38E)	NT		NT	>10,000 ^a	Partial, 70%
2A3.H7-hlgG4-df-hIL-2 (D20A/R38E)	NT		NT	6603 ^a	Partial, 60%
1H9-hlgG4-df-hIL-2 (D20A/R38E)	NT		NT	9769 ^a	Partial, 90%
1D5-hlgG4-df-hIL-2 (D20A/R38E)	NT		NT	7420 ^a	Partial, 80%
1D5-hlgG4-LE-df-hIL-2 (T3A/D20A/R38E/C125A)	NT		NT	NC ^a	Inactive
1D5-hlgG4-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A)	NT		NT	NC ^a	Partial, 20%
2H7-hlgG1-df-hIL-2 (T3A/D20A/R38E/C125A)	4839 ^a		Full	2057 ^a	Full
2H7-hlgG1-LE-df-hIL-2 (T3A/D20A/R38E/C125A)	7727 ^a		Full	6729 ^a	Partial, 80%

2H7-hlgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A)	>10,000 ^a	Full	3428 ^a	Partial, 50 - 60%
2H7-hlgG4-df-hIL-2 (T3A/D20A/R38E/C125A)	707 - 7206 ^a	Full	>10,000 ^a	Partial, 60% - Full
2H7-hlgG4-LE-df-hIL-2 (T3A/D20A/R38E/C125A)	>10,000	Full	>10,000 ^a	Partial, 50 - 60%
2H7-hlgG4-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A)	>10,000	Full	7480 ^a	Partial, 40 - 50%
H7-767	>10,000 ^a	Partial, Full	>10,000 ^a	Full
2H7-hlgG1-df-hIL-2 (T3A/R38E/D84K/C125A)	1500	Partial, 90%	140 ^a	Full
2H7-hlgG1-LE-df-hIL-2 (T3A/R38E/D84K/C125A)	1268	Partial, 90%	517 ^a	Full
2H7-hlgG1-LAGA-df-hIL-2 (T3A/R38E/D84K/C125A)	2157 - 4035	Partial, 90% - Full	774 - 1650 ^a	Full
2H7-hlgG4-df-hIL-2 (T3A/R38E/D84K/C125A)	1602	Partial, 90%	>10,000 ^a	Full
2H7-hlgG4-LE-df-hIL-2 (T3A/R38E/D84K/C125A)	1675 - 5096	Partial, 90%	1281 - 2842 ^a	Full
2H7-hlgG4-LAGA-df-hIL-2 (T3A/R38E/D84K/C125A)	1596 - 5689	Partial, 90% - Full	1203 - 3515 ^a	Partial, 60 - 80%
2H7-hlgG1-df-hIL-2 (T3A/R38E/I92K/C125A)	370	Full	160	Full
2H7-hlgG1-LE-df-hIL-2 (T3A/R38E/I92K/C125A)	319	Full	656	Full
2H7-hlgG1-LAGA-df-hIL-2 (T3A/R38E/I92K/C125A)	406 - 1280	Full	514 - 1569 ^a	Full
2H7-hlgG4-df-hIL-2 (T3A/R38E/I92K/C125A)	520	Full	789 - 926	Partial, 80% - Full
2H7-hlgG4-LE-df-hIL-2 (T3A/R38E/I92K/C125A)	610 - 1675	Full	474 - 2080 ^a	Full
2H7-hlgG4-LAGA-df-hIL-2 (T3A/R38E/I92K/C125A)	827 - 2888	Full	737 - 2845 ^a	Partial, 70% - Full

	2H7-hlgG1-LAGA-df-hIL2 (T3A/D20S/R38E/C125A)	6689	Full	9711 ^a	Partial, 70%
	2H7-hlgG1-LAGA-df-hIL2 (T3A/R38E/D84F/C125A)	6199	Full	3915	Full
	2H7-hlgG1-LAGA-df-hIL2 (T3A/R38E/I92R/C125A)	75	Full	89	Full
	2H7-hlgG1-LAGA-df-hIL2 (T3A/R38E/I92E/C125A)	118	Full	53	Full
	2H7-hlgG1-LAGA-df-hIL2 (T3A/R38E/I92S/C125A)	9	Full	30	Full
	2H7-hlgG1-LAGA-df-hIL2 (T3A/R38E/I92D/C125A)	2717	Full	3396 ^a	Partial, 80%
	2H7-hlgG1-LAGA-df-hIL2 (T3A/H16E/R38E/C125A)	126	Full	122	Full

NT = Not Tested
NC = Not Calculated by GraphPad Prism 7
^a = Fold change is an estimate only since a full four parameter logistic curve was not reached

Example 17: Rescue of IL-2 activity of anti-hPD-1-attenuated hIL-2 fusion proteins on a cell line expressing the intermediate-affinity hIL-2 receptor and hPD-1

[0202] Anti-hPD-1-attenuated hIL-2 fusion proteins were evaluated for rescue of hIL-2 activity using a targeted cell line expressing hPD-1. Briefly, the TF1+IL-2R β cell line described in General Methods Protocol D was modified through lentiviral transduction to express the hPD-1 receptor (SEQ ID NO: 580). Flow cytometry with a Brilliant Blue 515 conjugated hPD-1 antibody (BD Biosciences Cat#565936) was used to detect hPD-1 expressing TF1+IL-2R β cells. Cells were sorted for low hPD-1 expression (less than 10^3 intensity on the Brilliant Blue 515 fluorophore). The pool was sorted twice more to collect cells that approximated hPD-1 expression levels on activated primary cells. This cell line (TF1+IL-2R β +hPD-1) was expanded and frozen in aliquots for the cell-based proliferation assays. Proliferation assays were performed as described in General Methods Protocol E with an incubation period of 3 days. Some variants tested had a modified human IgG1 or IgG4 kappa light chain framework with additional L235E or L235A/G237A (LAGA) substitutions to abrogate effector function of the immunoglobulin.

[0203] Table 24 summarizes the results from the proliferation assays on the targeted TF1+IL-2R β +hPD-1 cell line. Agonistic activity was measured as full, partial, or inactive as determined by the maximal luminescence of antibody-attenuated hIL-2 fusion proteins in comparison to the maximal luminescence of rhIL-2. Antibody-attenuated hIL-2 fusion protein dose-titration curves that reached the maximal luminescence as the rhIL-2 were considered to be variants with full activity. Partial activity was calculated as a percentage of full activity using rhIL-2 maximal luminescence as 100%. Maximal RLU of antibody-attenuated hIL-2 fusion proteins with less than 10% of the rhIL-2 maximal RLU at the highest concentration of 1200 nM were considered to have no agonist activity or inactive. For some variants, EC₅₀ values were estimates only since a full curve was not reached. Many examples of anti-hPD-1-hIL-2 fusion proteins with attenuated hIL-2 showed rescued hIL-2 activity on the targeted cell line where the non-targeting antibody controls (denoted with 1H3) demonstrated no rescue of hIL-2 activity. Full rescue was illustrated by the reduction of fold-change from rhIL-2 to a value of 0 or 1.

Table 24. Fold change from rhIL-2 and agonistic activity of antibody-hIL-2 fusion proteins on TF1+IL-2R β +hPD-1 cell line (human PD-1 expressing cell line with intermediate-affinity IL-2R).

	Variants	Fold decrease from rhIL-2 (TF1+IL-2R β +hPD-1)	Agonistic Activity (TF1+IL-2R β +hPD-1)
Non-Targeted Antibody-Attenuated hIL-2 Fusion Proteins	1H3-hIgG4-df-hIL-2 (WT)	1	Full
	1H3-hIgG4-L6-hIL-2 (WT)	1	Full
	1H3-hIgG4-L6-hIL-2 (D20Y)	NC ^a	Inactive
	1H3-hIgG4-df-hIL-2 (D20Y)	NC ^a	Inactive
	1H3-hIgG4-L6-hIL-2 (D20A/R38P)	3074 ^a	Partial, 80%
	1H3-hIgG4-L6-hIL-2 (D20A/R38S)	4482 ^a	Partial, 80%
	1H3-hIgG4-L6-hIL-2 (D20A/R38D)	2964 ^a	Partial, 60%
	1H3-hIgG4-L6-hIL-2 (D20A/R38Q/E95A)	3538 ^a	Partial, 80%
	1H3-hIgG4-L6-hIL-2 (D20A/F42H/E95A)	657 ^a	Partial, 70%
	1H3-hIgG4-L6-hIL-2 (R38D/I92D)	1428 ^a	Full
	1H3-hIgG4-L6-hIL-2 (R38E/I92D)	1887 ^a	Full
	1H3-hIgG4-L6-hIL-2 (F42H/I92D)	2024 ^a	Full
	1H3-hIgG4-df-hIL-2 (D20A/R38E)	307 - 3628 ^a	Partial, 70% - Full
	1H3-hIgG4-L6-hIL-2 (D20A/R38E)	4883 - 5226	Partial, 70% - Full
	1H3-hIgG4-L6-hIL-2 (T3A/D20A/R38E)	9167 ^a	Partial, 80%
	1H3-hIgG4-L6-hIL-2 (D20A/R38E/C125A)	4714	Partial, 60%
	1H3-hIgG4-L6-hIL-2 (T3A/D20A/R38E/C125A)	4626	Partial, 60%
	1H3-hIgG1-L6-hIL-2 (D20A/R38E)	297	Full
	1H3-hIgG1-L6-hIL-2 (T3A/D20A/R38E)	513	Partial, 80%
	1H3-hIgG1-L6-hIL-2 (D20A/R38E/C125A)	3342	Partial, 80%
	1H3-hIgG1-L6-hIL-2 (T3A/D20A/R38E/C125A)	1081	Partial, 90%
	1H3-hIgG1-L6-hIL-2 (T3A/D20A/R38E/C125A)	6459	Full
	1H3-hIgG1-L6-hIL-2 (H16A)	4 ^a	Full
	1H3-hIgG1-L6-hIL-2 (F42A)	0 ^a	Full
	1H3-hIgG1-L6-hIL-2 (H16A/F42A)	2 ^a	Full
	1H3-hIgG1-L6-hIL-2 (D20T)	75 ^a	Full
	1H3-hIgG1-L6-hIL-2 (T3A/F42A/Y45A/L72G/C125A)	2 ^a	Full

Anti-hPD-1-Attenuated hIL-2 Fusion Proteins	A2-hIgG4-df-hIL-2 (D20A/R38E)	0-1 ^a	Full
	D12-hIgG4-df-hIL-2 (D20A/R38E)	1 ^a	Full
	G12-hIgG4-df-hIL-2 (D20A/R38E)	1 ^a	Full
	OMC476pB11-hIgG4-df-hIL-2 (D20A/R38E)	0 ^a	Full
	OMC476pE4-hIgG4-df-hIL-2 (D20A/R38E)	2 ^a	Full
	OMC476pG10-hIgG4-df-hIL-2 (D20A/R38E)	0 ^a	Full
	OMC476pH10-hIgG4-df-hIL-2 (D20A/R38E)	1 ^a	Full
	A2-hIgG4-df-hIL-2 (D20A/F42A)	2 ^a	Full
	A2-hIgG4-df-hIL-2 (D20A/F42S)	1 ^a	Full
	A2-hIgG4-df-hIL-2 (D20S/R38E)	0 ^a	Full
	A2-hIgG4-df-hIL-2 (F42A/N88R)	0 ^a	Full
	A2-hIgG4-df-hIL-2 (F42I/I92D)	9 ^a	Full
	A2-hIgG4-df-hIL-2 (F42Q/I92D)	5 ^a	Full
	A2-hIgG4-df-hIL-2 (F42T/I92D)	1 ^a	Full
	A2-hIgG4-df-hIL-2 (F42W/I92D)	4 ^a	Full
	A2-hIgG4-df-hIL-2 (R38E/D84K)	0 - 1 ^a	Full
	A2-hIgG4-df-hIL-2 (R38E/I92K)	0 - 1 ^a	Full
	C51E6-5-hIgG4-df-hIL-2 (D20A/R38E)	0 - 1 ^a	Partial, 70% - Full
	C51E6-5-hIgG4-L6-hIL-2 (D20A/R38E)	1 ^a	Partial, 90%
	C51E6-5-hIgG4-LE-df-hIL-2 (T3A/D20A/R38E/C125A)	1 ^a	Full
	C51E6-5-hIgG4-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A)	0 ^a	Full
	OMC.1.B6-hIgG4-L6-hIL-2 (D20A/R38E)	0 ^a	Partial, 60%
	OMC.1.D6-hIgG4-L6-hIL-2 (D20A/R38E)	0 ^a	Partial, 90%
	OMC.2.C6-hIgG4-L6-hIL-2 (D20A/R38E)	0 ^a	Partial, 60%
	2A3.H7-hIgG4-df-hIL-2 (D20A/R38E)	0 ^a	Full
	1H9-hIgG4-df-hIL-2 (D20A/R38E)	0 ^a	Full
	1D5-hIgG4-df-hIL-2 (D20A/R38E)	1 ^a	Full
	2H7-hIgG1-df-hIL-2 (T3A/D20A/R38E/C125A)	1 ^a	Full
	2H7-hIgG1-LE-df-hIL-2 (T3A/D20A/R38E/C125A)	0 ^a	Full
	2H7-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A)	1 ^a	Full

2H7-hIgG4-df-hIL-2 (T3A/D20A/R38E/C125A)	1 ^a	Full
2H7-hIgG4-LE-df-hIL-2 (T3A/D20A/R38E/C125A)	1 - 4 ^a	Full
2H7-hIgG4-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A)	1 ^a	Full
H7-767	0 - 1 ^a	Full
2H7-hIgG1-df-hIL-2 (T3A/R38E/D84K/C125A)	2 ^a	Full
2H7-hIgG1-LE-df-hIL-2 (T3A/R38E/D84K/C125A)	1 ^a	Full
2H7-hIgG1-LAGA-df-hIL-2 (T3A/R38E/D84K/C125A)	1 ^a	Full
2H7-hIgG4-df-hIL-2 (T3A/R38E/D84K/C125A)	1 ^a	Full
2H7-hIgG4-LE-df-hIL-2 (T3A/R38E/D84K/C125A)	0 - 2 ^a	Full
2H7-hIgG4-LAGA-df-hIL-2 (T3A/R38E/D84K/C125A)	1 - 3 ^a	Full
2H7-hIgG1-df-hIL-2 (T3A/R38E/I92K/C125A)	1 ^a	Full
2H7-hIgG1-LE-df-hIL-2 (T3A/R38E/I92K/C125A)	1 ^a	Full
2H7-hIgG1-LAGA-df-hIL-2 (T3A/R38E/I92K/C125A)	1 - 2 ^a	Full
2H7-hIgG4-df-hIL-2 (T3A/R38E/I92K/C125A)	1 ^a	Full
2H7-hIgG4-LE-df-hIL-2 (T3A/R38E/I92K/C125A)	1 ^a	Full
2H7-hIgG4-LAGA-df-hIL-2 (T3A/R38E/I92K/C125A)	1 ^a	Full
2H7-hIgG1-LAGA-df-hIL2 (T3A/D20S/R38E/C125A)	Not Attenuated on graph; NC ^a	Full
2H7-hIgG1-LAGA-df-hIL2 (T3A/R38E/D84F/C125A)	0 ^a	Full
2H7-hIgG1-LAGA-df-hIL2 (T3A/R38E/I92R/C125A)	0 ^a	Full
2H7-hIgG1-LAGA-df-hIL2 (T3A/R38E/I92E/C125A)	2 ^a	Full
2H7-hIgG1-LAGA-df-hIL2 (T3A/R38E/I92S/C125A)	Not Attenuated on graph; NC ^a	Full
2H7-hIgG1-LAGA-df-hIL2 (T3A/R38E/I92D/C125A)	0 ^a	Full
2H7-hIgG1-LAGA-df-hIL2 (T3A/H16E/R38E/C125A)	>10,000 ^a	Full

NC = Not Calculated by GraphPad Prism 7

^a = Fold change is an estimate only since a full four parameter logistic curve was not reached

Example 18: Evaluation of surrogate anti-hPD-1-attenuated hIL-2 fusion proteins that block or do not block mouse PD-L1 in an *in vivo* murine colon adenocarcinoma (MC38) model

[0204] Since there are no accepted models to explore *in vivo* efficacy of oncology therapeutics in primates, a surrogate anti-mPD-1-attenuated hIL-2 fusion protein was generated and tested in a syngeneic murine tumor model. This MC38 colon adenocarcinoma model is routinely used to test efficacy of immuno-oncology therapeutics. To explore the *in vivo* effect of the anti-PD-1-attenuated hIL-2 fusion protein, a surrogate anti-mouse PD-1 antibody designated RMP1-14 (known to block mouse PD-L1 binding) and RMP1-30 (described as a mouse PD-L1 non-blocker) was fused to an attenuated hIL-2 at the C-terminus of the mouse IgG2b-N297A heavy chain and tested in an MC38 colon adenocarcinoma model. The hIL-2 moiety included the substitutions F42K, Y45R, and V69R that were tested on an IL-2 dependent mouse T lymphoblast cell line (CTLL-2) and that were demonstrated to be attenuated for mouse IL-2 activity. Human IL-2 can stimulate proliferation of mouse T cells at similar concentrations, however the same substitutions that attenuate activity on human IL-2 dependent cell lines do not attenuate activity on the CTLL-2 cell line (data not shown). As such, the F42K/Y45R/V69R substitutions were used in hIL-2 as a surrogate since they demonstrated attenuated IL-2 activity on mouse cell lines. Sequences comprising the heavy and light chain variable region sequences of anti-mouse PD-1 antibodies RMP1-14 and RMP1-30 (as described in Matsumoto K *et al.*, J Immunol. 2004 Feb 15;172(4):2530-41) were also formatted onto a murine IgG2b-N297A background to generate anti-mPD-1 RMP1-14 mIgG2b-N297A (SEQ ID NOs: 564 and 566) and anti-mPD-1 RMP1-30 mIgG2b-N297A (SEQ ID NOs: 567 and 568). The mouse IgG2b isotype with an N297A substitution is the murine equivalent of an Fc isotype that abrogates Fc immune effector function. Surrogate antibodies and antibody-attenuated hIL-2 fusion proteins were produced, expressed and Protein-A purified using standard techniques.

[0205] In this murine tumor model, ten week old female C57BL/6NCrI (Charles River) mice were injected into the right flank with 5×10^5 MC38 colorectal carcinoma cells. When tumors reached 80-120 mm³, mice were sorted into cohorts (10 mice/group) and treatment began on day 1 of study. Anti-mPD-1 RMP1-14 mIgG2b-N297A, anti-mPD-1 RMP1-30 mIgG2b-N297A, anti-mPD-1 RMP1-14 mIgG2b-N297A-L6-hIL-2

(F42K/Y45R/V69R) (SEQ ID NOs: 565 and 566), and anti-mPD-1 RMP1-30 mIgG2b-N297A-L6-hIL-2 (F42K/Y45R/V69R) (SEQ ID NOs: 568 and 569) were dosed intraperitoneally at 5 mg/kg twice weekly for 4 weeks along with vehicle control (phosphate-buffered saline). Tumor size was measured with calipers twice weekly using the formula $(w^2 \times L)/2$ where w = width and L = length for the duration of the study. The study endpoint was a tumor volume of 1000 mm³ or survival at day 50, whichever came first.

[0206] FIG. 8 demonstrates that although the administration of anti-mPD-1 RMP1-14-mIgG2b-N297A or anti-mPD-1 RMP1-30-mIgG2b-N297A antibodies alone did not promote significant efficacy relative to treatment with vehicle control, the administration of anti-mPD-1 RMP1-14 mIgG2b-N297A-L6-hIL-2 (F42K/Y45R/V69R) or anti-mPD-1 RMP1-30 mIgG2b-N297A-L6-hIL-2 (F42K/Y45R/V69R) anti-PD-1-attenuated hIL-2 fusion proteins was associated with 90% and 100% complete tumor regressions respectively. These data demonstrate that the anti-tumor efficacy mediated by anti-mPD-1-hIL-2 (F42K/Y45R/V69R) fusion proteins does not require PD-1 checkpoint blockade and that efficacy is dependent on hIL-2 activity. The data further demonstrate that antibody mediated targeting of PD-1 expressing T cells is sufficient to promote potent anti-tumor efficacy in the MC38 tumor model.

Example 19: Surrogate anti-hPD-1-attenuated hIL-2 fusion protein expands effector memory CD8⁺ T cells in an *in vivo* murine colon adenocarcinoma model

[0207] To understand the mechanism-of-action of the surrogate anti-hPD-1-attenuated hIL-2 fusion protein *in vivo*, a similar *in vivo* experiment to Example 18 was performed, followed by immunophenotyping of the resultant T cell populations in tumors, blood, spleens and lymph nodes after three doses. Ten week old female C57BL/6NCrl (Charles River) mice were subcutaneously implanted with the 5×10^5 murine MC38 colon adenocarcinoma cancer tumor cells into the right flank and tumors were monitored for growth. Animals with tumors between 150-260 mm³ were divided between four groups with 10 mice per group for the study. After 21 days post-implantation, animals were dosed intraperitoneally with 0.2 mL/dose phosphate buffered saline (PBS) for the vehicle control, 5 mg/kg anti-KLH-C3-mIgG2b-N297A-L6-hIL-2 (F42K/Y45R/V69R), 5 mg/kg anti-mPD-1 RMP1-30 mIgG2b-N297A, or 5 mg/kg anti-mPD-1 RMP1-30 mIgG2b-N297A-L6-hIL-2 (F42K/Y45R/V69R) on days 1, 4 and 8. On day 9, tumors, spleens and inguinal lymph nodes

were harvested from all mice and processed into single cell suspensions for subsequent flow cytometry analysis.

[0208] FIG. 9A charts the tumor volume growth (mm^3) over 9 days from the first dose on day 1 where each point represents a mean of 10 mice. By day 8, anti-mPD-1 RMP1-30 mIgG2b-N297A-L6-hIL-2 (F42K/Y45R/V69R) had a reduction in tumor volume compared to other treatment groups. FIG. 9B summarizes the contribution of various CD8⁺ T cell subsets in the tumor of each treatment group in which T Central Memory were phenotyped as CD45⁺CD3⁺CD4⁺CD8⁺CD44⁺CD127⁺CD69⁺CD103⁻, T Effector Memory were CD45⁺CD3⁺CD4⁺CD8⁺CD44⁺CD127⁺CD69⁺CD103⁻CD62L⁻, T Resident Memory were CD45⁺CD3⁺CD4⁺CD8⁺CD44⁺CD127⁺CD69⁺CD103⁺, CD44⁺CD62L⁻ T cells were CD45⁺CD3⁺CD4⁺CD8⁺CD44⁺CD62L⁻ and T Naïve were CD45⁺CD3⁺CD4⁺CD8⁺CD44⁻CD62L⁺. In comparison to other treatment groups, there was expansion of the CD8⁺ T Effector Memory subset in the anti-mPD-1 RMP1-30 mIgG2b-N297A-L6-hIL-2 (F42K/Y45R/V69R) treated mice as indicated in the increase of the light grey slice of FIG. 9B. This was also illustrated in FIG. 9C in absolute counts (cells/ μL) within the MC38 dissected tumor. Furthermore, within the tumor, there was a decrease in the absolute counts (cells/ μL) of Regulatory T cells defined as expressing CD45⁺CD3⁺CD4⁺CD8⁺CD25⁺FoxP3⁺ markers.

[0209] The expansion of CD8⁺ T Effector Memory and decrease in Regulatory T cells has been associated with effective immunotherapy in both mice and humans.

Example 20: Anti-hPD-1-attenuated hIL-2 fusion proteins are active *in vivo* in an NCG-PBMC model

[0210] Engrafting human immune cells into NOD-*Prkdc^{em26Cd52}IL-2rg^{em26Cd22}*/NjuCrl (NCG) mice that lack functional T, B, and NK cells has been a valuable tool for evaluating efficacy of therapeutics hypothesized to stimulate human T cells. In this model, if the therapeutic activates human T cells, there would be a resulting expansion of T cells and accelerated graft-versus-host disease (GvHD).

[0211] Three independent donors for human peripheral mononuclear cell (hPBMC) engraftment were evaluated over a 4 week period for engraftment kinetics as well as expression of human PD-1 and human IL-2 receptors on T cells. Of the three donors tested, the donor that induced the most T cells with an intermediate window for GvHD was chosen. 1.5×10^7 hPBMCs were intravenously injected into NCG mice and divided into 8 groups of 8-16 mice. On days 7, 10, and 14, mice were intraperitoneally injected with three doses of

2H7-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) (SEQ ID NOs: 471, 425) (2.5 mg/kg, 5 mg/kg, or 10 mg/kg), 1H3-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) (SEQ ID NOs: 546, 374) (5 mg/kg or 10 mg/kg), 1H3-hIgG1-LAGA-df-hIL-2 (T3A/C125A) (SEQ ID NOs: 563, 374) (10 mg/kg), or 2H7-hIgG1-LAGA-df-hIL-2 (T3A/R38E/192K/C125A) (SEQ ID NOs: 474, 425) (5 mg/kg). The anti-DNase fusion protein both as a wild-type hIL-2 (1H3-hIgG1-LAGA-df-hIL-2 (T3A/C125A)) and with the attenuated hIL-2 moiety (1H3-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A)) was used as a non-targeting antibody control. Although the 1H3-hIgG1-LAGA-df-hIL-2 (T3A/C125A) fusion protein had no changes in the hIL-2 moiety which reduce hIL-2 activity, it did comprise the T3A and C125A substitutions to remove the predicted O-linked glycosylation site on human IL-2 (see for example Int'l Pub. No. WO2012/107417) and unpaired cysteine residue (see for example Int'l Pub. No. WO2018/184964), respectively. These substitutions have not demonstrated reduced hIL-2 potency in the clinic. On Day 21, blood, spleen, and lungs were harvested in which blood and spleens were processed for flow cytometry immunophenotyping while lungs were weighed.

[0212] After 21 days, flow cytometry immunophenotyping was performed on the blood and spleens of animals. Table 25 summarizes the markers used to delineate human T cell populations for subsequent analysis.

Table 25. Phenotypic markers to define human T cell subsets in NCG-PBMC mice

Cell Population	Phenotypic Markers
Pan T cells	CD3+
CD8+ Naïve	CD3+CD4-CD8+CD45RO-CCR7+
CD8+ Effector	CD3+CD4-CD8+CD45RO-CCR7-
CD8+ Effector Memory	CD3+CD4-CD8+CD45RO+CCR7-
CD8+ Central Memory	CD3+CD4-CD8+CD45RO+CCR7+
CD4+ Naïve	CD3+CD4+CD8-CD45RO-CCR7+
CD4+ Effector	CD3+CD4+CD8-CD45RO-CCR7-
CD4+ Effector Memory	CD3+CD4+CD8-CD45RO+CCR7-
CD4+ Central Memory	CD3+CD4+CD8-CD45RO+CCR7+
Regulatory T cells	CD3+CD4+CD8-CD25+Foxp3+
NK Cells	CD3-CD56+

[0213] Body weight was measured for 21 days and normalized to day 1 for each individual animal as an assessment of graft-versus-host disease (GvHD) as illustrated in FIG. 10. Accelerated GvHD was observed in the 2H7-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) treated mice at 10 mg/kg. A small decrease in body weight was also observed in the 2H7-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) treated mice at 2.5 mg/kg, 5 mg/kg, and 2H7-hIgG1-LAGA-df-hIL-2 (T3A/R38E/I92K/C125A) at 5 mg/kg. Although body weight loss was seen in the 1H3-hIgG1-LAGA-df-hIL-2 (T3A/C125A), it was not sustained.

[0214] The flow cytometry analysis correlated with the accelerated graft-versus-host disease (GvHD) observed. Using the phenotypic markers for human T cell subset delineation provided in Table 25, flow cytometry analysis of peripheral blood demonstrated only a minor expansion of CD3⁺, CD4⁺, and CD8⁺ T cell subsets (as quantified by a fold change from vehicle control of between 10-fold to 50-fold for CD3⁺ T cells) in mice treated with 2H7-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) at 2.5 mg/kg and 5 mg/kg, and mice treated with 1H3-hIgG1-LAGA-df-hIL-2 (T3A/C125A) at 10 mg/kg. Furthermore, CD3⁺, CD4⁺, and CD8⁺ T cell subsets were greatly expanded (fold change from vehicle control was greater than 50-fold for CD3⁺ T cells) in the peripheral blood of mice treated with 2H7-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) at 10 mg/kg. Table 26 summarizes the expanded human T cell subsets.

Table 26. Expansion of human CD3⁺, CD4⁺, and CD8⁺ T cell subsets in NCG-PBMC mice

Agent	Fold Change in numbers (Blood)		
	CD3 ⁺ T cells	CD4 ⁺ T cells	CD8 ⁺ T cells
Vehicle (PBS)	1	1	1
1H3-hIgG1-LAGA-df-hIL-2 (T3A/C125A) 10 mg/kg	22.76	27.73	16.13
1H3-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) 5 mg/kg	1.94	2.12	1.74
1H3-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) 10 mg/kg	0.56	0.56	0.57
2H7-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) 2.5 mg/kg	24.57	32.4	14.4
2H7-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) 5 mg/kg	53.03	70.74	22.86
2H7-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) 10 mg/kg	203.3	296.94	58.82
2H7-hIgG1-LAGA-df-hIL-2 (T3A/R38E/I92K/C125A) 5 mg/kg	31.79	48.76	8.79

N/A = Not Applicable

[0215] In addition to evaluating CD3⁺, CD4⁺, and CD8⁺ T cells between treatment groups, the memory and naïve subsets for CD4⁺ and CD8⁺ T cell subsets were also assessed. The phenotypic markers used for delineation of Naïve, Effector, Effector Memory and Central Memory for both CD4⁺ and CD8⁺ T cell is summarized in Table 25. There were no changes in Naïve, Effector or Central Memory T cells between treatment groups (data not shown). However, mice treated with 2H7-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) at 10 mg/kg had greatly expanded CD4⁺ and CD8⁺ Effector Memory (EM) T cells in the peripheral blood with an average cell number per milliliter greater than 5 million for CD8⁺ T cells and greater than 50 million for CD4⁺ T cells (FIG. 11A and 11B). Box-and-whisker plots were graphed with the box around the first and third quartile, the horizontal line as the median, and lines indicated the minimum and maximum points. There was moderate expansion of CD8⁺ Effector Memory (EM) T cells defined as an average cell number per million between 1 to 5 million per milliliter for animals treated with 2H7-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) at 2.5 mg/kg and 5 mg/kg as well as for 1H3-hIgG1-LAGA-df-hIL-2 (T3A/C125A). There was moderate expansion of CD4⁺ Effector Memory (EM) T cells between 6 to 13 million per milliliter for CD4⁺ T cells in the mice treated with 2H7-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) at 2.5 mg/kg and 5 mg/kg.

[0216] In addition to stimulating effector T cells, IL-2 has been described to stimulate NK cells and regulatory T cells (Tregs) and since Tregs express high levels of CD25 and NK cells express CD122, these immune cell types were also evaluated. FIG. 12 illustrates that animals treated with 2H7-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) at the highest dose of 10 mg/kg did not expand human regulatory T cells and instead had the lowest percent of regulatory T cells (as phenotypically defined in Table 25) in the peripheral blood of animals. There was a dose-dependent decrease of human regulatory T cells and in comparison to vehicle control that had an average of 1.6% human CD3⁺ T cells that were Tregs, 2H7-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) at 10 mg/kg had an average of 0.16% human CD3⁺ T cells that were Tregs. There were no changes in the percentage of human NK cells in peripheral blood (phenotype defined in Table 25) in all treatment groups in comparison to vehicle control (data not shown).

Example 21: Non-clinical safety profile of anti-hPD-1-attenuated hIL-2 fusion proteins

[0217] Cynomolgus monkeys previously have been used to evaluate the toxicity of unmodified IL-2. Lethality was observed in cynomolgus monkeys at exogenous recombinant IL-2 doses as low as 50 µg/kg/day. Since the binding of H7-767 to cynomolgus monkey hPD-1 on primary activated PBMCs was confirmed by flow cytometry (Example 12), a single-dose study for preliminary safety assessment was performed with both a variant of H7-767 (H7-02-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) (SEQ ID NOs: 582 and 583) and H7-767. H7-02-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) was delivered by 15 minute iv infusion to 8 monkeys at 1 mg/kg (4 animals) or 10 mg/kg (4 animals). Sampling at time-points up to 360 hours following infusion was performed. No adverse effects, gross toxicities, body weight loss, or lethality was observed (data not shown). A follow-up single-dose study using H7-767 was performed at higher doses of 5 mg/kg and 50 mg/kg similar to the first study, with sampling at time-points up to 360 hours post-infusion. Again, no adverse effects, gross toxicities, body weight loss or lethality was observed (data not shown).

Example 22: Attenuation of IL-2 activity of modified hIL-2 proteins

[0218] The attenuation of IL-2 activity of modified hIL-2 proteins comprising a substitution at amino acid position 20 (D20) and a substitution at amino acid position 38 (R38) was tested in proliferation assays in both the NK-92 and TF1+IL-2Rβ cell lines as described in Example 5 above. The modified hIL-2 proteins were grouped into 7 groups (1 to 7) based upon the maximal agonist activity of the modified hIL-2 protein and the level of attenuation of potency on both the intermediate and high-affinity receptors (Table 27) relative to non-modified recombinant hIL-2. The criteria used for grouping the modified hIL-2 proteins was:

- Group 1: Variants with the highest attenuation (*i.e.*, >10,000-fold) and at least about 80% activity on the intermediate-affinity receptor but also had high attenuation and at least about 70% activity on the high-affinity receptor.
- Group 2: Variants with at least about 70% activity and >1,000-fold attenuation on the intermediate-affinity receptor, and about 20% activity to about 30% activity on the high-affinity receptor.
- Group 3: Variants with about 50% activity to about 70% activity and >1,000-fold attenuation on the intermediate-affinity receptor, and about 20% activity on the high-affinity receptor.

- Group 4: Variants with at least about 70% activity but only >500-fold attenuation on the intermediate-affinity receptor, and about 50% activity on the high-affinity receptor.
- Group 5: Variants with at least about 70% activity on both receptors but >10-fold to >300-fold attenuation on the intermediate-affinity receptor in descending order and 70-fold to 1500-fold attenuation on the high-affinity receptor also in descending order.
- Group 6: Variants with only about 30% activity and >2,500-fold attenuation on the intermediate-affinity receptor, and no activity on the high-affinity receptor.
- Group 7: Variants with no activity on both the intermediate-affinity receptor and high-affinity receptor.

Table 27. Fold change from rhIL-2 and agonistic activity of modified hIL-2 proteins comprising a substitution at amino acid position 20 (D20) and a substitution at amino acid position 38 (R38) in a cell-based proliferation assay

	Variants	SEQ ID NO of hIL-2 variant	Fold change from rhIL-2 (NK-92)	Agonistic Activity (NK-92)	Fold change from rhIL-2 (TF1+IL-2R β)	Agonistic Activity (TF1+IL-2R β)
Group 1	1H3-hIgG1-L6-hIL-2 (D20A/R38E)	149	1183 - 2016	at least about 70%	>10,000 ^a	at least about 80%
Group 2	1H3-hIgG1-L6-hIL-2 (D20Q/R38E)	608	>10,000 ^a	about 30%	6665	at least about 70%
Group 2	1H3-hIgG1-L6-hIL-2 (D20M/R38E)	614	>10,000 ^a	about 30%	2607	at least about 70%
Group 2	1H3-hIgG1-L6-hIL-2 (D20I/R38E)	611	>10,000 ^a	about 20%	1782	at least about 70%
Group 3	1H3-hIgG1-L6-hIL-2 (D20V/R38E)	620	>10,000 on graph, NC ^a	about 20%	1849	about 50%
Group 4	1H3-hIgG1-L6-hIL-2 (D20S/R38E)	307	>10,000 on graph, NC ^a	about 50%	626	at least about 70%
Group 5	1H3-hIgG1-L6-hIL-2 (D20N/R38E)	607	1521	at least about 70%	378	at least about 70%
Group 5	1H3-hIgG1-L6-hIL-2 (D20G/R38E)	610	1288	at least about 70%	212	at least about 70%

Group 5	1H3-hIgG1-L6-hIL-2 (D20T/R38E)	617	524	at least about 70%	75	at least about 70%
Group 5	1H3-hIgG1-L6-hIL-2 (D20E/R38E)	609	77	at least about 70%	12	at least about 70%
Group 6	1H3-hIgG1-L6-hIL-2 (D20H/R38E)	306	No activity	No activity	2945	about 30%
Group 7	1H3-hIgG1-L6-hIL-2 (D20L/R38E)	612	>10,000 ^a	No activity	>10,000 ^a	No activity
Group 7	1H3-hIgG1-L6-hIL-2 (D20K/R38E)	613	No activity	No activity	544	No activity
Group 7	1H3-hIgG1-L6-hIL-2 (D20F/R38E)	615	>10,000 ^a	No activity	>10,000 ^a	No activity
Group 7	1H3-hIgG1-L6-hIL-2 (D20P/R38E)	616	>10,000 ^a	No activity	>10,000 ^a	No activity
Group 7	1H3-hIgG1-L6-hIL-2 (D20W/R38E)	618	>10,000 ^a	No activity	>10,000 ^a	No activity
Group 7	1H3-hIgG1-L6-hIL-2 (D20Y/R38E)	619	>10,000 ^a	No activity	1	No activity
Group 7	1H3-hIgG1-L6-hIL-2 (D20R/R38E)	606	>10,000 ^a	No activity	>10,000 ^a	No activity

Example 23: Activity of surrogate fusion protein in a murine MC38 Colo-rectal tumor model

[0219] Ten week old female C57BL/6NCrl mice were injected into the right flank with 5×10^5 syngeneic MC38 colorectal carcinoma cells. When tumors reached 80-120 mm³, mice were sorted into cohorts (10 mice/group) and treatment began on day 1 of study. All agents except hIL-2 were dosed intraperitoneally at 5 mg/kg twice weekly for 4 weeks, starting on day 1. hIL-2 was dosed intraperitoneally at 36,000 International Units once a day from days 1-5. Tumor size was measured with calipers twice weekly for the duration of the study. The study endpoint was a tumor volume of 1000 mm³ or survival at day 50 or progression free survival at day 70, whichever came first.

[0220] All test agents including antibody molecules and antibody-hIL-2 fusion proteins were generated using a mouse IgG2b Fc region with a single N297A amino-acid substitution at position 297, which prevents glycosylation of the Fc region and significantly reduces any Fc region-mediated immune effector function, thereby preventing cellular depletion *in vivo*. Anti-mPD-1 RMP1-14 is a monoclonal antibody antagonist of the mouse PD-1 receptor (Matsumoto, J Immunol 172: 2530-2541, 2004). Anti-mPD-1 RMP1-14-hIL-2 F42K/Y45R/V69R is a bi-functional fusion protein consisting of the monoclonal RMP1-14 antibody antagonist of the mouse PD-1 receptor fused at its C-terminus via a flexible six amino-acid glycine/serine linker to hIL-2 F42K/Y45R/V69R (SEQ ID NO: 621) that is a reduced potency IL-2 variant. This molecule was designed to target a reduced potency hIL-2 variant directly to PD-1 expressing T cells *in vivo* in mice. Anti-KLH-hIL-2 F42K, Y45R, V69R is a control fusion protein consisting of an isotype control monoclonal antibody recognizing a non-mammalian antigen (keyhole limpet hemocyanin, KLH) fused at its C-terminus via a flexible six amino-acid glycine/serine linker to hIL-2 F42K, Y45R, V69R that is a reduced potency IL-2 variant.

[0221] Results are presented in FIG. 19. The MC38 colo-rectal tumor model is particularly responsive to antibody mediated PD-1 receptor inhibition. Although tumors growing in vehicle-treated mice rapidly reached study endpoint, 50% of mice treated with anti-mPD-1 RMP1-14 experienced complete tumor regression. In contrast, 100% of mice treated with an anti-mPD-1 RMP1-14-hIL-2 F42K, Y45R, V69R fusion protein experienced durable, long-term tumor regression. Mice treated with various combinations of the individual components of anti-mPD-1 RMP1-14-hIL-2 F42K, Y45R, V69R fusion protein, including either anti-mPD-1 RMP1-14 combined with hIL-2 free cytokine (administered at a dose and regimen equivalent to a therapeutic dose in humans) or anti-mPD-1 RMP1-14 combined with a non-targeted anti-KLH-hIL-2 F42K, Y45R, V69R fusion protein did not recapitulate the efficacy seen with anti-mPD-1 RMP1-14-hIL-2 F42K, Y45R, V69R. These data demonstrate that targeting a reduced potency hIL-2 to PD-1 expressing cells significantly improves anti-tumor efficacy relative to an anti-PD-1 receptor antagonist and that the activity of the fusion protein is not due to the additive effects of the molecule's individual components.

Example 24: Evaluation of protective anti-tumor immunity induced by surrogate anti-mPD-1 RMP1-14-hIL-2 F42K, Y45R, V69R in the MC38 Colo-rectal tumor model

[0222] Mice that had undergone a complete tumor regression in the primary tumor study described in Example 23 and that had survived to day 50 were subjected to a secondary tumor challenge without any additional drug therapy. For tumor re-challenge, mice were implanted on the left flank contralateral to the location of the primary tumor with 5×10^5 MC38 tumor cells. As a control group, 10 age-matched tumor naïve mice were also implanted with MC38 tumor cells.

[0223] FIG. 20 shows that all mice that had previously undergone a complete tumor regression in a prior primary tumor study and had survived to day 50 after treatment with anti-mPD-1 RMP1-14-hIL-2 F42K, Y45R, V69R were completely protected from secondary tumor development. In contrast, all tumor-naïve mice implanted with MC38 tumor cells went on to develop tumors that rapidly reached study endpoint of tumor volume of 100 mm^3 . The development of protective anti-tumor immunity in the absence of continued drug therapy suggests that anti-mPD-1 RMP1-14-hIL-2 F42K, Y45R, V69R induced an anti-tumor memory T cell response.

Example 25: Evaluation of the compatibility of combination therapy with surrogate anti-mPD-1 RMP1-30-hIL-2 F42K, Y45R, V69R and anti-mPD-1 RMP1-14 antibodies in a mouse MC38 colorectal tumor model

[0224] To evaluate the compatibility of the disclosed immunoconjugates for use in combination therapy with antagonistic anti-PD-1 antibodies, surrogate antagonist anti-mouse PD-1 antibodies and surrogate immunoconjugates were used because antagonistic anti-human PD-1 antibodies do not bind mouse PD-1 and the modified IL-2 proteins do not work on mouse IL-2 receptors. Ten week old female C57BL/6NCrl mice were injected into the right flank with 5×10^5 syngeneic MC38 colorectal carcinoma cells. When tumors reached $80\text{-}120 \text{ mm}^3$, mice were sorted into cohorts (10 mice/group) and treatment began on day 1 of study. All agents were dosed intraperitoneally, once weekly for 4 weeks, starting on day 1. Anti-mPD-1 RMP1-30-hIL-2 F42K, Y45R, V69R was dosed at 1 mg/kg and anti-mPD-1 RMP1-14 at 2 mg/kg. Tumor size was measured with calipers twice weekly for the duration of the study. The study endpoint was a mean tumor weight of 1500 mm^3 in the vehicle-treated control group, or 45 days, whichever

came first. Endpoint sampling was conducted over two days due to the high number of mice needed to be sampled.

[0225] Both test agents were generated using a mouse IgG2b Fc region with a single N297A amino-acid substitution at position 297, which prevents glycosylation of the Fc region and significantly reduces any Fc region-mediated immune effector function, thereby preventing cellular depletion *in vivo*. Anti-mPD-1 RMP1-14 is a monoclonal antibody antagonist of the mouse PD-1 receptor (Matsumoto, J Immunol 172: 2530-2541, 2004). Anti-mPD-1 RMP1-30-hIL-2 F42K/Y45R/V69R is a bi-functional fusion protein consisting of the monoclonal RMP1-30 antibody non-antagonist of the mouse PD-1 receptor fused at its C-terminus via a flexible six amino-acid glycine/serine linker to hIL-2 F42K/Y45R/V69R (SEQ ID NO: 621) that is a IL-2 variant with reduced potency on IL-2 receptors in mice. This molecule was designed to target the reduced potency hIL-2 variant directly to PD-1 expressing T cells *in vivo* in mice.

[0226] Results are presented in FIG. 21. Tumors growing in vehicle-treated mice reached study endpoint by day 25. In contrast, mice treated with anti-mPD-1 RMP1-14 or anti-mPD-1 RMP1-30-hIL-2 F42K/Y45R/V69R experienced partial tumor regression, with a better outcome in the anti- mPD-1 RMP1-30-hIL-2 F42K/Y45R/V69R group. The effect in the combination group led to the most effective tumor volume reduction. This data demonstrated that neither antibody interfered with the other's ability to bind to PD-1, and when administered in combination could achieve greater efficacy than each agent individually.

[0227] This data, combined with the data presented herein demonstrating that the disclosed immunoconjugates bind PD-1 in the presence of antagonistic anti-PD-1 antibodies and the data presented herein demonstrating that the disclosed immunoconjugates are designed to deliver the modified hIL-2 protein to IL-2 receptors rather than antagonizing PD-1, shows that the disclosed immunoconjugates and antagonistic anti-PD-1 antibodies are effective for use as a combination therapy to reduce tumor volume.

Example 26: Combination therapy with anti-human PD-1 (hPD-1) antibody-modified human interleukin-2 (hIL-2) immunoconjugates and antagonistic anti-PD-1 antibodies

[0228] The data in Example 25 above demonstrates that a greater therapeutic efficacy can be achieved by combining anti-hPD-1 antibody-modified hIL-2 immunoconjugates with antagonistic anti-PD-1 antibodies. A single-dose study for preliminary safety assessment will be

performed in Cynomolgus monkeys with: 1) the disclosed immunoconjugates with and without nivolumab; and 2) the disclosed immunoconjugates with and without pembrolizumab. Sampling at time-points up to 360 hours following infusion will be performed. Adverse effects, gross toxicities, body weight loss, and lethality will be evaluated. Follow-up studies using higher doses of immunoconjugate and/or antagonistic anti-PD-1 antibody will be performed.

[0229] Those skilled in the art will appreciate that numerous changes and modifications can be made to the preferred embodiments disclosed herein and that such changes and modifications can be made without departing from the spirit of the invention. It is, therefore, intended that the appended claims cover all such equivalent variations as fall within the true spirit and scope of the invention.

[0230] The disclosures of each patent, patent application, and publication cited or described in this document are hereby incorporated herein by reference, in its entirety.

Table 28. Exemplary Antibodies

Antibody Name	Heavy chain	Light chain
Anti-hPD-1 #1-mIgG2b-N297A	Anti-hPD-1 #1-mIgG2b-N297A HC (SEQ ID NO: 348)	Anti-hPD-1 #1-mKappa LC (SEQ ID NO: 349)
Anti-hPD-1 #2-mIgG2b-N297A	Anti-hPD-1 #2-mIgG2b-N297A HC (SEQ ID NO: 350)	Anti-hPD-1 #2-mKappa LC (SEQ ID NO: 351)
hIL-2 Nterm light chain df	hIL-2-hlgG1 HC (SEQ ID NO: 379)	hIL-2-df-1H3-hkappa LC (SEQ ID NO: 356)
hIL-2 Nterm light chain L6 fusion	hIL-2-hlgG1 HC (SEQ ID NO: 379)	hIL-2-L6-1H3-hkappa LC (SEQ ID NO: 357)
hIL-2 Nterm heavy chain df	hIL-2-df-1H3-hlgG1 HC (SEQ ID NO: 358)	1H3-hKappa LC (SEQ ID NO: 374)
hIL-2 Nterm heavy chain L6 fusion	hIL-2-L6-1H3-hlgG1 HC (SEQ ID NO: 359)	1H3-hKappa LC (SEQ ID NO: 374)
hIL-2 Cterm heavy chain df	1H3-hlgG1-df-hIL-2 HC (SEQ ID NO: 360)	1H3-hKappa LC (SEQ ID NO: 374)
hIL-2 Cterm heavy chain L6 fusion	1H3-hlgG1-L6-hIL-2 HC (SEQ ID NO: 361)	1H3-hKappa LC (SEQ ID NO: 374)
hIL-2 Cterm light chain df	1H3-hlgG1 HC (SEQ ID NO: 379)	1H3-hKappa-df-hIL-2 (WT) LC (SEQ ID NO: 362)
hIL-2 Cterm light chain L6 fusion	1H3-hlgG1 HC (SEQ ID NO: 379)	1H3-hKappa-L6-hIL-2 (WT) LC (SEQ ID NO: 363)
hCD25-L20-hIL-2 Nterm heavy chain df	hCD25-L20-hIL-2-df-1H3-hlgG1 HC (SEQ ID NO: 365)	1H3-hKappa LC (SEQ ID NO: 374)
hCD25-L20-hIL-2 Nterm heavy chain L6 fusion	hCD25-L20-hIL-2-L6-1H3-hlgG1 HC (SEQ ID NO: 366)	1H3-hKappa LC (SEQ ID NO: 374)
hCD25-L20-hIL-2 Nterm light chain df	1H3-hlgG1 HC (SEQ ID NO: 379)	hCD25-L20-hIL-2-df-1H3-hKappa LC (SEQ ID NO: 367)
hCD25-L20-hIL-2 Nterm light chain L6 fusion	1H3-hlgG1 HC (SEQ ID NO: 379)	hCD25-L20-hIL-2-L6-1H3-hKappa LC (SEQ ID NO: 368)
hCD25-L20-hIL-2 Cterm heavy chain df	1H3-hlgG1-df-hCD25-L20-hIL-2 HC (SEQ ID NO: 369)	1H3-hKappa LC (SEQ ID NO: 374)

hCD25-L20-hIL-2 Cterm heavy chain L6 fusion	1H3-hIgG1-L6-hCD25-L20-hIL-2 HC (SEQ ID NO: 370)	1H3-hKappa LC (SEQ ID NO: 374)
hCD25-L20-hIL-2 Cterm light chain df	1H3-hIgG1 HC (SEQ ID NO: 379)	1H3-hKappa-df-hCD25-L20-hIL-2 LC (SEQ ID NO: 371)
hCD25-L20-hIL-2 Cterm light chain L6 fusion	1H3-hIgG1 HC (SEQ ID NO: 379)	1H3-hKappa-L6-hCD25-L20-hIL-2 LC (SEQ ID NO: 372)
2D12-mIgG1-D265A-L6-hIL-2	2D12-mIgG1-D265A-L6-hIL-2 HC (SEQ ID NO: 375)	2D12-mKappa LC (SEQ ID NO: 376)
2H7-hIgG4	2H7-hIgG4 HC (SEQ ID NO: 424)	2H7-hKappa LC (SEQ ID NO: 425)
C51E6-5-hIgG4	C51E6-5-hIgG4 HC (SEQ ID NO: 426)	C51E6-5-hKappa LC (SEQ ID NO: 427)
A2-hIgG4	A2-hIgG4 HC (SEQ ID NO: 428)	A2-hLambda LC (SEQ ID NO: 429)
H7-632-hIgG1-LAGA	H7-632 HC (SEQ ID NO: 414)	H7-632 LC (SEQ ID NO: 415)
2H7-hIgG4-df-hIL-2 (D20A/R38E)	2H7-hIgG4-df-hIL-2 (D20A/R38E) HC (SEQ ID NO: 430)	2H7-hKappa LC (SEQ ID NO: 425)
C51E6-5-hIgG4-L6-hIL-2 (D20A/R38E)	C51E6-5-hIgG4-L6-hIL-2 (D20A/R38E) HC (SEQ ID NO: 432)	C51E6-5-hKappa LC (SEQ ID NO: 427)
A2-hIgG4-df-hIL-2 (D20A/R38E)	A2-hIgG4-df-hIL-2 (D20A/R38E) HC (SEQ ID NO: 433)	A2-hLambda LC (SEQ ID NO: 429)
1H3-hIgG4-df-hIL-2 (D20A/R38E)	1H3-hIgG4-df-hIL-2 (D20A/R38E) HC (SEQ ID NO: 434)	1H3-hKappa LC (SEQ ID NO: 374)
2H7-hIgG4-df-hIL-2 (T3A/D20A/R38E/C125A)	2H7-hIgG4-df-hIL-2 (T3A/D20A/R38E/C125A) HC (SEQ ID NO: 435)	2H7-hKappa LC (SEQ ID NO: 425)
OMC.1.B6-hIgG4	OMC.1.B6-hIgG4 HC (SEQ ID NO: 438)	OMC.1.B6-hLambda LC (SEQ ID NO: 439)
OMC.2.C6-hIgG4	OMC.2.C6-hIgG4 HC (SEQ ID NO: 440)	OMC.2.C6-hLambda LC (SEQ ID NO: 441)
OMC.1.D6-hIgG4	OMC.1.D6-hIgG4 HC (SEQ ID NO: 442)	OMC.1.D6-hLambda LC (SEQ ID NO: 443)
D12-hIgG4	D12-hIgG4 HC (SEQ ID NO: 444)	D12-hLambda LC (SEQ ID NO: 445)
G12-hIgG4	G12-hIgG4 HC (SEQ ID NO: 446)	G12-hLambda LC (SEQ ID NO: 447)
Abz1mod-hIgG4	Abz1mod-hIgG4 HC (SEQ ID NO: 449)	Abz1mod-hKappa LC (SEQ ID NO: 450)

Anti-hPD-1 #1-hIgG4-L6-hIL-2 (D20A/R38E)	Anti-hPD-1 #1-hIgG4-L6-hIL-2 (D20A/R38E) (SEQ ID NO: 451)	Anti-hPD-1 #1-hKappa (SEQ ID NO: 452)
OMC.1.B6-hIgG4-L6-hIL-2 (D20A/R38E)	OMC.1.B6-hIgG4-L6-hIL-2 (D20A/R38E) HC (SEQ ID NO: 453)	OMC.1.B6-hLambda LC (SEQ ID NO: 439)
OMC.2.C6-hIgG4-L6-hIL-2 (D20A/R38E)	OMC.2.C6-hIgG4-L6-hIL-2 (D20A/R38E) HC (SEQ ID NO: 454)	OMC.2.C6-hLambda LC (SEQ ID NO: 441)
OMC.1.D6-hIgG4-L6-hIL-2 (D20A/R38E)	OMC.1.D6-hIgG4-L6-hIL-2 (D20A/R38E) HC (SEQ ID NO: 455)	OMC.1.D6-hLambda LC (SEQ ID NO: 443)
D12-hIgG4-df-hIL-2 (D20A/R38E)	D12-hIgG4-df-hIL-2 (D20A/R38E) HC (SEQ ID NO: 456)	D12-hLambda LC (SEQ ID NO: 445)
G12-hIgG4-df-hIL-2 (D20A/R38E)	G12-hIgG4-df-hIL-2 (D20A/R38E) HC (SEQ ID NO: 457)	G12-hLambda LC (SEQ ID NO: 447)
2H7-hIgG4-LE	2H7-hIgG4-LE HC (SEQ ID NO: 458)	2H7-hKappa LC (SEQ ID NO: 425)
2H7-hIgG4-LAGA	2H7-hIgG4-LAGA HC (SEQ ID NO: 459)	2H7-hKappa LC (SEQ ID NO: 425)
OMC476pH7-hIgG4	OMC476pH7-hIgG4 HC (SEQ ID NO: 461)	OMC476pB11.H7 LC (SEQ ID NO: 462)
OMC476pB11-hIgG4	OMC476pB11-hIgG4 HC (SEQ ID NO: 463)	OMC476pB11.H7 LC (SEQ ID NO: 462)
OMC476pG10-hIgG4	OMC476pG10-hIgG4 HC (SEQ ID NO: 464)	OMC476pG10.H10 LC (SEQ ID NO: 466)
OMC476pH10-hIgG4	OMC476pH10-hIgG4 HC (SEQ ID NO: 465)	OMC476pG10.H10 LC (SEQ ID NO: 466)
OMC476pE4-hIgG4	OMC476pE4-hIgG4 HC (SEQ ID NO: 467)	OMC476pE4 LC (SEQ ID NO: 468)
J110-hIgG1	J110-hIgG1 HC (SEQ ID NO: 469)	J110-hKappa LC (SEQ ID NO: 470)
2H7-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A)	2H7-hIgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) HC (SEQ ID NO: 471)	2H7-hKappa LC (SEQ ID NO: 425)
2H7-hIgG4-LE-df-hIL-2 (T3A/D20A/R38E/C125A)	2H7-hIgG4-LE-df-hIL-2 (T3A/D20A/R38E/C125A) HC (SEQ ID NO: 472)	2H7-hKappa LC (SEQ ID NO: 425)

2H7-hlgG4-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A)	2H7-hlgG4-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) HC (SEQ ID NO: 473)	2H7-hKappa LC (SEQ ID NO: 425)
2H7-hlgG1-LAGA-df-hIL-2 (T3A/R38E/I92K/C125A)	2H7-hlgG1-LAGA-df-hIL-2 (T3A/R38E/I92K/C125A) HC (SEQ ID NO: 474)	2H7-hKappa LC (SEQ ID NO: 425)
hlgG4-LE-df-hIL-2 (T3A/R38E/I92K/C125A)	hlgG4-LE-df-hIL-2 (T3A/R38E/I92K/C125A) HC (SEQ ID NO: 475)	2H7-hKappa LC (SEQ ID NO: 425)
2H7-hlgG4-LAGA-df-hIL-2 (T3A/R38E/I92K/C125A)	2H7-hlgG4-LAGA-df-hIL-2 (T3A/R38E/I92K/C125A) HC (SEQ ID NO: 476)	2H7-hKappa LC (SEQ ID NO: 425)
2H7-hlgG1-LAGA-df-hIL-2 (T3A/R38E/D84K/C125A)	2H7-hlgG1-LAGA-df-hIL-2 (T3A/R38E/D84K/C125A) HC (SEQ ID NO: 477)	2H7-hKappa LC (SEQ ID NO: 425)
2H7-hlgG4-LE-df-hIL-2 (T3A/R38E/D84K/C125A)	2H7-hlgG4-LE-df-hIL-2 (T3A/R38E/D84K/C125A) HC (SEQ ID NO: 478)	2H7-hKappa LC (SEQ ID NO: 425)
2H7-hlgG4-LAGA-df-hIL-2 (T3A/R38E/D84K/C125A)	2H7-hlgG4-LAGA-df-hIL-2 (T3A/R38E/D84K/C125A) HC (SEQ ID NO: 479)	2H7-hKappa LC (SEQ ID NO: 425)
1H3-hlgG4-df-hIL-2 (WT)	1H3-hlgG4-df-hIL-2 (WT) HC (SEQ ID NO: 480)	1H3-hKappa LC (SEQ ID NO: 374)
1H3-hlgG4-L6-hIL-2 (WT)	1H3-hlgG4-L6-hIL-2 (WT) HC (SEQ ID NO: 481)	1H3-hKappa LC (SEQ ID NO: 374)
1H3-hlgG4-df-hIL-2 (WT) LC fusion	1H3-hlgG4 HC (SEQ ID NO: 482)	1H3-hKappa-df-hIL-2 (WT) LC (SEQ ID NO: 362)
1H3-hlgG4-L6-hIL-2 (WT) LC fusion	1H3-hlgG4 HC (SEQ ID NO: 482)	1H3-hKappa-L6-hIL-2 (WT) LC (SEQ ID NO: 363)
1H3-hlgG4-L6-hIL-2 (D20Y)	1H3-hlgG4-L6-hIL-2 (D20Y) HC (SEQ ID NO: 485)	1H3-hKappa LC (SEQ ID NO: 374)
1H3-hlgG4-df-hIL-2 (D20Y)	1H3-hlgG4-df-hIL-2 (D20Y) HC (SEQ ID NO: 486)	1H3-hKappa LC (SEQ ID NO: 374)

1H3-hlgG1-df-hIL-2 (D20Y)	1H3-hlgG1-df-hIL-2 (D20Y) HC (SEQ ID NO: 487)	1H3-hKappa LC (SEQ ID NO: 374)
1H3-hlgG4-L6-hIL-2 (D20A/R38P)	1H3-hlgG4-L6-hIL-2 (D20A/R38P) HC (SEQ ID NO: 488)	1H3-hKappa LC (SEQ ID NO: 374)
1H3-hlgG4-L6-hIL-2 (D20A/R38S)	1H3-hlgG4-L6-hIL-2 (D20A/R38S) HC (SEQ ID NO: 489)	1H3-hKappa LC (SEQ ID NO: 374)
1H3-hlgG4-L6-hIL-2 (D20A/R38D)	1H3-hlgG4-L6-hIL-2 (D20A/R38D) HC (SEQ ID NO: 490)	1H3-hKappa LC (SEQ ID NO: 374)
1H3-hlgG4-L6-hIL-2 (D20A/R38Q/E95A)	1H3-hlgG4-L6-hIL-2 (D20A/R38Q/E95A) HC (SEQ ID NO: 491)	1H3-hKappa LC (SEQ ID NO: 374)
1H3-hlgG4-L6-hIL-2 (D20A/F42H/E95A)	1H3-hlgG4-L6-hIL-2 (D20A/F42H/E95A) HC (SEQ ID NO: 492)	1H3-hKappa LC (SEQ ID NO: 374)
1H3-hlgG4-L6-hIL-2 (R38D/I92D)	1H3-hlgG4-L6-hIL-2 (R38D/I92D) HC (SEQ ID NO: 493)	1H3-hKappa LC (SEQ ID NO: 374)
1H3-hlgG4-L6-hIL-2 (R38E/I92D)	1H3-hlgG4-L6-hIL-2 (R38E/I92D) HC (SEQ ID NO: 494)	1H3-hKappa LC (SEQ ID NO: 374)
1H3-hlgG4-L6-hIL-2 (F42H/I92D)	1H3-hlgG4-L6-hIL-2 (F42H/I92D) HC (SEQ ID NO: 495)	1H3-hKappa LC (SEQ ID NO: 374)
1H3-hlgG4-L6-hIL-2 (D20A/R38E)	1H3-hlgG4-L6-hIL-2 (D20A/R38E) HC (SEQ ID NO: 496)	1H3-hKappa LC (SEQ ID NO: 374)
1H3-hlgG4-L6-hIL-2 (T3A/D20A/R38E)	1H3-hlgG4-L6-hIL-2 (T3A/D20A/R38E) HC (SEQ ID NO: 497)	1H3-hKappa LC (SEQ ID NO: 374)
1H3-hlgG4-L6-hIL-2 (D20A/R38E/C125A)	1H3-hlgG4-L6-hIL-2 (D20A/R38E/C125A) HC (SEQ ID NO: 498)	1H3-hKappa LC (SEQ ID NO: 374)
1H3-hlgG4-L6-hIL-2 (T3A/D20A/R38E/C125A)	1H3-hlgG4-L6-hIL-2 (T3A/D20A/R38E/C125A) HC (SEQ ID NO: 499)	1H3-hKappa LC (SEQ ID NO: 374)
1H3-hlgG1-L6-hIL-2 (D20A/R38E)	1H3-hlgG1-L6-hIL-2 (D20A/R38E) HC (SEQ ID NO: 500)	1H3-hKappa LC (SEQ ID NO: 374)

1H3-hlgG1-L6-hIL-2 (T3A/D20A/R38E)	1H3-hlgG1-L6-hIL-2 (T3A/D20A/R38E) HC (SEQ ID NO: 501)	1H3-hKappa LC (SEQ ID NO: 374)
1H3-hlgG1-L6-hIL-2 (D20A/R38E/C125A)	1H3-hlgG1-L6-hIL-2 (D20A/R38E/C125A) HC (SEQ ID NO: 502)	1H3-hKappa LC (SEQ ID NO: 374)
1H3-hlgG4-df-hIL-2 (D20A/R38E) LC fusion	1H3-hlgG4 HC (SEQ ID NO: 482)	1H3-hKappa-df-hIL-2 (D20A/R38E) LC (SEQ ID NO: 503)
1H3-hlgG4-L6-hIL-2 (D20A/R38E) LC fusion	1H3-hlgG4 HC (SEQ ID NO: 482)	1H3-hKappa-L6-hIL-2 (D20A/R38E) LC (SEQ ID NO: 504)
OMC476pB11-hlgG4-df-hIL-2 (D20A/R38E)	OMC476pB11-hlgG4-df-hIL-2 (D20A/R38E) HC (SEQ ID NO: 505)	OMC476pB11.H7 LC (SEQ ID NO: 462)
OMC476pE4-hlgG4-df-hIL-2 (D20A/R38E)	OMC476pE4-hlgG4-df-hIL-2 (D20A/R38E) HC (SEQ ID NO: 506)	OMC476pE4 LC (SEQ ID NO: 468)
OMC476pG10-hlgG4-df-hIL-2 (D20A/R38E)	OMC476pG10-hlgG4-df-hIL-2 (D20A/R38E) HC (SEQ ID NO: 507)	OMC476pG10.H10 LC (SEQ ID NO: 466)
OMC476pH10-hlgG4-df-hIL-2 (D20A/R38E)	OMC476pH10-hlgG4-df-hIL-2 (D20A/R38E) HC (SEQ ID NO: 508)	OMC476pG10.H10 LC (SEQ ID NO: 466)
A2-hlgG4-df-hIL-2 (D20A/F42A)	A2-hlgG4-df-hIL-2 (D20A/F42A) HC (SEQ ID NO: 509)	A2-hLambda LC (SEQ ID NO: 429)
A2-hlgG4-df-hIL-2 (D20A/F42S)	A2-hlgG4-df-hIL-2 (D20A/F42S) HC (SEQ ID NO: 510)	A2-hLambda LC (SEQ ID NO: 429)
A2-hlgG4-df-hIL-2 (D20S/R38E)	A2-hlgG4-df-hIL-2 (D20S/R38E) HC (SEQ ID NO: 511)	A2-hLambda LC (SEQ ID NO: 429)
A2-hlgG4-df-hIL-2 (F42A/N88R)	A2-hlgG4-df-hIL-2 (F42A/N88R) HC (SEQ ID NO: 512)	A2-hLambda LC (SEQ ID NO: 429)
A2-hlgG4-df-hIL-2 (F42I/I92D)	A2-hlgG4-df-hIL-2 (F42I/I92D) HC (SEQ ID NO: 513)	A2-hLambda LC (SEQ ID NO: 429)
A2-hlgG4-df-hIL-2 (F42Q/I92D)	A2-hlgG4-df-hIL-2 (F42Q/I92D) HC (SEQ ID NO: 514)	A2-hLambda LC (SEQ ID NO: 429)
A2-hlgG4-df-hIL-2 (F42T/I92D)	A2-hlgG4-df-hIL-2 (F42T/I92D) HC (SEQ ID NO: 515)	A2-hLambda LC (SEQ ID NO: 429)
A2-hlgG4-df-hIL-2 (F42W/I92D)	A2-hlgG4-df-hIL-2 (F42W/I92D) HC (SEQ ID NO: 516)	A2-hLambda LC (SEQ ID NO: 429)

A2-hlgG4-df-hIL-2 (R38E/D84K)	A2-hlgG4-df-hIL-2 (R38E/D84K) HC (SEQ ID NO: 517)	A2-hLambda LC (SEQ ID NO: 429)
A2-hlgG4-df-hIL-2 (R38E/I92K)	A2-hlgG4-df-hIL-2 (R38E/I92K) HC (SEQ ID NO: 518)	A2-hLambda LC (SEQ ID NO: 429)
C51E6-5-hlgG4-df-hIL-2 (D20A/R38E)	C51E6-5-hlgG4-df-hIL-2 (D20A/R38E) HC (SEQ ID NO: 519)	C51E6-5-hKappa LC (SEQ ID NO: 427)
C51E6-5-hlgG4-LE-df-hIL-2 (T3A/D20A/R38E/C125A)	C51E6-5-hlgG4-LE-df-hIL-2 (T3A/D20A/R38E/C125A) HC (SEQ ID NO: 520)	C51E6-5-hKappa LC (SEQ ID NO: 427)
C51E6-5-hlgG4-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A)	C51E6-5-hlgG4-LAGA-df-hIL-2 (D20A/R38E) HC (SEQ ID NO: 521)	C51E6-5-hKappa LC (SEQ ID NO: 427)
2A3.H7-hlgG4-df-hIL-2 (D20A/R38E)	2H7-hlgG4-df-hIL-2 (D20A/R38E) HC (SEQ ID NO: 430)	2A3-hKappa LC (SEQ ID NO: 523)
1H9-hlgG4-df-hIL-2 (D20A/R38E)	1H9-hlgG4-df-hIL-2 (D20A/R38E) HC (SEQ ID NO: 524)	1H9-hKappa LC (SEQ ID NO: 525)
1D5-hlgG4-df-hIL-2 (D20A/R38E)	1D5-hlgG4-df-hIL-2 (D20A/R38E) HC (SEQ ID NO: 526)	1D5-hKappa LC (SEQ ID NO: 527)
1D5-hlgG4-LE-df-hIL-2 (T3A/D20A/R38E/C125A)	1D5-hlgG4-LE-df-hIL-2 (T3A/D20A/R38E/C125A) HC (SEQ ID NO: 528)	1D5-hKappa LC (SEQ ID NO: 527)
1D5-hlgG4-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A)	1D5-hlgG4-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) HC (SEQ ID NO: 529)	1D5-hKappa LC (SEQ ID NO: 527)
2H7-hlgG1-df-hIL-2 (T3A/D20A/R38E/C125A)	2H7-hlgG1-df-hIL-2 (T3A/D20A/R38E/C125A) HC (SEQ ID NO: 530)	2H7-hKappa LC (SEQ ID NO: 425)
2H7-hlgG1-LE-df-hIL-2 (T3A/D20A/R38E/C125A)	2H7-hlgG1-LE-df-hIL-2 (T3A/D20A/R38E/C125A) HC (SEQ ID NO: 531)	2H7-hKappa LC (SEQ ID NO: 425)
2H7-hlgG1-LE-df-hIL-2 (T3A/R38E/D84K/C125A)	2H7-hlgG1-LE-df-hIL-2 (T3A/R38E/D84K/C125A) HC (SEQ ID NO: 533)	2H7-hKappa LC (SEQ ID NO: 425)

2H7-hlgG4-df-hIL-2 (T3A/R38E/D84K/C125A)	2H7-hlgG4-df-hIL-2 (T3A/R38E/D84K/C125A) HC (SEQ ID NO: 534)	2H7-hKappa LC (SEQ ID NO: 425)
2H7-hlgG1-df-hIL-2 (T3A/R38E/I92K/C125A)	2H7-hlgG1-df-hIL-2 (T3A/R38E/I92K/C125A) HC (SEQ ID NO: 535)	2H7-hKappa LC (SEQ ID NO: 425)
2H7-hlgG1-LE-df-hIL-2 (T3A/R38E/I92K/C125A)	2H7-hlgG1-LE-df-hIL-2 (T3A/R38E/I92K/C125A) HC (SEQ ID NO: 536)	2H7-hKappa LC (SEQ ID NO: 425)
2H7-hlgG4-df-hIL-2 (T3A/R38E/I92K/C125A)	2H7-hlgG4-df-hIL-2 (T3A/R38E/I92K/C125A) HC (SEQ ID NO: 537)	2H7-hKappa LC (SEQ ID NO: 425)
2H7-hlgG1-LAGA-df-hIL2 (T3A/D20S/R38E/C125A)	2H7-hlgG1-LAGA-df-hIL2 (T3A/D20S/R38E/C125A) HC (SEQ ID NO: 538)	2H7-hKappa LC (SEQ ID NO: 425)
2H7-hlgG1-LAGA-df-hIL2 (T3A/R38E/D84F/C125A)	2H7-hlgG1-LAGA-df-hIL2 (T3A/R38E/D84F/C125A) HC (SEQ ID NO: 539)	2H7-hKappa LC (SEQ ID NO: 425)
2H7-hlgG1-LAGA-df-hIL2 (T3A/R38E/I92R/C125A)	2H7-hlgG1-LAGA-df-hIL2 (T3A/R38E/I92R/C125A) HC (SEQ ID NO: 540)	2H7-hKappa LC (SEQ ID NO: 425)
2H7-hlgG1-LAGA-df-hIL2 (T3A/R38E/I92E/C125A)	2H7-hlgG1-LAGA-df-hIL2 (T3A/R38E/I92E/C125A) HC (SEQ ID NO: 541)	2H7-hKappa LC (SEQ ID NO: 425)
2H7-hlgG1-LAGA-df-hIL2 (T3A/R38E/I92S/C125A)	2H7-hlgG1-LAGA-df-hIL2 (T3A/R38E/I92S/C125A) HC (SEQ ID NO: 542)	2H7-hKappa LC (SEQ ID NO: 425)
2H7-hlgG1-LAGA-df-hIL2 (T3A/R38E/I92D/C125A)	2H7-hlgG1-LAGA-df-hIL2 (T3A/R38E/I92D/C125A) HC (SEQ ID NO: 543)	2H7-hKappa LC (SEQ ID NO: 425)
2H7-hlgG1-LAGA-df-hIL2 (T3A/H16E/R38E/C125A)	2H7-hlgG1-LAGA-df-hIL2 (T3A/H16E/R38E/C125A) HC (SEQ ID NO: 544)	2H7-hKappa LC (SEQ ID NO: 425)

1H3-hlgG1-L6-hIL-2 (T3A/D20A/R38E/C125A)	1H3-hlgG1-L6-hIL-2 (T3A/D20A/R38E/C125A) HC (SEQ ID NO: 545)	1H3-hKappa LC (SEQ ID NO: 374)
1H3-hlgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A)	1H3-hlgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) HC (SEQ ID NO: 546)	1H3-hKappa LC (SEQ ID NO: 374)
C51E6-5-hlgG4/k-LE	C51E6-5-hlgG4/k-LE HC (SEQ ID NO: 547)	C51E6-5-hKappa LC (SEQ ID NO: 427)
C51E6-5-hlgG4/k-LAGA	C51E6-5-hlgG4/k-LAGA HC (SEQ ID NO: 548)	C51E6-5-hKappa LC (SEQ ID NO: 427)
C51E6-5-hlgG4/k-LEPG	C51E6-5-hlgG4/k-LEPG HC (SEQ ID NO: 549)	C51E6-5-hKappa LC (SEQ ID NO: 427)
C51E6-5-hlgG4/k-df-hIL-2 (T3A/D20A/R38E/C125A)	C51E6-5-hlgG4/k-df-hIL-2 (T3A/D20A/R38E/C125A) HC (SEQ ID NO: 550)	C51E6-5-hKappa LC (SEQ ID NO: 427)
C51E6-5-hlgG4/k-LEPG-hIL-2 (T3A/D20A/R38E/C125A)	C51E6-5-hlgG4/k-LEPG-hIL-2 (T3A/D20A/R38E/C125A) HC (SEQ ID NO: 551)	C51E6-5-hKappa LC (SEQ ID NO: 427)
A2-hlgG4/k-LE	A2-hlgG4/k-LE HC (SEQ ID NO: 552)	A2-hLambda LC (SEQ ID NO: 429)
A2-hlgG4/k-LAGA	A2-hlgG4/k-LAGA HC (SEQ ID NO: 553)	A2-hLambda LC (SEQ ID NO: 429)
A2-hlgG4/k-LEPG	A2-hlgG4/k-LEPG HC (SEQ ID NO: 554)	A2-hLambda LC (SEQ ID NO: 429)
A2-hlgG4/k-df-hIL-2 (T3A/D20A/R38E/C125A)	A2-hlgG4/k-df-hIL-2 (T3A/D20A/R38E/C125A) HC (SEQ ID NO: 555)	A2-hLambda LC (SEQ ID NO: 429)
A2-hlgG4/k-LE-df-hIL-2 (T3A/D20A/R38E/C125A)	A2-hlgG4/k-LE-df-hIL-2 (T3A/D20A/R38E/C125A) HC (SEQ ID NO: 556)	A2-hLambda LC (SEQ ID NO: 429)
A2-hlgG4/k-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A)	A2-hlgG4/k-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) HC (SEQ ID NO: 557)	A2-hLambda LC (SEQ ID NO: 429)

A2-hIgG4/k-LEPG-df-hIL-2 (T3A/D20A/R38E/C125A)	A2-hIgG4/k-LEPG-df-hIL-2 (T3A/D20A/R38E/C125A) HC (SEQ ID NO: 558)	A2-hLambda LC (SEQ ID NO: 429)
Anti-CD20-hIgG1/k	Anti-CD20-hIgG1/k HC (SEQ ID NO: 560)	Anti-CD20-hKappa LC (SEQ ID NO: 562)
Anti-CD20-hIgG1/k-LAGA	Anti-CD20-hIgG1/k-LAGA HC (SEQ ID NO: 561)	Anti-CD20-hKappa LC (SEQ ID NO: 562)
1H3-hIgG1-LAGA-df-hIL-2 (T3A/C125A)	1H3-hIgG1-LAGA-df-hIL-2 (T3A/C125A) HC (SEQ ID NO: 563)	1H3-hKappa LC (SEQ ID NO: 374)
anti-mPD-1 RMP1-14 mIgG2b-N297A	anti-mPD-1 RMP1-14 mIgG2b-N297A HC (SEQ ID NO: 564)	anti-mPD-1 RMP1-14 mKappa LC (SEQ ID NO: 566)
anti-mPD-1 RMP1-14 mIgG2b-N297A-L6-hIL-2 (F42K/Y45R/V69R)	anti-mPD-1 RMP1-14 mIgG2b-N297A-L6-hIL-2 (F42K/Y45R/V69R) HC (SEQ ID NO: 565)	anti-mPD-1 RMP1-14 mKappa LC (SEQ ID NO: 566)
anti-mPD-1 RMP1-30 mIgG2b-N297A	anti-mPD-1 RMP1-30 mIgG2b-N297A HC (SEQ ID NO: 567)	anti-mPD-1 RMP1-30 mKappa LC (SEQ ID NO: 568)
anti-mPD-1 RMP1-30 mIgG2b-N297A-L6-hIL-2 (F42K/Y45R/V69R)	anti-mPD-1 RMP1-30 mIgG2b-N297A-L6-hIL-2 (F42K/Y45R/V69R) HC (SEQ ID NO: 569)	anti-mPD-1 RMP1-30 mKappa LC (SEQ ID NO: 568)
anti-KLH-C3-mIgG2b-N297A-L6-hIL-2 (F42K/Y45R/V69R)	anti-KLH-C3-mIgG2b-N297A-L6-hIL-2 (F42K/Y45R/V69R) HC (SEQ ID NO: 570)	KLH-C3-mKappa LC (SEQ ID NO: 571)
2D12-hIgG1-L6-hIL-2	2D12-hIgG1-L6-hIL-2 HC (SEQ ID NO: 572)	2D12-hKappa LC (SEQ ID NO: 573)
1H9-hIgG4	1H9-hIgG4 HC (SEQ ID NO: 576)	1H9-hKappa LC (SEQ ID NO: 525)
1D5-hIgG4	1D5-hIgG4 HC (SEQ ID NO: 577)	1D5-hKappa LC (SEQ ID NO: 527)
2A3.H7-hIgG4	2H7-hIgG4 HC (SEQ ID NO: 424)	2A3-hKappa LC (SEQ ID NO: 523)

H7-02-hlgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A)	H7-02-hlgG1-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) HC (SEQ ID NO: 582)	H7-02-hKappa LC (SEQ ID NO: 583)
KLH-C3-hlgG4	KLH-C3-hlgG4 HC (SEQ ID NO: 585)	KLH-C3-hKappa LC (SEQ ID NO: 586)
1H3-hlgG1-L6-hCD25(1-164)-L20-hIL-2 (E15A)	1H3-hlgG1-L6-hCD25(1-164)-L20-hIL-2 (E15A) HC (SEQ ID NO: 587)	1H3-hkappa LC (SEQ ID NO: 374)
1H3-hlgG1-L6-hCD25(1-164)-L20-hIL-2 (D20I)	1H3-hlgG1-L6-hCD25(1-164)-L20-hIL-2 (D20I) HC (SEQ ID NO: 588)	1H3-hkappa LC (SEQ ID NO: 374)
1H3-hlgG1-L6-hCD25(1-164)-L20-hIL-2 (D20S)	1H3-hlgG1-L6-hCD25(1-164)-L20-hIL-2 (D20S) HC (SEQ ID NO: 589)	1H3-hkappa LC (SEQ ID NO: 374)
1H3-hlgG1-L6-hCD25(1-164)-L20-hIL-2 (D20H)	1H3-hlgG1-L6-hCD25(1-164)-L20-hIL-2 (D20H) HC (SEQ ID NO: 590)	1H3-hkappa LC (SEQ ID NO: 374)
1H3-hlgG1-L6-hCD25(1-164)-L20-hIL-2 (D20W)	1H3-hlgG1-L6-hCD25(1-164)-L20-hIL-2 (D20W) HC (SEQ ID NO: 591)	1H3-hkappa LC (SEQ ID NO: 374)
1H3-hlgG1-L6-hCD25(1-164)-L20-hIL-2 (D20Y)	1H3-hlgG1-L6-hCD25(1-164)-L20-hIL-2 (D20Y) HC (SEQ ID NO: 592)	1H3-hkappa LC (SEQ ID NO: 374)
1H3-hlgG1-L6-hCD25(1-164)-L20-hIL-2 (D20R)	1H3-hlgG1-L6-hCD25(1-164)-L20-hIL-2 (D20R) HC (SEQ ID NO: 593)	1H3-hkappa LC (SEQ ID NO: 374)
1H3-hlgG1-L6-hCD25(1-164)-L20-hIL-2 (D20F)	1H3-hlgG1-L6-hCD25(1-164)-L20-hIL-2 (D20F) HC (SEQ ID NO: 594)	1H3-hkappa LC (SEQ ID NO: 374)
1H3-hlgG1-L6-hCD25(1-164)-L20-hIL-2 (D84K)	1H3-hlgG1-L6-hCD25(1-164)-L20-hIL-2 (D84K) HC (SEQ ID NO: 595)	1H3-hkappa LC (SEQ ID NO: 374)
1H3-hlgG1-L6-hCD25(1-164)-L20-hIL-2 (S87A)	1H3-hlgG1-L6-hCD25(1-164)-L20-hIL-2 (S87A) HC (SEQ ID NO: 596)	1H3-hkappa LC (SEQ ID NO: 374)

1H3-hlgG1-L6-hCD25(1-164)-L20-hIL-2 (N88Y)	1H3-hlgG1-L6-hCD25(1-164)-L20-hIL-2 (N88Y) HC (SEQ ID NO: 597)	1H3-hkappa LC (SEQ ID NO: 374)
1H3-hlgG1-L6-hCD25(1-164)-L20-hIL-2 (N88D)	1H3-hlgG1-L6-hCD25(1-164)-L20-hIL-2 (N88D) HC (SEQ ID NO: 598)	1H3-hkappa LC (SEQ ID NO: 374)
1H3-hlgG1-L6-hCD25(1-164)-L20-hIL-2 (N88R)	1H3-hlgG1-L6-hCD25(1-164)-L20-hIL-2 (N88R) HC (SEQ ID NO: 599)	1H3-hkappa LC (SEQ ID NO: 374)
1H3-hlgG1-L6-hCD25(1-164)-L20-hIL-2 (N88E)	1H3-hlgG1-L6-hCD25(1-164)-L20-hIL-2 (N88E) HC (SEQ ID NO: 600)	1H3-hkappa LC (SEQ ID NO: 374)
1H3-hlgG1-L6-hCD25(1-164)-L20-hIL-2 (N88F)	1H3-hlgG1-L6-hCD25(1-164)-L20-hIL-2 (N88F) HC (SEQ ID NO: 601)	1H3-hkappa LC (SEQ ID NO: 374)
1H3-hlgG1-L6-hCD25(1-164)-L20-hIL-2 (N88I)	1H3-hlgG1-L6-hCD25(1-164)-L20-hIL-2 (N88I) HC (SEQ ID NO: 602)	1H3-hkappa LC (SEQ ID NO: 374)
1H3-hlgG1-L6-hCD25(1-164)-L20-hIL-2 (I92A)	1H3-hlgG1-L6-hCD25(1-164)-L20-hIL-2 (I92A) HC (SEQ ID NO: 603)	1H3-hkappa LC (SEQ ID NO: 374)
1H3-hlgG1-L6-hCD25(1-164)-L20-hIL-2 (E95A)	1H3-hlgG1-L6-hCD25(1-164)-L20-hIL-2 (E95A) HC (SEQ ID NO: 604)	1H3-hkappa LC (SEQ ID NO: 374)
1H3-hlgG1-L6-hCD25(1-164)-L20-hIL-2 (E95K)	1H3-hlgG1-L6-hCD25(1-164)-L20-hIL-2 (E95K) HC (SEQ ID NO: 605)	1H3-hkappa LC (SEQ ID NO: 374)
H7-02-hlgG4	H7-02-hlgG4 HC (SEQ ID NO: 373)	H7-02 hKappa LC (SEQ ID NO: 607)
H7-632-hlgG1-LAGA-df-hIL-2 (T3A/C125A)	H7-632-hlgG1-LAGA-df-hIL-2 (T3A/C125A) HC (SEQ ID NO: 431)	H7-632 LC (SEQ ID NO: 415)
1H3-hlgG1-LAGA-L6-hIL-2 (T3A/D20A/R38E/C125A)	1H3-hlgG1-LAGA-L6-hIL-2 (T3A/D20A/R38E/C125A) (SEQ ID NO: 522)	1H3-hKappa LC (SEQ ID NO: 374)

1H3-hlgG1	1H3-hlgG1 HC (SEQ ID NO: 379)	1H3-hKappa LC (SEQ ID NO: 374)
H7-767	H7-767 HC (SEQ ID NO: 532)	H7-632 LC (SEQ ID NO: 415)
Anti-hPD-1 #1	Anti-hPD-1 #1 HC (SEQ ID NO: 559)	Anti-hPD-1#1-hKappa (SEQ ID NO: 452)
Anti-hPD-1 #2	Anti-hPD-1 #2 HC (SEQ ID NO: 578)	Anti-hPD-1 #2 LC (SEQ ID NO: 579)
2H7-hlgG4-LE-df-hIL-2 (T3A/R38E/I92K/C125A)	2H7-hlgG4-LE-df-hIL-2 (T3A/R38E/I92K/C125A) HC (SEQ ID NO: 475)	2H7-hKappa LC (SEQ ID NO: 425)

Table 29. Sequences

SEQ ID NO:	Name	Sequence
1	hIL-2 F42K	APTSSSTKKKTQLQLEHLLLDLQMLNGINNYKNPKLTRMLT K KFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETT F MCEYADETATIV E FLNRWITFCQSIISTLT
2	hIL-2 V69A	APTSSSTKKKTQLQLEHLLLDLQMLNGINNYKNPKLTRMLT F KFYMPKKATELKHLCLEEEELKPLEEA LNLAQSKNFHLRPRDLISNINVIVLELKGSETT F MCEYADETATIV E FLNRWITFCQSIISTLT
3	hIL-2 V69E	APTSSSTKKKTQLQLEHLLLDLQMLNGINNYKNPKLTRMLT F KFYMPKKATELKHLCLEEEELKPLEEE LNLAQSKNFHLRPRDLISNINVIVLELKGSETT F MCEYADETATIV E FLNRWITFCQSIISTLT
4	hIL-2 V69F	APTSSSTKKKTQLQLEHLLLDLQMLNGINNYKNPKLTRMLT F KFYMPKKATELKHLCLEEEELKPLEEF LNLAQSKNFHLRPRDLISNINVIVLELKGSETT F MCEYADETATIV E FLNRWITFCQSIISTLT
5	hIL-2 V69G	APTSSSTKKKTQLQLEHLLLDLQMLNGINNYKNPKLTRMLT F KFYMPKKATELKHLCLEEEELKPLEEG LNLAQSKNFHLRPRDLISNINVIVLELKGSETT F MCEYADETATIV E FLNRWITFCQSIISTLT
6	hIL-2 V69H	APTSSSTKKKTQLQLEHLLLDLQMLNGINNYKNPKLTRMLT F KFYMPKKATELKHLCLEEEELKPLEEH LNLAQSKNFHLRPRDLISNINVIVLELKGSETT F MCEYADETATIV E FLNRWITFCQSIISTLT
7	hIL-2 V69I	APTSSSTKKKTQLQLEHLLLDLQMLNGINNYKNPKLTRMLT F KFYMPKKATELKHLCLEEEELKPLEEI LNLAQSKNFHLRPRDLISNINVIVLELKGSETT F MCEYADETATIV E FLNRWITFCQSIISTLT
8	hIL-2 V69K	APTSSSTKKKTQLQLEHLLLDLQMLNGINNYKNPKLTRMLT F KFYMPKKATELKHLCLEEEELKPLEEK LNLAQSKNFHLRPRDLISNINVIVLELKGSETT F MCEYADETATIV E FLNRWITFCQSIISTLT

9	h1L-2 V69L	APTSSTKKTQIQLEHLLLDQMI LINGINNYKNPKLTRMLT FKFYMPKKATELKHLCLEEEELKPLEEL LNLAQSKNFHLRPRDLISININVI VLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
10	h1L-2 V69M	APTSSTKKTQIQLEHLLLDQMI LINGINNYKNPKLTRMLT FKFYMPKKATELKHLCLEEEELKPLEEM LNLAQSKNFHLRPRDLISININVI VLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
11	h1L-2 V69Q	APTSSTKKTQIQLEHLLLDQMI LINGINNYKNPKLTRMLT FKFYMPKKATELKHLCLEEEELKPLEEQ LNLAQSKNFHLRPRDLISININVI VLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
12	h1L-2 V69S	APTSSTKKTQIQLEHLLLDQMI LINGINNYKNPKLTRMLT FKFYMPKKATELKHLCLEEEELKPLEES LNLAQSKNFHLRPRDLISININVI VLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
13	h1L-2 V69T	APTSSTKKTQIQLEHLLLDQMI LINGINNYKNPKLTRMLT FKFYMPKKATELKHLCLEEEELKPLEET LNLAQSKNFHLRPRDLISININVI VLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
14	h1L-2 V69W	APTSSTKKTQIQLEHLLLDQMI LINGINNYKNPKLTRMLT FKFYMPKKATELKHLCLEEEELKPLEEW LNLAQSKNFHLRPRDLISININVI VLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
15	h1L-2 V69Y	APTSSTKKTQIQLEHLLLDQMI LINGINNYKNPKLTRMLT FKFYMPKKATELKHLCLEEEELKPLEEY LNLAQSKNFHLRPRDLISININVI VLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
16	h1L-2 F42K/F44K	APTSSTKKTQIQLEHLLLDQMI LINGINNYKNPKLTRMLT KK YMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININVI VLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
17	h1L-2 F44K/Y45R	APTSSTKKTQIQLEHLLLDQMI LINGINNYKNPKLTRMLT KKRR PKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININVI VLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
18	h1L-2 F42K/V69R	APTSSTKKTQIQLEHLLLDQMI LINGINNYKNPKLTRMLT KK YMPKKATELKHLCLEEEELKPLEER LNLAQSKNFHLRPRDLISININVI VLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
19	h1L-2 Y45R/V69R	APTSSTKKTQIQLEHLLLDQMI LINGINNYKNPKLTRMLT KKFR MPKKATELKHLCLEEEELKPLEER LNLAQSKNFHLRPRDLISININVI VLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
20	h1L-2 F42K/F44K/Y45R	APTSSTKKTQIQLEHLLLDQMI LINGINNYKNPKLTRMLT KKRR MPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININVI VLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
21	h1L-2 R38A/F42K/Y45R	APTSSTKKTQIQLEHLLLDQMI LINGINNYKNPKLT AMLT KKFR MPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININVI VLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
22	h1L-2 R38E/F42K/Y45R	APTSSTKKTQIQLEHLLLDQMI LINGINNYKNPKLT EMLT KKFR MPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININVI VLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
23	h1L-2 K43E/F42K/Y45R	APTSSTKKTQIQLEHLLLDQMI LINGINNYKNPKLTRMLT KEFR MPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININVI VLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
24	h1L-2 K43T/F42K/Y45R	APTSSTKKTQIQLEHLLLDQMI LINGINNYKNPKLT KTFR MPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININVI VLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
25	h1L-2 F42K/Y45R/E62A	APTSSTKKTQIQLEHLLLDQMI LINGINNYKNPKLTRMLT KKFR MPKKATELKHLCLEEEALKPLEEV LNLAQSKNFHLRPRDLISININVI VLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
26	h1L-2 P65R/F42K/Y45R	APTSSTKKTQIQLEHLLLDQMI LINGINNYKNPKLTRMLT KKFR MPKKATELKHLCLEEEELKRLEEV LNLAQSKNFHLRPRDLISININVI VLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT

27	hIL-2 P65S/F42K/Y45R	APTSSTKKTQLQLEHLLLDLQMI LINGINNYKNPKLTRMLTKKFRMPKKATELKHLCLEEEELKSLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
28	hIL-2 V69A/F42K/Y45R	APTSSTKKTQLQLEHLLLDLQMI LINGINNYKNPKLTRMLTKKFRMPKKATELKHLCLEEEELKPLEEA LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
29	hIL-2 V69D/F42K/Y45R	APTSSTKKTQLQLEHLLLDLQMI LINGINNYKNPKLTRMLTKKFRMPKKATELKHLCLEEEELKPLEED LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
30	hIL-2 V69R/F42K/Y45R	APTSSTKKTQLQLEHLLLDLQMI LINGINNYKNPKLTRMLTKKFRMPKKATELKHLCLEEEELKPLEER LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
31	hIL-2 D20A	APTSSTKKTQLQLEHLLLDLQMI LINGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
32	hIL-2 D20N	APTSSTKKTQLQLEHLLLDLQMI LINGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
33	hIL-2 D20K	APTSSTKKTQLQLEHLLLDLQMI LINGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
34	hIL-2 N88A	APTSSTKKTQLQLEHLLLDLQMI LINGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISAINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
35	hIL-2 N88G	APTSSTKKTQLQLEHLLLDLQMI LINGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISGINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
36	hIL-2 N88H	APTSSTKKTQLQLEHLLLDLQMI LINGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISHINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
37	hIL-2 N88K	APTSSTKKTQLQLEHLLLDLQMI LINGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISKINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
38	hIL-2 D20A/D84A	APTSSTKKTQLQLEHLLLDLQMI LINGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRALISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
39	hIL-2 D20A/E15A	APTSSTKKTQLQLEHLLLDLQMI LINGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
40	hIL-2 D20A/E95A	APTSSTKKTQLQLEHLLLDLQMI LINGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLAINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
41	hIL-2 D20A/N88A	APTSSTKKTQLQLEHLLLDLQMI LINGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISAINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
42	hIL-2 D20A/S87A	APTSSTKKTQLQLEHLLLDLQMI LINGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLIANINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
43	hIL-2 D84A/N88A	APTSSTKKTQLQLEHLLLDLQMI LINGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRALISAINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
44	hIL-2 E15A/N88A	APTSSTKKTQLQLEHLLLDLQMI LINGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISAINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT

45	hIL-2 S87A/N88A	APTSSTKKTQIQLEHLLLDQMI LINGINNYKNPKLTRMLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLI AA INVI VLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
46	hIL-2 R38A	APTSSTKKTQIQLEHLLLDQMI LINGINNYKNPKLT A MLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLI SNINVI VLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
47	hIL-2 R38D	APTSSTKKTQIQLEHLLLDQMI LINGINNYKNPKLT D MLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLI SNINVI VLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
48	hIL-2 R38E	APTSSTKKTQIQLEHLLLDQMI LINGINNYKNPKLT E MLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLI SNINVI VLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
49	hIL-2 R38Q	APTSSTKKTQIQLEHLLLDQMI LINGINNYKNPKLT Q MLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLI SNINVI VLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
50	hIL-2 F42R	APTSSTKKTQIQLEHLLLDQMI LINGINNYKNPKLTRMLT R KFFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLI SNINVI VLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
51	hIL-2 F42A	APTSSTKKTQIQLEHLLLDQMI LINGINNYKNPKLTRMLT A KFFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLI SNINVI VLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
52	hIL-2 F42D	APTSSTKKTQIQLEHLLLDQMI LINGINNYKNPKLTRMLT D KFFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLI SNINVI VLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
53	hIL-2 F42H	APTSSTKKTQIQLEHLLLDQMI LINGINNYKNPKLTRMLT H KFFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLI SNINVI VLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
54	hIL-2 K43A	APTSSTKKTQIQLEHLLLDQMI LINGINNYKNPKLTRMLT A FYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLI SNINVI VLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
55	hIL-2 K43E	APTSSTKKTQIQLEHLLLDQMI LINGINNYKNPKLTRMLT E FYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLI SNINVI VLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
56	hIL-2 K43Q	APTSSTKKTQIQLEHLLLDQMI LINGINNYKNPKLTRMLT Q FYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLI SNINVI VLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
57	hIL-2 Y45A	APTSSTKKTQIQLEHLLLDQMI LINGINNYKNPKLTRMLT FKF A MPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLI SNINVI VLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
58	hIL-2 Y45K	APTSSTKKTQIQLEHLLLDQMI LINGINNYKNPKLTRMLT FKF K MPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLI SNINVI VLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
59	hIL-2 Y45S	APTSSTKKTQIQLEHLLLDQMI LINGINNYKNPKLTRMLT FKF S MPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLI SNINVI VLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
60	hIL-2 Y45R	APTSSTKKTQIQLEHLLLDQMI LINGINNYKNPKLTRMLT FKF R MPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLI SNINVI VLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
61	hIL-2 E61A	APTSSTKKTQIQLEHLLLDQMI LINGINNYKNPKLTRMLT FKFYMPKKATELKHLCLE A EELKPLEEV LNLAQSKNFHLRPRDLI SNINVI VLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
62	hIL-2 E61R	APTSSTKKTQIQLEHLLLDQMI LINGINNYKNPKLTRMLT FKFYMPKKATELKHLCLE R EELKPLEEV LNLAQSKNFHLRPRDLI SNINVI VLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT

63	h1L-2 E61K	APTSSSTKKTQQLQLEHLLLDLQMLNGINNYKNPKLTRMLT FKFYMPKKATELKHLCLEELKELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETT FMCEYADETATIVE FLNRWITFCQSIISTLT
64	h1L-2 E62A	APTSSSTKKTQQLQLEHLLLDLQMLNGINNYKNPKLTRMLT FKFYMPKKATELKHLCLEELALKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETT FMCEYADETATIVE FLNRWITFCQSIISTLT
65	h1L-2 E62R	APTSSSTKKTQQLQLEHLLLDLQMLNGINNYKNPKLTRMLT FKFYMPKKATELKHLCLEELRLKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETT FMCEYADETATIVE FLNRWITFCQSIISTLT
66	h1L-2 E62K	APTSSSTKKTQQLQLEHLLLDLQMLNGINNYKNPKLTRMLT FKFYMPKKATELKHLCLEELKLKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETT FMCEYADETATIVE FLNRWITFCQSIISTLT
67	h1L-2 E62Y	APTSSSTKKTQQLQLEHLLLDLQMLNGINNYKNPKLTRMLT FKFYMPKKATELKHLCLEELYLKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETT FMCEYADETATIVE FLNRWITFCQSIISTLT
68	h1L-2 E68Y	APTSSSTKKTQQLQLEHLLLDLQMLNGINNYKNPKLTRMLT FKFYMPKKATELKHLCLEELKPLEYV LNLAQSKNFHLRPRDLISNINVIVLELKGSETT FMCEYADETATIVE FLNRWITFCQSIISTLT
69	h1L-2 E68A	APTSSSTKKTQQLQLEHLLLDLQMLNGINNYKNPKLTRMLT FKFYMPKKATELKHLCLEELKPLEAV LNLAQSKNFHLRPRDLISNINVIVLELKGSETT FMCEYADETATIVE FLNRWITFCQSIISTLT
70	h1L-2 E68K	APTSSSTKKTQQLQLEHLLLDLQMLNGINNYKNPKLTRMLT FKFYMPKKATELKHLCLEELKPLEKV LNLAQSKNFHLRPRDLISNINVIVLELKGSETT FMCEYADETATIVE FLNRWITFCQSIISTLT
71	h1L-2 E68R	APTSSSTKKTQQLQLEHLLLDLQMLNGINNYKNPKLTRMLT FKFYMPKKATELKHLCLEELKPLERV LNLAQSKNFHLRPRDLISNINVIVLELKGSETT FMCEYADETATIVE FLNRWITFCQSIISTLT
72	h1L-2 E68L	APTSSSTKKTQQLQLEHLLLDLQMLNGINNYKNPKLTRMLT FKFYMPKKATELKHLCLEELKPLELV LNLAQSKNFHLRPRDLISNINVIVLELKGSETT FMCEYADETATIVE FLNRWITFCQSIISTLT
73	h1L-2 L72Y	APTSSSTKKTQQLQLEHLLLDLQMLNGINNYKNPKLTRMLT FKFYMPKKATELKHLCLEELKPLEEV LN Y AQSKNFHLRPRDLISNINVIVLELKGSETT FMCEYADETATIVE FLNRWITFCQSIISTLT
74	h1L-2 L72R	APTSSSTKKTQQLQLEHLLLDLQMLNGINNYKNPKLTRMLT FKFYMPKKATELKHLCLEELKPLEEV LN R AQSKNFHLRPRDLISNINVIVLELKGSETT FMCEYADETATIVE FLNRWITFCQSIISTLT
75	h1L-2 L72A	APTSSSTKKTQQLQLEHLLLDLQMLNGINNYKNPKLTRMLT FKFYMPKKATELKHLCLEELKPLEEV LN A AQSKNFHLRPRDLISNINVIVLELKGSETT FMCEYADETATIVE FLNRWITFCQSIISTLT
76	h1L-2 L72D	APTSSSTKKTQQLQLEHLLLDLQMLNGINNYKNPKLTRMLT FKFYMPKKATELKHLCLEELKPLEEV LN D AQSKNFHLRPRDLISNINVIVLELKGSETT FMCEYADETATIVE FLNRWITFCQSIISTLT
77	h1L-2 L72H	APTSSSTKKTQQLQLEHLLLDLQMLNGINNYKNPKLTRMLT FKFYMPKKATELKHLCLEELKPLEEV LN H AQSKNFHLRPRDLISNINVIVLELKGSETT FMCEYADETATIVE FLNRWITFCQSIISTLT
78	h1L-2 L72F	APTSSSTKKTQQLQLEHLLLDLQMLNGINNYKNPKLTRMLT FKFYMPKKATELKHLCLEELKPLEEV LN F AQSKNFHLRPRDLISNINVIVLELKGSETT FMCEYADETATIVE FLNRWITFCQSIISTLT
79	h1L-2 R38D/E61R	APTSSSTKKTQQLQLEHLLLDLQMLNGINNYKNPKLT D MLT FKFYMPKKATELKHLCLEELRELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETT FMCEYADETATIVE FLNRWITFCQSIISTLT
80	h1L-2 R38D/E61R/K43E	APTSSSTKKTQQLQLEHLLLDLQMLNGINNYKNPKLT D MLT F E F YMPKKATELKHLCLEELRELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETT FMCEYADETATIVE FLNRWITFCQSIISTLT

81	h1L-2 T3A/F42A/Y45A/ L72G/C125A	APTSSSTKKTQQLQLEHLLLDLQMLNGINNYKNPKLTRMLT AK FAMPKKATELKHLCLEEEELKPLEEV LNQAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATIVEFLNRWIT FA QSIISTLT
82	h1L-2 E15A	APTSSSTKKTQQLQLE A HLLLDLQMLNGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
83	h1L-2 E15R	APTSSSTKKTQQLQLE R HLLLDLQMLNGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
84	h1L-2 E15K	APTSSSTKKTQQLQLE K HLLLDLQMLNGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
85	h1L-2 H16A	APTSSSTKKTQQLQLE A LHLLLDLQMLNGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
86	h1L-2 H16Y	APTSSSTKKTQQLQLE Y LHLLLDLQMLNGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
87	h1L-2 H16E	APTSSSTKKTQQLQLE E LHLLLDLQMLNGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
88	h1L-2 L19A	APTSSSTKKTQQLQLEHLL A DLQMLNGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
89	h1L-2 D20I	APTSSSTKKTQQLQLEHLL I LQMLNGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
90	h1L-2 D20S	APTSSSTKKTQQLQLEHLL S LQMLNGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
91	h1L-2 D20H	APTSSSTKKTQQLQLEHLL H LQMLNGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
92	h1L-2 D20T	APTSSSTKKTQQLQLEHLL T LQMLNGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
93	h1L-2 D20W	APTSSSTKKTQQLQLEHLL W LQMLNGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
94	h1L-2 D20Y	APTSSSTKKTQQLQLEHLL Y LQMLNGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
95	h1L-2 D20R	APTSSSTKKTQQLQLEHLL R LQMLNGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
96	h1L-2 D20F	APTSSSTKKTQQLQLEHLL F LQMLNGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
97	h1L-2 R81A	APTSSSTKKTQQLQLEHLL A PRDLISNINVIIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT

98	hIL-2 D84A	APTSSSTKKTQIQLEHLLLDLQMI L NGINNYKNPKLTRMLT F KFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISINIVIVLELKGSETT F MCEYADETAT I VEFLNRWITFCQSIISTLT
99	hIL-2 D84R	APTSSSTKKTQIQLEHLLLDLQMI L NGINNYKNPKLTRMLT F KFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISINIVIVLELKGSETT F MCEYADETAT I VEFLNRWITFCQSIISTLT
100	hIL-2 D84K	APTSSSTKKTQIQLEHLLLDLQMI L NGINNYKNPKLTRMLT F KFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISINIVIVLELKGSETT F MCEYADETAT I VEFLNRWITFCQSIISTLT
101	hIL-2 S87A	APTSSSTKKTQIQLEHLLLDLQMI L NGINNYKNPKLTRMLT F KFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISINIVIVLELKGSETT F MCEYADETAT I VEFLNRWITFCQSIISTLT
102	hIL-2 N88Y	APTSSSTKKTQIQLEHLLLDLQMI L NGINNYKNPKLTRMLT F KFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISINIVIVLELKGSETT F MCEYADETAT I VEFLNRWITFCQSIISTLT
103	hIL-2 N88D	APTSSSTKKTQIQLEHLLLDLQMI L NGINNYKNPKLTRMLT F KFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISINIVIVLELKGSETT F MCEYADETAT I VEFLNRWITFCQSIISTLT
104	hIL-2 N88R	APTSSSTKKTQIQLEHLLLDLQMI L NGINNYKNPKLTRMLT F KFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISINIVIVLELKGSETT F MCEYADETAT I VEFLNRWITFCQSIISTLT
105	hIL-2 N88E	APTSSSTKKTQIQLEHLLLDLQMI L NGINNYKNPKLTRMLT F KFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISINIVIVLELKGSETT F MCEYADETAT I VEFLNRWITFCQSIISTLT
106	hIL-2 N88F	APTSSSTKKTQIQLEHLLLDLQMI L NGINNYKNPKLTRMLT F KFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISINIVIVLELKGSETT F MCEYADETAT I VEFLNRWITFCQSIISTLT
107	hIL-2 N88I	APTSSSTKKTQIQLEHLLLDLQMI L NGINNYKNPKLTRMLT F KFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISINIVIVLELKGSETT F MCEYADETAT I VEFLNRWITFCQSIISTLT
108	hIL-2 I92A	APTSSSTKKTQIQLEHLLLDLQMI L NGINNYKNPKLTRMLT F KFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISINIVIVLELKGSETT F MCEYADETAT I VEFLNRWITFCQSIISTLT
109	hIL-2 I92Y	APTSSSTKKTQIQLEHLLLDLQMI L NGINNYKNPKLTRMLT F KFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISINIVIVLELKGSETT F MCEYADETAT I VEFLNRWITFCQSIISTLT
110	hIL-2 I92S	APTSSSTKKTQIQLEHLLLDLQMI L NGINNYKNPKLTRMLT F KFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISINIVIVLELKGSETT F MCEYADETAT I VEFLNRWITFCQSIISTLT
111	hIL-2 I92F	APTSSSTKKTQIQLEHLLLDLQMI L NGINNYKNPKLTRMLT F KFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISINIVIVLELKGSETT F MCEYADETAT I VEFLNRWITFCQSIISTLT
112	hIL-2 I92R	APTSSSTKKTQIQLEHLLLDLQMI L NGINNYKNPKLTRMLT F KFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISINIVIVLELKGSETT F MCEYADETAT I VEFLNRWITFCQSIISTLT
113	hIL-2 I92D	APTSSSTKKTQIQLEHLLLDLQMI L NGINNYKNPKLTRMLT F KFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISINIVIVLELKGSETT F MCEYADETAT I VEFLNRWITFCQSIISTLT
114	hIL-2 I92E	APTSSSTKKTQIQLEHLLLDLQMI L NGINNYKNPKLTRMLT F KFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISINIVIVLELKGSETT F MCEYADETAT I VEFLNRWITFCQSIISTLT
115	hIL-2 E95A	APTSSSTKKTQIQLEHLLLDLQMI L NGINNYKNPKLTRMLT F KFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISINIVIVLELKGSETT F MCEYADETAT I VEFLNRWITFCQSIISTLT

116	hIL-2 E95R	APTSSTKKTQQLQLEHLLLDLQMI LINGINNYKNPKLTRMLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLRLKGSETT FMCYADETAT IVEFLNRWITFCQSIISTLT
117	hIL-2 E95K	APTSSTKKTQQLQLEHLLLDLQMI LINGINNYKNPKLTRMLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLKLKGSETT FMCYADETAT IVEFLNRWITFCQSIISTLT
118	hIL-2 D20Y/H16E	APTSSTKKTQQLQLEHLLLDLQMI LINGINNYKNPKLTRMLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETT FMCYADETAT IVEFLNRWITFCQSIISTLT
119	hIL-2 D20Y/H16A	APTSSTKKTQQLQLEALLY LQMI LINGINNYKNPKLTRMLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETT FMCYADETAT IVEFLNRWITFCQSIISTLT
120	hIL-2 D20Y/H16Y	APTSSTKKTQQLQLEYLLLY LQMI LINGINNYKNPKLTRMLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETT FMCYADETAT IVEFLNRWITFCQSIISTLT
121	hIL-2 D20Y/I92A	APTSSTKKTQQLQLEHLLY LQMI LINGINNYKNPKLTRMLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVA VLELKGSETT FMCYADETAT IVEFLNRWITFCQSIISTLT
122	hIL-2 D20Y/I92S	APTSSTKKTQQLQLEHLLY LQMI LINGINNYKNPKLTRMLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVS VLELKGSETT FMCYADETAT IVEFLNRWITFCQSIISTLT
123	hIL-2 D20Y/I92R	APTSSTKKTQQLQLEHLLY LQMI LINGINNYKNPKLTRMLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVR VLELKGSETT FMCYADETAT IVEFLNRWITFCQSIISTLT
124	hIL-2 D20Y/E95R	APTSSTKKTQQLQLEHLLY LQMI LINGINNYKNPKLTRMLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVRLKGSETT FMCYADETAT IVEFLNRWITFCQSIISTLT
125	hIL-2 D20Y/E95A	APTSSTKKTQQLQLEHLLY LQMI LINGINNYKNPKLTRMLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLALKGSETT FMCYADETAT IVEFLNRWITFCQSIISTLT
126	hCD25 (1-164)	ELCDDDPPEIPHATFKAMAYKEGTMINCECKRGFRRIKSGSLYMLCTGNSSSHSWDNQCCTSSATRNT TKQVTPQPEEQKERKTTMQSPMPQVDQASLPGHCREPPPWENEATERIYHEVVGQMVYYQCVQGYRAL HRGPAESVCMTGKTRWTQPOLICT
127	hIL-2 F42D/D20A	APTSSTKKTQQLQLEHLLY LQMI LINGINNYKNPKLTRMLT DKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETT FMCYADETAT IVEFLNRWITFCQSIISTLT
128	hIL-2 F42R/D20A	APTSSTKKTQQLQLEHLLY LQMI LINGINNYKNPKLTRMLT RKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETT FMCYADETAT IVEFLNRWITFCQSIISTLT
129	hIL-2 F42K/D20A	APTSSTKKTQQLQLEHLLY LQMI LINGINNYKNPKLTRMLT KKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETT FMCYADETAT IVEFLNRWITFCQSIISTLT
130	hIL-2 F42A/D20A	APTSSTKKTQQLQLEHLLY LQMI LINGINNYKNPKLTRMLT AKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETT FMCYADETAT IVEFLNRWITFCQSIISTLT
131	hIL-2 F42H/D20A	APTSSTKKTQQLQLEHLLY LQMI LINGINNYKNPKLTRMLT HKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETT FMCYADETAT IVEFLNRWITFCQSIISTLT
132	hIL-2 Y45R/D20A	APTSSTKKTQQLQLEHLLY LQMI LINGINNYKNPKLTRMLT FKF RMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETT FMCYADETAT IVEFLNRWITFCQSIISTLT

133	h1L-2 Y45K/D20A	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLT RMLT FK KMP KKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETT FMCEY ADETAT IVE FLNRWIT FCQSI IISTLT
134	h1L-2 R38N/D20A	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLT NMLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETT FMCEY ADETAT IVE FLNRWIT FCQSI IISTLT
135	h1L-2 R38G/D20A	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLT GMLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETT FMCEY ADETAT IVE FLNRWIT FCQSI IISTLT
136	h1L-2 R38H/D20A	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLT HMLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETT FMCEY ADETAT IVE FLNRWIT FCQSI IISTLT
137	h1L-2 R38I/D20A	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLT TMLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETT FMCEY ADETAT IVE FLNRWIT FCQSI IISTLT
138	h1L-2 R38L/D20A	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLT TMLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETT FMCEY ADETAT IVE FLNRWIT FCQSI IISTLT
139	h1L-2 R38M/D20A	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLT TMLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETT FMCEY ADETAT IVE FLNRWIT FCQSI IISTLT
140	h1L-2 R38F/D20A	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLT FMLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETT FMCEY ADETAT IVE FLNRWIT FCQSI IISTLT
141	h1L-2 R38P/D20A	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLT PMLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETT FMCEY ADETAT IVE FLNRWIT FCQSI IISTLT
142	h1L-2 R38S/D20A	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLT SMLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETT FMCEY ADETAT IVE FLNRWIT FCQSI IISTLT
143	h1L-2 R38T/D20A	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLT TMLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETT FMCEY ADETAT IVE FLNRWIT FCQSI IISTLT
144	h1L-2 R38W/D20A	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLT WMLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETT FMCEY ADETAT IVE FLNRWIT FCQSI IISTLT
145	h1L-2 R38Y/D20A	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLT YMLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETT FMCEY ADETAT IVE FLNRWIT FCQSI IISTLT
146	h1L-2 R38V/D20A	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLT VMLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETT FMCEY ADETAT IVE FLNRWIT FCQSI IISTLT
147	h1L-2 R38A/D20A	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLT AMLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETT FMCEY ADETAT IVE FLNRWIT FCQSI IISTLT
148	h1L-2 R38Q/D20A	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLT QMLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETT FMCEY ADETAT IVE FLNRWIT FCQSI IISTLT
149	h1L-2 D20A/R38E	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLT EMLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETT FMCEY ADETAT IVE FLNRWIT FCQSI IISTLT
150	h1L-2 R38D/D20A	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLT DMLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETT FMCEY ADETAT IVE FLNRWIT FCQSI IISTLT

151	h1L-2 K43E/D20A	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLTRMLT F FYMPKKATELKHLCLEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETT FM CEYADETAT IVE FLNRWITFCQSIISTLT
152	h1L-2 E61A/D20A	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLTRMLT FK FYMPKKATELKHLCLE AE LKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETT FM CEYADETAT IVE FLNRWITFCQSIISTLT
153	h1L-2 E62A/D20A	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLTRMLT FK FYMPKKATELKHLCLE AE LKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETT FM CEYADETAT IVE FLNRWITFCQSIISTLT
154	h1L-2 E62Y/D20A	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLTRMLT FK FYMPKKATELKHLCLE Y LKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETT FM CEYADETAT IVE FLNRWITFCQSIISTLT
155	h1L-2 L72D/D20A	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLTRMLT FK FYMPKKATELKHLCLEELKPLEEV LN DA QSKNFHLRPRDLISNINVIVLELKGSETT FM CEYADETAT IVE FLNRWITFCQSIISTLT
156	h1L-2 L72H/D20A	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLTRMLT FK FYMPKKATELKHLCLEELKPLEEV LN HA QSKNFHLRPRDLISNINVIVLELKGSETT FM CEYADETAT IVE FLNRWITFCQSIISTLT
157	h1L-2 L72R/D20A	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLTRMLT FK FYMPKKATELKHLCLEELKPLEEV LN RA QSKNFHLRPRDLISNINVIVLELKGSETT FM CEYADETAT IVE FLNRWITFCQSIISTLT
158	h1L-2 F42D/I92D	APTSSTKKTQIQLEHLLDLQMILNGINNYKNPKLTRMLT DK FYMPKKATELKHLCLEELKPLEEV LNLAQSKNFHLRPRDLISNINV VD VLELKGSETT FM CEYADETAT IVE FLNRWITFCQSIISTLT
159	h1L-2 F42R/I92D	APTSSTKKTQIQLEHLLDLQMILNGINNYKNPKLTRMLT RK FYMPKKATELKHLCLEELKPLEEV LNLAQSKNFHLRPRDLISNINV VD VLELKGSETT FM CEYADETAT IVE FLNRWITFCQSIISTLT
160	h1L-2 F42H/I92D	APTSSTKKTQIQLEHLLDLQMILNGINNYKNPKLTRMLT HK FYMPKKATELKHLCLEELKPLEEV LNLAQSKNFHLRPRDLISNINV VD VLELKGSETT FM CEYADETAT IVE FLNRWITFCQSIISTLT
161	h1L-2 F42A/I92D	APTSSTKKTQIQLEHLLDLQMILNGINNYKNPKLTRMLT AK FYMPKKATELKHLCLEELKPLEEV LNLAQSKNFHLRPRDLISNINV VD VLELKGSETT FM CEYADETAT IVE FLNRWITFCQSIISTLT
162	h1L-2 K43E/I92D	APTSSTKKTQIQLEHLLDLQMILNGINNYKNPKLTRMLT F FYMPKKATELKHLCLEELKPLEEV LNLAQSKNFHLRPRDLISNINV VD VLELKGSETT FM CEYADETAT IVE FLNRWITFCQSIISTLT
163	h1L-2 Y45R/I92D	APTSSTKKTQIQLEHLLDLQMILNGINNYKNPKLTRMLT FK R MPKKATELKHLCLEELKPLEEV LNLAQSKNFHLRPRDLISNINV VD VLELKGSETT FM CEYADETAT IVE FLNRWITFCQSIISTLT
164	h1L-2 Y45K/I92	APTSSTKKTQIQLEHLLDLQMILNGINNYKNPKLTRMLT FK K MPKKATELKHLCLEELKPLEEV LNLAQSKNFHLRPRDLISNINV VD VLELKGSETT FM CEYADETAT IVE FLNRWITFCQSIISTLT
165	h1L-2 E62A/I92D	APTSSTKKTQIQLEHLLDLQMILNGINNYKNPKLTRMLT FK FYMPKKATELKHLCLE AE LKPLEEV LNLAQSKNFHLRPRDLISNINV VD VLELKGSETT FM CEYADETAT IVE FLNRWITFCQSIISTLT
166	h1L-2 E62Y/I92D	APTSSTKKTQIQLEHLLDLQMILNGINNYKNPKLTRMLT FK FYMPKKATELKHLCLE Y LKPLEEV LNLAQSKNFHLRPRDLISNINV VD VLELKGSETT FM CEYADETAT IVE FLNRWITFCQSIISTLT
167	h1L-2 L72D/I92D	APTSSTKKTQIQLEHLLDLQMILNGINNYKNPKLTRMLT FK FYMPKKATELKHLCLEELKPLEEV LN DA QSKNFHLRPRDLISNINV VD VLELKGSETT FM CEYADETAT IVE FLNRWITFCQSIISTLT
168	h1L-2 L72H/I92D	APTSSTKKTQIQLEHLLDLQMILNGINNYKNPKLTRMLT FK FYMPKKATELKHLCLEELKPLEEV LN HA QSKNFHLRPRDLISNINV VD VLELKGSETT FM CEYADETAT IVE FLNRWITFCQSIISTLT

169	h1L-2 L72R/I92D	APTSSTKKTQQLQLEHLLLDLQMI LINGINNYKNPKLTRMLT FKFYMPKKATELKHLCLEEEELKPLEEV LNRAQSKNFHLRPRDLISININVDVLELKGSETT FCEYADETAT IVEFLNRWITFCQSIISTLT
170	h1L-2 R38D/I92D	APTSSTKKTQQLQLEHLLLDLQMI LINGINNYKNPKLTDMLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININVDVLELKGSETT FCEYADETAT IVEFLNRWITFCQSIISTLT
171	h1L-2 R38E/I92D	APTSSTKKTQQLQLEHLLLDLQMI LINGINNYKNPKLT EMLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININVDVLELKGSETT FCEYADETAT IVEFLNRWITFCQSIISTLT
172	h1L-2 R38Q/I92D	APTSSTKKTQQLQLEHLLLDLQMI LINGINNYKNPKLT QMLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININVDVLELKGSETT FCEYADETAT IVEFLNRWITFCQSIISTLT
173	h1L-2 R38A/I92D	APTSSTKKTQQLQLEHLLLDLQMI LINGINNYKNPKLT AMLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININVDVLELKGSETT FCEYADETAT IVEFLNRWITFCQSIISTLT
174	h1L-2 R38E/N88R	APTSSTKKTQQLQLEHLLLDLQMI LINGINNYKNPKLT EMLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININVLVLELKGSETT FCEYADETAT IVEFLNRWITFCQSIISTLT
175	h1L-2 R38E/D84R	APTSSTKKTQQLQLEHLLLDLQMI LINGINNYKNPKLT EMLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININVLVLELKGSETT FCEYADETAT IVEFLNRWITFCQSIISTLT
176	h1L-2 R38E/D84K	APTSSTKKTQQLQLEHLLLDLQMI LINGINNYKNPKLT EMLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININVLVLELKGSETT FCEYADETAT IVEFLNRWITFCQSIISTLT
177	h1L-2 F42A/Y45R/D20A	APTSSTKKTQQLQLEHLLLDLQMI LINGINNYKNPKLTRMLT AKFRMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININVLVLELKGSETT FCEYADETAT IVEFLNRWITFCQSIISTLT
178	h1L-2 F42H/Y45R/D20A	APTSSTKKTQQLQLEHLLLDLQMI LINGINNYKNPKLTRMLT HKFRMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININVLVLELKGSETT FCEYADETAT IVEFLNRWITFCQSIISTLT
179	h1L-2 R38D/E61R/D20A	APTSSTKKTQQLQLEHLLLDLQMI LINGINNYKNPKLTDMLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININVLVLELKGSETT FCEYADETAT IVEFLNRWITFCQSIISTLT
180	h1L-2 R38E/E61R/D20A	APTSSTKKTQQLQLEHLLLDLQMI LINGINNYKNPKLT EMLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININVLVLELKGSETT FCEYADETAT IVEFLNRWITFCQSIISTLT
181	h1L-2 R38Q/E61R/D20A	APTSSTKKTQQLQLEHLLLDLQMI LINGINNYKNPKLT QMLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININVLVLELKGSETT FCEYADETAT IVEFLNRWITFCQSIISTLT
182	h1L-2 R38A/E61R/D20A	APTSSTKKTQQLQLEHLLLDLQMI LINGINNYKNPKLT AMLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININVLVLELKGSETT FCEYADETAT IVEFLNRWITFCQSIISTLT
183	h1L-2 R38A/D20A/E95A	APTSSTKKTQQLQLEHLLLDLQMI LINGINNYKNPKLT AMLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININVLVLELKGSETT FCEYADETAT IVEFLNRWITFCQSIISTLT
184	h1L-2 D20A/E95A/R38D	APTSSTKKTQQLQLEHLLLDLQMI LINGINNYKNPKLTDMLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININVLVLELKGSETT FCEYADETAT IVEFLNRWITFCQSIISTLT
185	h1L-2 D20A/ E95A/ R38E	APTSSTKKTQQLQLEHLLLDLQMI LINGINNYKNPKLT EMLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININVLVLELKGSETT FCEYADETAT IVEFLNRWITFCQSIISTLT
186	h1L-2 D20A/E95A/R38Q	APTSSTKKTQQLQLEHLLLDLQMI LINGINNYKNPKLT QMLT FKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININVLVLELKGSETT FCEYADETAT IVEFLNRWITFCQSIISTLT

187	hIL-2 D20A/E95A/F42R	APTSSSTKKTQLQLEHLLLAQMILNGINNYKNPKLTRMLT R KFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVI V LALKGSETT F MCEYADETATIVEFLNRWITFCQSIISTLT
188	hIL-2 D20A/E95A/F42A	APTSSSTKKTQLQLEHLLLAQMILNGINNYKNPKLTRMLT A KFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVI V LALKGSETT F MCEYADETATIVEFLNRWITFCQSIISTLT
189	hIL-2 D20A/E95A /F42D	APTSSSTKKTQLQLEHLLLAQMILNGINNYKNPKLTRMLT D KFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVI V LALKGSETT F MCEYADETATIVEFLNRWITFCQSIISTLT
190	hIL-2 D20A/E95A /F42H	APTSSSTKKTQLQLEHLLLAQMILNGINNYKNPKLTRMLT H KFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVI V LALKGSETT F MCEYADETATIVEFLNRWITFCQSIISTLT
191	hIL-2 D20A/E95A/F42K	APTSSSTKKTQLQLEHLLLAQMILNGINNYKNPKLTRMLT K KFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVI V LALKGSETT F MCEYADETATIVEFLNRWITFCQSIISTLT
192	hIL-2 D20A/E95A /K43A	APTSSSTKKTQLQLEHLLLAQMILNGINNYKNPKLTRMLT F AFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVI V LALKGSETT F MCEYADETATIVEFLNRWITFCQSIISTLT
193	hIL-2 D20A/E95A /K43E	APTSSSTKKTQLQLEHLLLAQMILNGINNYKNPKLTRMLT F E F YMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVI V LALKGSETT F MCEYADETATIVEFLNRWITFCQSIISTLT
194	hIL-2 D20A/E95A /K43Q	APTSSSTKKTQLQLEHLLLAQMILNGINNYKNPKLTRMLT Q FYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVI V LALKGSETT F MCEYADETATIVEFLNRWITFCQSIISTLT
195	hIL-2 D20A/E95A /Y45A	APTSSSTKKTQLQLEHLLLAQMILNGINNYKNPKLTRMLT F K A MPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVI V LALKGSETT F MCEYADETATIVEFLNRWITFCQSIISTLT
196	hIL-2 D20A/E95A /Y45K	APTSSSTKKTQLQLEHLLLAQMILNGINNYKNPKLTRMLT F K K MPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVI V LALKGSETT F MCEYADETATIVEFLNRWITFCQSIISTLT
197	hIL-2 D20A/E95A /Y45S	APTSSSTKKTQLQLEHLLLAQMILNGINNYKNPKLTRMLT F K S MPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVI V LALKGSETT F MCEYADETATIVEFLNRWITFCQSIISTLT
198	hIL-2 D20A/E95A /Y45R	APTSSSTKKTQLQLEHLLLAQMILNGINNYKNPKLTRMLT F K R MPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVI V LALKGSETT F MCEYADETATIVEFLNRWITFCQSIISTLT
199	hIL-2 D20A/E95A /E61A	APTSSSTKKTQLQLEHLLLAQMILNGINNYKNPKLTRMLT F KFYMPKKATELKHLCLE A EELKPLEEV LNLAQSKNFHLRPRDLISNINVI V LALKGSETT F MCEYADETATIVEFLNRWITFCQSIISTLT

200	hIL-2 D20A/E95A /E62A	APTSSTKKTQLQLEHLL AL QMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEELKPLEEV LNLAQSKNFHLRPDLISNINVI VLAL KGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
201	hIL-2 D20A/E95A/E62R	APTSSTKKTQLQLEHLL AL QMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEELKPLEEV LNLAQSKNFHLRPDLISNINVI VLAL KGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
202	hIL-2 D20A/E95A /E62K	APTSSTKKTQLQLEHLL AL QMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEELKPLEEV LNLAQSKNFHLRPDLISNINVI VLAL KGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
203	hIL-2 D20A/E95A /E62Y	APTSSTKKTQLQLEHLL AL QMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEELKPLEEV LNLAQSKNFHLRPDLISNINVI VLAL KGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
204	hIL-2 D20A/E95A /E68Y	APTSSTKKTQLQLEHLL AL QMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEELKPLE YV LNLAQSKNFHLRPDLISNINVI VLAL KGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
205	hIL-2 D20A/E95A/E68A	APTSSTKKTQLQLEHLL AL QMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEELKPLE AV LNLAQSKNFHLRPDLISNINVI VLAL KGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
206	hIL-2 D20A/E95A /E68L	APTSSTKKTQLQLEHLL AL QMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEELKPLE LV LNLAQSKNFHLRPDLISNINVI VLAL KGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
207	hIL-2 D20A/E95A /L72Y	APTSSTKKTQLQLEHLL AL QMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEELKPLEEV LN YA QSKNFHLRPDLISNINVI VLAL KGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
208	hIL-2 D20A/E95A /L72R	APTSSTKKTQLQLEHLL AL QMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEELKPLEEV LN RA QSKNFHLRPDLISNINVI VLAL KGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
209	hIL-2 D20A/E95A /L72A	APTSSTKKTQLQLEHLL AL QMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEELKPLEEV LN AA QSKNFHLRPDLISNINVI VLAL KGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
210	hIL-2 D20A/E95A/L72D	APTSSTKKTQLQLEHLL AL QMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEELKPLEEV LN DA QSKNFHLRPDLISNINVI VLAL KGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
211	hIL-2 D20A/E95A /L72H	APTSSTKKTQLQLEHLL AL QMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEELKPLEEV LN HA QSKNFHLRPDLISNINVI VLAL KGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
212	hIL-2 D20A/E95A /L72F	APTSSTKKTQLQLEHLL AL QMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEELKPLEEV LN FA QSKNFHLRPDLISNINVI VLAL KGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT

213	hIL-2 F42K/Y45R/D20A /S87A	APTSSTKKTQLQLEHLLLAALQMILNGINNYKNPKLT EMLT KKFRMPKKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
214	hIL-2 F42K/Y45R/D20A /E95A	APTSSTKKTQLQLEHLLLAALQMILNGINNYKNPKLT EMLT KKFRMPKKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLALKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
215	hIL-2 D20A/R38E/C125 A	APTSSTKKTQLQLEHLLLAALQMILNGINNYKNPKLT EMLT FKFYMPKKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATIVEFLNRWITFAQSIISTLT
216	hIL-2 T3A/D20A/R38E	AP A SSSTKKTQLQLEHLLLAALQMILNGINNYKNPKLT EMLT FKFYMPKKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
217	hIL-2 T3A/D20A/R38E/ C125A	AP A SSSTKKTQLQLEHLLLAALQMILNGINNYKNPKLT EMLT FKFYMPKKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATIVEFLNRWITFAQSIISTLT
	(IL-2-AAEA)	
218	hIL-2 Δ1- 3APT/D20A/R38E	SSSTKKTQLQLEHLLLAALQMILNGINNYKNPKLT EMLT FKFYMPKKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
219	hIL-2 Δ1- 3APT/D20A/R38E /C125A	SSSTKKTQLQLEHLLLAALQMILNGINNYKNPKLT EMLT FKFYMPKKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATIVEFLNRWITFAQSIISTLT
220	hIL-2 R38E/Q22A	APTSSTKKTQLQLEHLLLDLAALQMILNGINNYKNPKLT EMLT FKFYMPKKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
221	hIL-2 R38E/T123A	APTSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT EMLT FKFYMPKKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATIVEFLNRWIAFCQSIISTLT
222	hIL-2 R38E/I129A	APTSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT EMLT FKFYMPKKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
223	hIL-2 R38E/S130A	APTSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT EMLT FKFYMPKKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
224	hIL-2 R38E/Q126A	APTSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT EMLT FKFYMPKKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATIVEFLNRWITFCASIISTLT
225	hIL-2 R38E/Q126D	APTSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT EMLT FKFYMPKKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATIVEFLNRWITFCDSIISTLT
226	hIL-2 R38E/Q126V	APTSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLT EMLT FKFYMPKKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATIVEFLNRWITFCVSIISTLT

227	hIL-2 R38E/Q22A/S130 A	APTSSTKKTQQLQLEHLLLD AM ILNGINNYKNPKLT EM LTKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSI AT LTLT
228	hIL-2 F42K/Y45R/Q126 D	APTSSTKKTQQLQLEHLLLD Q MLNGINNYKNPKLTRMLTK KF RMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATIVEFLNRWITFC DS IIISTLT
229	hIL-2 D20A/E95A/Q126 D	APTSSTKKTQQLQLEHLL LAL QMLNGINNYKNPKLTRMLTKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIV LAL KGSETTFMCEYADETATIVEFLNRWITFC DS IIISTLT
230	hIL-2 D20A/E61R	APTSSTKKTQQLQLEHLL LAL QMLNGINNYKNPKLTRMLTKFYMPKKATELKHLCCL RE LKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSI II STLT
231	hIL-2 D20A/E61N	APTSSTKKTQQLQLEHLL LAL QMLNGINNYKNPKLTRMLTKFYMPKKATELKHLCCL EN LKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSI II STLT
232	hIL-2 D20A/E61D	APTSSTKKTQQLQLEHLL LAL QMLNGINNYKNPKLTRMLTKFYMPKKATELKHLCCL DE LKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSI II STLT
233	hIL-2 D20A/E61Q	APTSSTKKTQQLQLEHLL LAL QMLNGINNYKNPKLTRMLTKFYMPKKATELKHLCCL Q ELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSI II STLT
234	hIL-2 D20A/E61G	APTSSTKKTQQLQLEHLL LAL QMLNGINNYKNPKLTRMLTKFYMPKKATELKHLCCL GE LKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSI II STLT
235	hIL-2 D20A/E61H	APTSSTKKTQQLQLEHLL LAL QMLNGINNYKNPKLTRMLTKFYMPKKATELKHLCCL HE LKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSI II STLT
236	hIL-2 D20A/E61I	APTSSTKKTQQLQLEHLL LAL QMLNGINNYKNPKLTRMLTKFYMPKKATELKHLCCL IE LKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSI II STLT
237	hIL-2 D20A/E61L	APTSSTKKTQQLQLEHLL LAL QMLNGINNYKNPKLTRMLTKFYMPKKATELKHLCCL LE LKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSI II STLT
238	hIL-2 D20A/E61K	APTSSTKKTQQLQLEHLL LAL QMLNGINNYKNPKLTRMLTKFYMPKKATELKHLCCL KE LKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSI II STLT
239	hIL-2 D20A/E61M	APTSSTKKTQQLQLEHLL LAL QMLNGINNYKNPKLTRMLTKFYMPKKATELKHLCCL ME LKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSI II STLT
240	hIL-2 D20A/E61F	APTSSTKKTQQLQLEHLL LAL QMLNGINNYKNPKLTRMLTKFYMPKKATELKHLCCL FE LKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSI II STLT
241	hIL-2 D20A/E61P	APTSSTKKTQQLQLEHLL LAL QMLNGINNYKNPKLTRMLTKFYMPKKATELKHLCCL PE LKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSI II STLT
242	hIL-2 D20A/E61S	APTSSTKKTQQLQLEHLL LAL QMLNGINNYKNPKLTRMLTKFYMPKKATELKHLCCL SE LKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSI II STLT

243	h1L-2 D20A/E61T	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLTRMLT FKFYMPKKATEL KHLQCLE TEL KPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
244	h1L-2 D20A/E61W	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLTRMLT FKFYMPKKATEL KHLQCLE WEL KPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
245	h1L-2 D20A/E61Y	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLTRMLT FKFYMPKKATEL KHLQCLE YEL KPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
246	h1L-2 D20A/E61V	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLTRMLT FKFYMPKKATEL KHLQCLE VEL KPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
247	h1L-2 D20A/F42N	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLTRMLT NKFYMPKKATEL KHLQCLE EEEL KPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
248	h1L-2 D20A/F42Q	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLTRMLT QKFYMPKKATEL KHLQCLE EEEL KPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
249	h1L-2 D20A/F42E	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLTRMLT EKFYMPKKATEL KHLQCLE EEEL KPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
250	h1L-2 D20A/F42G	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLTRMLT GKFYMPKKATEL KHLQCLE EEEL KPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
251	h1L-2 D20A/F42I	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLTRMLT IKFYMPKKATEL KHLQCLE EEEL KPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
252	h1L-2 D20A/F42L	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLTRMLT LKFYMPKKATEL KHLQCLE EEEL KPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
253	h1L-2 D20A/F42M	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLTRMLT TKFYMPKKATEL KHLQCLE EEEL KPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
254	h1L-2 D20A/F42P	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLTRMLT PKFYMPKKATEL KHLQCLE EEEL KPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
255	h1L-2 D20A/F42S	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLTRMLT SKFYMPKKATEL KHLQCLE EEEL KPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
256	h1L-2 D20A/F42T	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLTRMLT TKFYMPKKATEL KHLQCLE EEEL KPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
257	h1L-2 D20A/F42W	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLTRMLT WKFYMPKKATEL KHLQCLE EEEL KPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
258	h1L-2 D20A/F42Y	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLTRMLT YKFYMPKKATEL KHLQCLE EEEL KPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
259	h1L-2 D20A/F42V	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLTRMLT VKFYMPKKATEL KHLQCLE EEEL KPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
260	h1L-2 D20A/Y45A	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLTRMLT FKFAMPKKATEL KHLQCLE EEEL KPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT

261	h1L-2 D20A/Y45N	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLTRMLT FKNMP KKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETT FMCE YADETAT IVEFLNR WITFCQSIISTLT
262	h1L-2 D20A/Y45D	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLTRMLT FKDMP KKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETT FMCE YADETAT IVEFLNR WITFCQSIISTLT
263	h1L-2 D20A/Y45Q	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLTRMLT FKFQMP KKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETT FMCE YADETAT IVEFLNR WITFCQSIISTLT
264	h1L-2 D20A/Y45E	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLTRMLT FKFEMP KKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETT FMCE YADETAT IVEFLNR WITFCQSIISTLT
265	h1L-2 D20A/Y45G	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLTRMLT FKFGMP KKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETT FMCE YADETAT IVEFLNR WITFCQSIISTLT
266	h1L-2 D20A/Y45H	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLTRMLT FKFHP MPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETT FMCE YADETAT IVEFLNR WITFCQSIISTLT
267	h1L-2 D20A/Y45I	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLTRMLT FKFIMP KKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETT FMCE YADETAT IVEFLNR WITFCQSIISTLT
268	h1L-2 D20A/Y45L	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLTRMLT FKFLMP KKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETT FMCE YADETAT IVEFLNR WITFCQSIISTLT
269	h1L-2 D20A/Y45M	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLTRMLT FKFMP MPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETT FMCE YADETAT IVEFLNR WITFCQSIISTLT
270	h1L-2 D20A/Y45F	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLTRMLT FKFMP KKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETT FMCE YADETAT IVEFLNR WITFCQSIISTLT
271	h1L-2 D20A/Y45P	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLTRMLT FKFPMP KKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETT FMCE YADETAT IVEFLNR WITFCQSIISTLT
272	h1L-2 D20A/Y45S	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLTRMLT FKFSMP KKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETT FMCE YADETAT IVEFLNR WITFCQSIISTLT
273	h1L-2 D20A/Y45T	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLTRMLT FKFTMP KKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETT FMCE YADETAT IVEFLNR WITFCQSIISTLT
274	h1L-2 D20A/Y45W	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLTRMLT FKFWMP KKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETT FMCE YADETAT IVEFLNR WITFCQSIISTLT
275	h1L-2 D20A/Y45V	APTSSTKKTQIQLEHLL AL QMILNGINNYKNPKLTRMLT FKFVMP KKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIVLELKGSETT FMCE YADETAT IVEFLNR WITFCQSIISTLT
276	h1L-2 I92D/F42N	APTSSTKKTQIQLEHLLDQMILNGINNYKNPKLTRMLT NKFYMP KKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINV VD VLELKGSETT FMCE YADETAT IVEFLNR WITFCQSIISTLT
277	h1L-2 I92D/F42Q	APTSSTKKTQIQLEHLLDQMILNGINNYKNPKLTRMLT QKFYMP KKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINV VD VLELKGSETT FMCE YADETAT IVEFLNR WITFCQSIISTLT
278	h1L-2 I92D/F42E	APTSSTKKTQIQLEHLLDQMILNGINNYKNPKLTRMLT EKFYMP KKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINV VD VLELKGSETT FMCE YADETAT IVEFLNR WITFCQSIISTLT

279	h1L-2 I92D/F42G	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLTRMLT G KFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININ VD VLELKGSETT F MCEYADETATATIVEFLNRWITFCQSIISTLT
280	h1L-2 I92D/F42I	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLTRMLT I KFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININ VD VLELKGSETT F MCEYADETATATIVEFLNRWITFCQSIISTLT
281	h1L-2 I92D/F42L	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLTRMLT L KFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININ VD VLELKGSETT F MCEYADETATATIVEFLNRWITFCQSIISTLT
282	h1L-2 I92D/F42K	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLTRMLT K KFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININ VD VLELKGSETT F MCEYADETATATIVEFLNRWITFCQSIISTLT
283	h1L-2 I92D/F42M	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLTRMLT M KFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININ VD VLELKGSETT F MCEYADETATATIVEFLNRWITFCQSIISTLT
284	h1L-2 I92D/F42P	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLTRMLT P KFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININ VD VLELKGSETT F MCEYADETATATIVEFLNRWITFCQSIISTLT
285	h1L-2 I92D/F42S	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLTRMLT S KFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININ VD VLELKGSETT F MCEYADETATATIVEFLNRWITFCQSIISTLT
286	h1L-2 I92D/F42T	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLTRMLT T KFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININ VD VLELKGSETT F MCEYADETATATIVEFLNRWITFCQSIISTLT
287	h1L-2 I92D/F42W	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLTRMLT W KFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININ VD VLELKGSETT F MCEYADETATATIVEFLNRWITFCQSIISTLT
288	h1L-2 I92D/F42Y	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLTRMLT Y KFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININ VD VLELKGSETT F MCEYADETATATIVEFLNRWITFCQSIISTLT
289	h1L-2 I92D/F42V	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLTRMLT V KFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININ VD VLELKGSETT F MCEYADETATATIVEFLNRWITFCQSIISTLT
290	h1L-2 I92D/Y45A	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLTRMLT A KFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININ VD VLELKGSETT F MCEYADETATATIVEFLNRWITFCQSIISTLT
291	h1L-2 I92D/Y45N	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLTRMLT N KFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININ VD VLELKGSETT F MCEYADETATATIVEFLNRWITFCQSIISTLT
292	h1L-2 I92D/Y45D	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLTRMLT D KFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININ VD VLELKGSETT F MCEYADETATATIVEFLNRWITFCQSIISTLT
293	h1L-2 I92D/Y45Q	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLTRMLT Q KFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININ VD VLELKGSETT F MCEYADETATATIVEFLNRWITFCQSIISTLT
294	h1L-2 I92D/Y45E	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLTRMLT E KFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININ VD VLELKGSETT F MCEYADETATATIVEFLNRWITFCQSIISTLT
295	h1L-2 I92D/Y45G	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLTRMLT G KFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININ VD VLELKGSETT F MCEYADETATATIVEFLNRWITFCQSIISTLT
296	h1L-2 I92D/Y45H	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLTRMLT H KFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININ VD VLELKGSETT F MCEYADETATATIVEFLNRWITFCQSIISTLT

297	h1L-2 I92D/Y45I	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLTRMLT FKFI MPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININVDVLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
298	h1L-2 I92D/Y45L	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLTRMLT FKFI MPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININVDVLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
299	h1L-2 I92D/Y45M	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLTRMLT FKFI MPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININVDVLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
300	h1L-2 I92D/Y45F	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLTRMLT FKFI MPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININVDVLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
301	h1L-2 I92D/Y45P	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLTRMLT FKFI MPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININVDVLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
302	h1L-2 I92D/Y45S	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLTRMLT FKFI SMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININVDVLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
303	h1L-2 I92D/Y45T	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLTRMLT FKFI TMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININVDVLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
304	h1L-2 I92D/Y45W	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLTRMLT FKFI WMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININVDVLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
305	h1L-2 I92D/Y45V	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLTRMLT FKFI VMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININVDVLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
306	h1L-2 R38E/D20H	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLT EMLT FKFI MPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININVI VLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
307	h1L-2 R38E/D20S	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLT EMLT FKFI MPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININVI VLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
308	h1L-2 F42A/N88R	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLTRMLT AKFI MPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININVI VLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
309	h1L-2 F42A/N88D	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLTRMLT AKFI MPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININVI VLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
310	h1L-2 R38E/D84A	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLT EMLT FKFI MPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRALI SININVI VLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
311	h1L-2 R38E/D84N	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLT EMLT FKFI MPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRNLI SININVI VLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
312	h1L-2 R38E/D84Q	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLT EMLT FKFI MPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRQLI SININVI VLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
313	h1L-2 R38E/D84E	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLT EMLT FKFI MPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRELI SININVI VLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT
314	h1L-2 R38E/D84G	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLT EMLT FKFI MPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRGLI SININVI VLELKGSETT FMCEYADETAT IVEFLNRWITFCQSIISTLT

315	h1L-2 R38E/D84H	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLT EM LTKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPR HL ISININVI VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
316	h1L-2 R38E/D84I	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLT EM LTKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPR LI ISININVI VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
317	h1L-2 R38E/D84L	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLT EM LTKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPR LL ISININVI VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
318	h1L-2 R38E/D84M	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLT EM LTKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPR ML ISININVI VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
319	h1L-2 R38E/D84F	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLT EM LTKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPR FL ISININVI VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
320	h1L-2 R38E/D84P	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLT EM LTKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPR PL ISININVI VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
321	h1L-2 R38E/D84S	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLT EM LTKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPR SL ISININVI VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
322	h1L-2 R38E/D84T	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLT EM LTKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPR TL ISININVI VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
323	h1L-2 R38E/D84W	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLT EM LTKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPR WL ISININVI VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
324	h1L-2 R38E/D84Y	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLT EM LTKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPR YL ISININVI VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
325	h1L-2 R38E/D84V	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLT EM LTKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPR VL ISININVI VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
326	h1L-2 R38E/I92A	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLT EM LTKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRD LI SNIN V A VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
327	h1L-2 R38E/I92R	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLT EM LTKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRD LI SNIN V R VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
328	h1L-2 R38E/I92N	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLT EM LTKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRD LI SNIN VN VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
329	h1L-2 R38E/I92Q	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLT EM LTKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRD LI SNIN VQ VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
330	h1L-2 R38E/I92E	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLT EM LTKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRD LI SNIN VE VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
331	h1L-2 R38E/I92G	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLT EM LTKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRD LI SNIN VG VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
332	h1L-2 R38E/I92H	APTSSTKKTQIQLEHLLLDLQMI LINGINNYKNPKLT EM LTKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRD LI SNIN VH VLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT

333	hIL-2 R38E/I92L	APTSSTKKKTQQLQLEHLLLDLQMLINGINNYKNPKLT EM LTKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININ VL VLELKGSETT FM CEYADETATIVEFLNRWITFCQSIISTLT
334	hIL-2 R38E/I92K	APTSSTKKKTQQLQLEHLLLDLQMLINGINNYKNPKLT EM LTKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININ VK VLELKGSETT FM CEYADETATIVEFLNRWITFCQSIISTLT
335	hIL-2 R38E/I92M	APTSSTKKKTQQLQLEHLLLDLQMLINGINNYKNPKLT EM LTKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININ VM VLELKGSETT FM CEYADETATIVEFLNRWITFCQSIISTLT
336	hIL-2 R38E/I92F	APTSSTKKKTQQLQLEHLLLDLQMLINGINNYKNPKLT EM LTKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININ VF VLELKGSETT FM CEYADETATIVEFLNRWITFCQSIISTLT
337	hIL-2 R38E/I92P	APTSSTKKKTQQLQLEHLLLDLQMLINGINNYKNPKLT EM LTKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININ P VLELKGSETT FM CEYADETATIVEFLNRWITFCQSIISTLT
338	hIL-2 R38E/I92S	APTSSTKKKTQQLQLEHLLLDLQMLINGINNYKNPKLT EM LTKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININ VS VLELKGSETT FM CEYADETATIVEFLNRWITFCQSIISTLT
339	hIL-2 R38E/I92T	APTSSTKKKTQQLQLEHLLLDLQMLINGINNYKNPKLT EM LTKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININ TV VLELKGSETT FM CEYADETATIVEFLNRWITFCQSIISTLT
340	hIL-2 R38E/I92W	APTSSTKKKTQQLQLEHLLLDLQMLINGINNYKNPKLT EM LTKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININ VV VLELKGSETT FM CEYADETATIVEFLNRWITFCQSIISTLT
341	hIL-2 R38E/I92Y	APTSSTKKKTQQLQLEHLLLDLQMLINGINNYKNPKLT EM LTKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININ VV VLELKGSETT FM CEYADETATIVEFLNRWITFCQSIISTLT
342	hIL-2 R38E/I92V	APTSSTKKKTQQLQLEHLLLDLQMLINGINNYKNPKLT EM LTKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININ VV VLELKGSETT FM CEYADETATIVEFLNRWITFCQSIISTLT
343	hIL-2 R38E/H16E	APTSSTKKKTQQLQLE EL LLDLQMLINGINNYKNPKLT EM LTKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININ VI VLELKGSETT FM CEYADETATIVEFLNRWITFCQSIISTLT
344	hIL-2 R38K/D20A	APTSSTKKKTQQLQLEHLL AL QMLINGINNYKNPKLT KML T K FYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININ VI VLELKGSETT FM CEYADETATIVEFLNRWITFCQSIISTLT
345	WT hIL-2	APTSSTKKKTQQLQLEHLLLDLQMLINGINNYKNPKLT RML T R FYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISININ VI VLELKGSETT FM CEYADETATIVEFLNRWITFCQSIISTLT
346	Human PD-1	PGWFLDSPDRPWNPTTFSPALLVVTGEDNATFTCSFSNTSESVLNWYRMSPSNQTDKLAAPEDRSQP GQDCRFRVTQLPNGRDFHMSVVRARRNDSGTYLCGATSLAPKAQIKESLRaelRVtERRAEVPTAHPSP FQWREKTPPPVPCVPEQTEYATIVFPsGMGTSSPARRGSADGPRSAQPLRPEDGHCSWPL
347	Human PD-1	CCAGGATGGTCTTAGACTCCGACAGAGCCCTGGAAACCCGCCACCTTCTCCCGAGCCCTGCTCGTG GTGACCGAAGGGACAAACGCCACCTCACCTGCAGCTTCTCCACACATCGGAGAGCTTCGTGCTAAAC TGGTACCGCATGAGCCCGACGACACGAGGACAACTGGCGCGCTTCCCGAGGACCGCAGCCAGCCC GGCCAGGACTGCCGCTCCGCTGTCACACAACTGCCACGCGGTGACTTCCACATGAGCGTGGTCAGG GCCCCGGCAATGACAGCGGCACTACCTCTGTGGGGCATCTCCCTGGCCCCCAAGGCGCAGATCAAA GAGAGCCTGCGGGCAGAGCTAGGGTGACAGAGAGAGGCGAAGTGCACAGACCCACCCAGCCCC

		TCACCCAGGCCAGCCGCCAGTTCCAAAACCCCTGGTGGTGGTGGTGGTGGCGGCGCTGCTGGCGACGCGCTG GTGCTGCTAGTCTGGGTCCTGGCGGTCACTGCTCCCGGGCGGCACGAGGACATAGAGACCGAGCGC ACCGCCAGCCCCCTGAAGGAGACCCCTCAGCCGTCCCTGTGTCTCTGTGGACTATGGGAGCTGGAT TTCCACTGGCGAGAGAACCCCGAGCCCCCGCTGCCCTGTGTCCCTGAGCAGACGAGATATGCCACC ATTGCTCTTCTAGCGGAATGGGACCTCATCCCGCCGCGAGCGGCTCAGCTGACGCGCCCTCGGAGT GCCAGCCACTGAGGCTGAGGATGGACACTGCTCTTGGCCCCCTC
348	Anti-hPD-1 #1- mIgG2b-N297A HC	QVQLVESGGGVQPGRSLRLDCKASGTFSNSGMHWVRQAPGKGLGEWAVIWIYDGSKRYIYADSVKGRFT ISRDNKNTLFLQMNSLRAEDAVYYCATNDDYWGQGLVTVSSAKTTPPSVYPLAPGCGDITGSSVTL GCLVGYFPESVTVTWNSGLSSSVHTFPALLQSGLYTMSSSVTVPSSTWPSQVTVCSVAHPASSTVD KKLEPSGPISTINPCPPCKECHKCPAPNLEGGPSVFI FPNIKDVLMI SLTPKVTGVVDVSEDDPDVQ ISWVFNNEVHTAQQTTHREDYASTIRVVS TLPIQHQDMMSGKEFKCKVNNKDLPSPIERTISKIKGLV RAPQVYILPPAEQLSRKDVSLTCLVGFNP GDISVEWTSNGHTEENYKDTAPVLDS DGSYFIYSKLNLM KTSKWEKTD SFSCNVRHEGLKNYYLKKTI SRSPGK
349	Anti-hPD-1 #1- mkappa LC	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASN RATGIPARFSGSGGT DFTLTISLLEPEDFAVYYCQQSSNWPRTFGQGTKVEIKRADAAPTVSI FPPSSEQLTSGGASVVCFLNN FYPKDINVVKWKIDGSE RQNGVLNSWTDQDSKDSITYSMSSTLTLT KDEYERHNSYTCEATHKTTSTSPIVK SFNRNEC
350	Anti-hPD-1 #2- mIgG2b-N297A HC	QVQLVQSGVEVKKPGASVKVSKASGYFTFNYYMYWVRQAPGQGLEWMGGINPSNGGTNFEKFKNRVT LT TDSSTTTAYMELKSLQFD DTA VYYCARRDYRFDMGFDYWGQGTIVTVSSAKTTPPSVYPLAPGCGDT TGSSVTIGCLVKGYPFESVTVTWNSGLSSSVHTFPALLQSGLYTMSSSVTVPSSTWPSQVTVCSVAHP ASSTTVDDKKLEPSGPISTINPCPPCKECHKCPAPNLEGGPSVFI FPNIKDVLMI SLTPKVTGVVDV EDDPDVQISWVFNNEVHTAQQTTHREDYASTIRVVS TLPIQHQDMMSGKEFKCKVNNKDLPSPIERTI SKI KGLVRAPQVYILPPAEQLSRKDVSLTCLVGFNP GDISVEWTSNGHTEENYKDTAPVLDS DGSYF IYSKLNMKTSKWEKTD SFSCNVRHEGLKNYYLKKTI SRSPGK
351	Anti-hPD-1 #2- mkappa LC	EIVLTQSPATLSLSPGERATLSCRASKGVSTSGYSYLHWYQQKPGQAPRLLIYLASYLESGVPARFSGS GSGTDFTLT ISSLEPEDFAVYYCQHSRD LPLTFGGGTKVEIKRADAAPTVSI FPPSSEQLTSGGASVVC FLNNFYPKDINVVKWKIDGSE RQNGVLNSWTDQDSKDSITYSMSSTLTLT KDEYERHNSYTCEATHKTTST PIVKSFN RNEC
352	IL-2Rγ	LN TTTILTPNGNEDTTADFFELTTPMTDLSVSTLPLPEVQC FVFNVEYMNCTWNSSSEFPQPTNLTILHWY KNSDNDKVQKCSHYLFEEITSGQLQKKEIHLIYQTFVYQLQDPREPRRQATQMLKLQNLVIPWAPENL TLHKLSESQLELNWNNRFLNHCLHLVQYRTDWDHSTEQSDYRHKFSLPSVDGQKRYTFRVRSRFP LCGSAQHWESEWSHP IHWGNTSKENPFLFALEAVVISVGSMLIIISLLCVYFWLERTMPRIPTLKNLED LVTEYHGNFSAWSGVSKGLAESLQPDYSERLCLVSEIIPKGGALGEGPGASPCNQHSFPYWAPCYTTLKP ET
353	human CD122 (IL-2Rβ)	AVNGTSQFTCFYNSTRANISCVWSQD GALQDTSQVHAWPDRRRWNQTCELLPVSQASWACNLILGAPDS QKLTVDIVTLRLVLCREGVRWRVMAIQDFKPFENLRMAPISLQVVHVETHRCNISWEISQASHYFERH LEFEARTLSPGHTWEEAPLLTLKKQKEWICLETLTLPDTQYEFQVRVKPLQGEFTTSPSPWSQPLAFRTKP

		AALGKDTIPWLGHLVLGSGAFGIILVYLLINCRNTGPWLKKVLKCNTPDPKFFSQLSSEHGGDVQK WLSSPFSSSPGGGLAPEISPLEVLERDKVTQLLQDKVPEPASLSSNHSLSCTFTNQGYFFHLLPD ALEIEACQVYFTYDPYSEEDPDGVAGAPTGSSPQLPLSGEDDAYCTFPSRDDLLLFSPSLLGGPSP PSTAPGSGAGEERMPPSLQERVPRDWDPPQLGPTTPGVPLVDFQPPELVLREAGEEVPDAGPREGV SFPWSRPPGGGEFRALNPLNTDAYLSLQELQGQDPHLV
354	IL-2Rα	ELCDDDPPEIPHATFKAMAYKEGTMLNCEKRGFRRIKSGSLYMLCTGNSSHSWDNQCCQTSSATRNT TKQVTPQPEEQKERKTTTEMQSPMPVDQASLPGHCREPPWENEATERIYHFVVGQMVYYQCVQGYRAL HRGPAESVCKMTHGKTRWTQPQLICTGEMETSQFPGEKPKQASPEGRPESETSLVTTTDFQIQTEMAA TMETSIFTTEYQVAVAGCVFLLISVLLSGLTWQRRQRKRRTI
355	L6 linker amino acid	SGGGGS
356	hIL-2-df-1H3- hkappa LC hIL-2 in italics	APTSSSTKKTQLQLEHLLLDLQMLINGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINIVLELKGSETTFMCEYADETATIVFELNRWITFCQSIISTLTDTVLT QSPALAVSPGERVTISCRASESVRTGVHWYQQKPGQPKLLIYGASNLESGVPARFSGSGSGTDFTLTI DPVEADDTATYFCQQSWNDPFTFGSGTKLEIKRTVAAPSVFIFFPSDEQLKSGTASVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKKVYACEVTHQGLSSPVTKSFNRGE C
357	hIL-2-L6-1H3- hkappa LC Linker in dashed underline hIL-2 in italics	APTSSSTKKTQLQLEHLLLDLQMLINGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINIVLELKGSETTFMCEYADETATIVFELNRWITFCQSIISTLTSGGGG SDTVLTQSPALAVSPGERVTISCRASESVRTGVHWYQQKPGQPKLLIYGASNLESGVPARFSGSGSGT DFTLTDPEADDTATYFCQQSWNDPFTFGSGTKLEIKRTVAAPSVFIFFPSDEQLKSGTASVCLLN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKKVYACEVTHQGLSSPVTK SFNRGEC
358	hIL-2-df-1H3- hIgG1 HC hIL-2 in italics	APTSSSTKKTQLQLEHLLLDLQMLINGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINIVLELKGSETTFMCEYADETATIVFELNRWITFCQSIISTLVEQLV ESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFTISRDN AKITLYLQMDSLRSEDATYYCARHGSGYFDYWGQGVMTVSSASTKGPSVFPLAPSSKSTSGGTAALG CLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHHKPSNTKVD KKVEPKSCDKTHTCPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIISKAKGQPREPQVYIT LPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQ GNVFCVMHEALHNHYTQKSLSLSPGK
359	hIL-2-L6-1H3- hIgG1 HC	APTSSSTKKTQLQLEHLLLDLQMLINGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINIVLELKGSETTFMCEYADETATIVFELNRWITFCQSIISTLTSGGGG

	Linker in dashed underline hIL-2 in italics	SEVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRF TISRDNAKITLYLQMDSLRSEDATYYCARHGSYFDYWGQGMVTVSSASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPPSSSLGTQTYICNVNHKP SNTKVDKKEPKSCDKTHTCPPCPAPELGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPR EPQVYITLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPPVLDSGDSFFLYSKLTVD KSRWQOGNVSFCSVMHEALHNHYTQKSLSLSPGK
360	1H3-hIgG1-df- hIL-2 HC hIL-2 in italics	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDATYYCARHGSYFDYWGQGMVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPPSSSLGTQTYICNVNHKPS NTKVDKKEPKSCDKTHTCPPCPAPELGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE POVYITLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPPVLDSGDSFFLYSKLTVDK SRWQOGNVSFCSVMHEALHNHYTQKSLSLSPGKAPTSSSTKKTKQLQLEHLLLDLQMLINGINNYKNPKL TRMLTFKYPMPKKATELKHLCLEELKPLEEVNLQAQSKNFHLRPRDLISNINIVLELKGSETTFMC EYADETATIVEFLNRWITFCQSIISTLT
361	1H3-hIgG1-L6- hIL-2 HC Linker in dashed underline hIL-2 in italics	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDATYYCARHGSYFDYWGQGMVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPPSSSLGTQTYICNVNHKPS NTKVDKKEPKSCDKTHTCPPCPAPELGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE POVYITLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPPVLDSGDSFFLYSKLTVDK SRWQOGNVSFCSVMHEALHNHYTQKSLSLSPGKSGGSAPTSSSTKKTKQLQLEHLLLDLQMLINGINN YKNPKLTRMLTFKYPMPKKATELKHLCLEELKPLEEVNLQAQSKNFHLRPRDLISNINIVLELKG ETTFMCEYADETATIVEFLNRWITFCQSIISTLT
362	1H3-hKappa-df- hIL-2 (Wt) LC hIL-2 in italics	DTVLTQSPALAVSPGERVTISCRASESVRTGVHWYQQKPGQPQLLIYGASNLESGVPARFSGSGGTD FTLTIDPVEADDTATYFCQQSWNDPFTFGSGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNE YPREAKVQWKVDNALQSGNSQESVTEQDSKDSITYLSSTITLSKADYEKHKVYACEVTHQGLSSPVTKS FNRGECAPTSSSTKKTKQLQLEHLLLDLQMLINGINNYKNPKLTRMLTFKYPMPKKATELKHLCLEEL KPLEEVNLQAQSKNFHLRPRDLISNINIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT T
363	1H3-hKappa-L6- hIL-2 (Wt) LC Linker in dashed underline	DTVLTQSPALAVSPGERVTISCRASESVRTGVHWYQQKPGQPQLLIYGASNLESGVPARFSGSGGTD FTLTIDPVEADDTATYFCQQSWNDPFTFGSGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNE YPREAKVQWKVDNALQSGNSQESVTEQDSKDSITYLSSTITLSKADYEKHKVYACEVTHQGLSSPVTKS FNRGECGGGSAPTSSSTKKTKQLQLEHLLLDLQMLINGINNYKNPKLTRMLTFKYPMPKKATELKHLC CLEELKPLEEVNLQAQSKNFHLRPRDLISNINIVLELKGSETTFMCEYADETATIVEFLNRWITFCQ SIISTLT

364	hIL-2 in italics L20 linker	SGGGSGGGSGGGSGGGG
365	hCD25-L20-hIL- 2-df-1H3-hIG1 HC Linker in dashed underline hIL-2 in italics	ELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRIKSGSLYMLCTGNSSSHSWDNQCQCTSSATRNT TKQVTPQPEEQKERKTTTEMQSPMPQVDQASLPGHCREPPWENEATERIYHFVVGQMVYIQCVCQYRAL HRGPAESVCMTGKTRWTQPOLICTSGGGSGGGSGGGGSAPTSSSTKKTKQLQLEHLLLDLQ ILNGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEELKPLEEVNLAQSKNFHLRPRDLISININVI VLELKGSETTFMCEYADETATIVFELNRWITFCQSIISTLTVEQLVESGGGLVQGRSLKLSCAVSGFT FSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFTISRDNAKITLYLQMSLSRSEDATYYCA RHGSGYFDYWGQGMVTVSSATKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKHTCTPPCPAPELL GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYITLPPSRDELTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYTKTTPPVLDSGDSFFLYSKLTVDKSRWQOGNVPFSCSVMHEALHNHYTQKSLS LSPGK
366	hCD25-L20-hIL- 2-L6-1H3-hIG1 HC Linkers in dashed underline hIL-2 in italics	ELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRIKSGSLYMLCTGNSSSHSWDNQCQCTSSATRNT TKQVTPQPEEQKERKTTTEMQSPMPQVDQASLPGHCREPPWENEATERIYHFVVGQMVYIQCVCQYRAL HRGPAESVCMTGKTRWTQPOLICTSGGGSGGGSGGGGSAPTSSSTKKTKQLQLEHLLLDLQ ILNGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEELKPLEEVNLAQSKNFHLRPRDLISININVI VLELKGSETTFMCEYADETATIVFELNRWITFCQSIISTLTSGGGSEVQLVESGGGLVQGRSLKLS AVSGFTPSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFTISRDNAKITLYLQMSLSRSED ATYYCARHSGSGYFDYWGQGMVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKHTCTPPC PAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVTLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYITLPPSRDELTKNQVSLTCL LVKGFYPSDIAVEWESNGQPENNYTKTTPPVLDSGDSFFLYSKLTVDKSRWQOGNVPFSCSVMHEALHNHY TQKSLSLSPGK
367	hCD25-L20-hIL- 2-df-1H3- hKappa IC Linker in dashed underline	ELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRIKSGSLYMLCTGNSSSHSWDNQCQCTSSATRNT TKQVTPQPEEQKERKTTTEMQSPMPQVDQASLPGHCREPPWENEATERIYHFVVGQMVYIQCVCQYRAL HRGPAESVCMTGKTRWTQPOLICTSGGGSGGGSGGGGSAPTSSSTKKTKQLQLEHLLLDLQ ILNGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEELKPLEEVNLAQSKNFHLRPRDLISININVI VLELKGSETTFMCEYADETATIVFELNRWITFCQSIISTLTDTVLTQSPALAVSPGERVTISCRASESV RTGVHWYQQKPKGQQPKLLIYGASNLSEGVPARFSGSGGTDFTLTIDPVEADDTATYFCQQSWNDPFTF GSGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD SKDSTYLSSTLTLSKADYERHKVYACEVTHQGLSSPVTKSFNRGEC

	hIL-2 in italics	
368	hCD25-L20-hIL-2-L6-1H3-hKappa LC Linkers in dashed underline hIL-2 in italics	ELCDDDPPEIPHATFKAMAYKEGTMINCECKRGFRRIKSGSLYMLCTGNSSSHSWDNQCQCTSSATRNT TKQVTPQPEEQKERKTTTEMQSPQVVDQASLPGHCREPPWENEATERIYHFVVGQMVVYQCVCQGYRAL HRGPAESVCKMTHGKTRWTQPOLICTSGGGSGGGSGGGSGGSAPTSSSTKKTLQLEHLLLDLQM IILNGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEELKPLEEVINLAQSKNFHLRPRDLISNINVI VLELKGSETTFMCEYADETATIVFELNRWITFCQSIISTLTSGGGSDTLVTQSPALAVSPGERVTISC RASESVRTGVHWYQQKPGQQKLLIYGASNLESGVPARFSGSGGSDFTLTIDPVEADDTATYFCQQSW NDPFTFCSGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVCLLNNFYPREAKVQWKVDNALQSGNSQE SVTEQDSKDSITYSLSTLTLSKADYEKHKVYACEVTHQGLSPVTKSFNRGEC
369	1H3-hIgG1-df-hCD25-L20-hIL-2 HC Linker in dashed underline hIL-2 in italics	EVQLVESGGGLVQPGRSILKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDATYYCARHSGSYFDYWGQGMVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPPELLGGPSVFLFPPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDLWLNKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDK SRWQOGNVFSCVMHEALHNHYTQKSLSLSPGKELCDDDPPEIPHATFKAMAYKEGTMINCECKRGFR IKSGSLYMLCTGNSSSHSWDNQCQCTSSATRNTTKQVTPQPEEQKERKTTTEMQSPQVVDQASLPGHCR EPPWENEATERIYHFVVGQMVVYQCVCQGYRALHRGPAESVCKMTHGKTRWTQPOLICTSGGGSGGGG SGGGSGGGGSAPTSSSTKKTLQLEHLLLDLQMIILNGINNYKNPKLTRMLTFKFYMPKKATELKHLCCL EEELKPLEEVINLAQSKNFHLRPRDLISNINVI VLELKGSETTFMCEYADETATIVFELNRWITFCQSI ISTLT
370	1H3-hIgG1-L6-hCD25-L20-hIL-2 HC Linkers in dashed underline hIL-2 in italics	EVQLVESGGGLVQPGRSILKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDATYYCARHSGSYFDYWGQGMVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPPELLGGPSVFLFPPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDLWLNKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDK SRWQOGNVFSCVMHEALHNHYTQKSLSLSPGKSGGGSELCDDDPPEIPHATFKAMAYKEGTMINCEC KRGFRRIKSGSLYMLCTGNSSSHSWDNQCQCTSSATRNTTKQVTPQPEEQKERKTTTEMQSPQVVDQAS LPGHCREPPPWENEATERIYHFVVGQMVVYQCVCQGYRALHRGPAESVCKMTHGKTRWTQPOLICTSGGG GGGGSGGGSGGGGSAPTSSSTKKTLQLEHLLLDLQMIILNGINNYKNPKLTRMLTFKFYMPKKATEL KHLCLEELKPLEEVINLAQSKNFHLRPRDLISNINVI VLELKGSETTFMCEYADETATIVFELNRWI TFCQSIISTLT

371	1H3-hKappa-df- hCD25-L20-hIL- 2 LC Linker in dashed underline hIL-2 in italics	DTVLTQSPALAVSPGERVTISCRASESVRTGVVHWYQQKPGQPKLLIYGASNLESGVPARFSGSGSGTD FTLTIDPVEADDTATYFCQQSWNDPFTFGSGTKLEIKRTVAAPSFIIPPSPDEQLKSGTASVVCLLNNF YPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKS FNRGECELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRIKSGSLYMLCTGNSSHSWDNQCCQCTS SATRNTTKQVTPQPEEKERTTEMQSPMQPVDQASLPGHCREPPWENEATERIYHFVVGQMYIQCVCV QYRALHRGPAESVCKMTHGKTRWTQPQLICTSGGGSGGGSGGGSGGSAPTSSSTKKTKQLQLEHL LLDLQMLINGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEELKPLEEVNLQAQSKNFHLRPRDLI SNINVIIVLELKGSETTFMCEYADETATIVFELNRWITFCQSIISTLT
372	1H3-hKappa-L6- hCD25-L20-hIL- 2 LC Linkers in dashed underline hIL-2 in italics	DTVLTQSPALAVSPGERVTISCRASESVRTGVVHWYQQKPGQPKLLIYGASNLESGVPARFSGSGSGTD FTLTIDPVEADDTATYFCQQSWNDPFTFGSGTKLEIKRTVAAPSFIIPPSPDEQLKSGTASVVCLLNNF YPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKS FNRGECGGGSELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRIKSGSLYMLCTGNSSHSWDN QQCTSSATRNTTKQVTPQPEEKERTTEMQSPMQPVDQASLPGHCREPPWENEATERIYHFVVGQM VYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTSGGGSGGGSGGGSGGSAPTSSSTKKTKQ LQLEHLLLDLQMLINGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEELKPLEEVNLQAQSKNFHL RPRDLISININVIIVLELKGSETTFMCEYADETATIVFELNRWITFCQSIISTLT
373	H7-02-hIgG4 HC	EVQLLESGGGLVQPGGSLRLSCAASGFTTFKSYAMTWVRQAPGKGLEWVSAIVYSGGSTYVYADSVKGRFT ISRDNKNTLYLQMNLSRAEDTAVYCAKYTRASYFYDAMDVWGQGTFTVTVSSASTKGPSVFPLAPCSR STSESTAALGLVKDYFPEPTVTVSNWNSGALTSGVHTFPAVLQSSGLYSLSSVTPFSSSLGPKTYTCNV DHKPSNTKVDKRLVESKYGPCCPPCPAPEFLGGPSVFLFPPKPKDTILMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQP REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSGSFYLSRLTV DKSRWQEGNVFSCSVMHIALHNHYTQKSLSLSLG
374	1H3-hkappa LC	DTVLTQSPALAVSPGERVTISCRASESVRTGVVHWYQQKPGQPKLLIYGASNLESGVPARFSGSGSGTD FTLTIDPVEADDTATYFCQQSWNDPFTFGSGTKLEIKRTVAAPSFIIPPSPDEQLKSGTASVVCLLNNF YPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKS FNRGEC
375	2D12-mIgG1- D265A-L6-hIL-2 HC	EVQLQQSGGPELVKPGASVKISCKTSGYTFTEYTMHWKQSHGKSLEWIGINPNNGGTTVYNQKPKGKAT LTVDKSSSTAYMELRSLTSQDSAVYCARDYIRYGHYAMDYWGQGTSTVTVSSAKTTTPPSVPLAPGSA AQTNMVTILGLVKGYFPEPTVTVTNWNSGSLSSGVHTFPAVLQSDLYTLSSSVTPSSSTWPSSETVTCNVA HPASSTKVDKKIVPRDCGCKPCICTVPEVSSVFIFFPKPKDVLITLTLPKVTQCVVVAISKDDPEVQFSW FVDDVEVHTAQTQPREEQFNSTFRSSELPIMHQDWLNGKEYKCKRVNSAAFPAPIEKTIISKTKGRPKAP QVYTIPPPKEQMAKDVKSLTCLMTITDFPEDITVEQWQNGQPAENYKNTQPIMDTDGSYFVYSKLVNQKS

		NWEAGNTFTCSVLHEGLHNHTEKSLSHSPGKSGGGSAPTSSSTKKTLQLEHLLDLQMIILNGINNY KNPKLTRMLTFKFYMPKKATELKHLCLEEEELKPLEEVNLNLAQSKNFHLRPRDLISNINVINVLELKGSE TTFMCEYADETATIVFELNRWITFCQSIISTLT
376	2D12-mkappa 1C	QIVLTQSPAIMSASPEGEKVTTCVSSSVRFMHWYQQKSGTSPKRWIYDTSKLASGVPARFSGSGSGTS YSLTISSEAEADAATYYCQOWSSNPPTFGGKTKLKRADAAPTYSIFPSEQLTSGGASVVCFLNNE YPKDINVKWKIDGSEKQNGVLNSWTQDQSKDSTYSMSSTLTLTKEDEYERHNSYTCETHKTSTSPIVKS FNRNEC
377	hIL-2 Q126L	APTSSTKKTLQLEHLLDLQMIILNGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVINVLELKGSETTFCMCEYADETATIVFELNRWITFCLSIISTLT
378	hIL-2 Q126E	APTSSTKKTLQLEHLLDLQMIILNGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVINVLELKGSETTFCMCEYADETATIVFELNRWITFCESIISTLT
379	1H3-hIgG1 HC	EVQLVESGGGLVQPGSRSLKLSCAVSGFTFSDYAMAVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDLSRSEDATYYCARHSGSYFDYWGQGVMTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPS NTKVDKKEPKSCDKTHTCPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDK SRWQQGNVFSCVSMHEALHNHYTQKSLSLSPGK
380	huPD-1-Fc	MQIPQAPWPVVWAVLQLGWRPGWFLESDRPNWNPPTFSPALLVTEGDNATFTCSFSNTSESFVLNWYR MSPSNQTDKLAAFPEDRSQPGQDCRFRTVQLPNGRDFHMSVVRARNDSGTLYLCAISLAPKAQIKESL RAELRVTERRAEVPATAHPSPPRPAQGFQIEGRMDPKCDKTHTCPPCPAPPELLGGPSVFLFPPKPKDT LMTSRTEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCVSMHEALHNHYTQKSLSLSPGK
381	cynomolgous- PD-1-Fc	MQIPQAPWPVVWAVLQLGWRPGWFLESDRPNWNPPTFSPALLVTEGDNATFTCSFSNTSESFVLNWYR MSPSNQTDKLAAFPEDRSQPGQDCRFRTVQLPNGRDFHMSVVRARNDSGTLYLCAISLAPKAQIKESL RAELRVTERRAEVPATAHPSPPRPAQGFQIEGRMDPKCDKTHTCPPCPAPPELLGGPSVFLFPPKPKDT LMTSRTEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCVSMHEALHNHYTQKSLSLSPGK
382	2H7 VH	GAGGTGCAGCTGTGGAAGCGGGCGGACTGTGTGAGCTGGAGGCAGCTGGCGTGTCTTGTGTC GCTTCTGGCTTCACTTCAAGACTACTGTCATGACCTGGTTCAGACAGGCCCTGGCAGGGCCTCGAG TGGGTGTCGCCCATCGTGTACAGCGGGGGTCAACATACAGCCGACAGCTGAAGGCAGATTACACA ATCAGCAGAGATAACAGCAAGAACACCCCTGTACCTGCAGATGAACAACCTGAGAGCTGAAGATACCGCC GTGTACTACTGCGCCAAGTACACAGAGCCAGCTACTTCTACGACGCCATGGACGTGTGGGGCCAGGGC ACCACGCTGACAGTGTCTCTCAT

383	2H7 VL	GAGATCGTGCTGACCCAGTCTCCTGGCACCCCTGAGCCTGAGCCCTGGCGAGAGAGCTACACTGTCTATGC AGAGCCTCTCAGAGCATCGGAAGAGCTTCTGGCCCTGGTACAGCAAAAGCCTGACAGAGGCCCTAGAG CTGCTGATCTACAGCGCCAGCAGACCGCTGATATCCCGCCAGATTTCAGCGGATCTGGCAGCGGC ACTGATTTCACCCCTACCATCAGCAGCCTGGAACCCGAGGACTTCGCCGTGTACTGCGCAGCAGTAC TACGACTGGCCCCCTGCTTTTGGCGGAGGCACAAAGGTGAAATCAAG
384	2H7 VH	EVQLLESGGGLVQPGSLRLCSAAAGFTFKDYCMTWVRAPGKGLEWVSAIVYSGSTYYADSVKGRFT ISRDNKNTLYLQMNINLRAEDTAVYCAKYTRASFYDAMDVWGQGT'TVTSS
385	2H7 VL	EIVLTQSPGTLSLSPGERATLSCRASQSIGKSFLAWYQQKPGQAPRLLIYDASTRAADIPARFSGSGSG TDFTLTISSLEPEDEFAVYYCQQYDWPPLSFGGGTVKEIK
386	2H7 HCDR1	GFTFKDYCMT
387	2H7 HCDR2	AIVYSGSTYYADSVKG
388	2H7 HCDR3	YTRASFYDAMDV
389	2H7 LCDR1	RASQSIGKSFLA
390	2H7 LCDR2	DASTRAA
391	2H7 LCDR3	QQYDWPPLS
392	C51E6-5 VH	CAGGTTCAAGCTGGTTCACTCTGGCAGCGAGCTGAAGAAACCTGGCGCCTCTGTGAAGGTGTCTTCAAG GCCTCTGGCTACAGCCTGTACGGCACCTCTATGCACCTGGGTCCGACAGGCTCCAGGACAGGACTTGAG TGGATGGGCTACATCAGCCCCCTTACCGGCAGAGCCATAGCCCCAGGGCTTCAGAGCAGATTCTGTG TTCAGCCTGGACACCAGCGTGTCCACAGCCTACCTGCAGATCAGTCTCTGAAGGCCGAGGACACCGCC GTGTACTACTGCGCCAGAGACTACGACTACCGGTACTACTATGCCATGGACTACTGGGGCCAGGGCACCC ACAGTTACAGTGTCTCTCA
393	C51E6-5 VL	GAAATTGTGCTGACACAGAGCCCCGACTTCCAGAGCGTGACCCCTAAAGAAAAAGTGACCATCACCTGT ACCGCCAGCGAGTCCGTGCCCTCTCAGTTCCTGCAATGGTATCAGCAGAAGCCCGCATCAGAGCCCCAAG CTGCTGATCTACGCCAGCAGAGAAAGAGCCAGCGGCTCCCAAGCAGATTTTCTGGCTCTGGCAGCGGC ACCGACTTCACCTGACAATCAATAGCCTGGAAGCCGAGGACGCCACCTACTACTGCCACCATTTT CACAGAAGCCCTCTGACCTTTGGCGGAGGCACCAAGCTGGAATCAAG
394	C51E6-5 VH	QVQLVQSGSELKPGASVKVSKASGYSLYGTSMHWVRQAPGQGLEWMGYISPFTGRATYAQGFTGRFV FSLDTSVSTAYLQISSLKAEDTAVYICARDYDYRYYYAMDYWGQGT'TVTSS
395	C51E6-5 VL	EIVLTQSPDFQSVTPKEKVTITCTASESVPPQFLHWYQQKPDQSPKLLIYASRERASGVPSRFSGSGSG TDFTLTINSLEAEDAATYYCHQPHRSPLTFGGGTVKEIK
396	C51E6-5 HCDR1	GYSLYGTSMH
397	C51E6-5 HCDR2	YISPFTGRATYAQGTG
398	C51E6-5 HCDR3	DYDYRYYYAMDY
399	C51E6-5 LCDR1	TASESVPPQFLH

400	C51E6-5 LCDR2	ASRERAS	
401	C51E6-5 LCDR3	HQFHRSPLT	
402	A2 VH	GACGTGACGCTGGTGGAAAGCGGCGGAGGCGCTGGTCCAGCCCGGGGCTCTCTGAGACTGAGCTGCGCCGCCAGCGGCTTCACTTCGACATCAGGCCCATGAGCTGGGTGGCGAGGCGCTTGGCAAGGCGCTGGAA TGGGTGAGCACAATCAGCGGATCTGCCCTACAGCACCTACTACGCCGACAGCGTGAAGGGCAGATTCACTATCTCAAGAGATAACAGCAAGAGCACCTGTACCTGCAGATGAACAGCCTGCGGGCCGAGGACACCGCC GTGTACTACTGCGCCAGAGAGATCTTACGCGACTACTTGGGCTTGGGCACCTGGTGACAGTGTCTCTCA 403A2 VL CAAAGCGTGTGACACAGCCCCCAGCGCTTCTGGCACCCCTGGCCAGAGAGTACCATCTCATGCAGC GGGTCAACAAGCAACATCGGCAGAGAGAGCGTGTACTGTGTACCAGCAGCTGCCGTGGAACCGCCCTAAG CTGTGATCTACAGCAACGTGCAGCGGCGCTAGCGGCGCCCTAACAGATTACGCGGCAGCAAGAGCGGC ACGAGCGCCAGCCTGGCCATCAGCGGCCCTGCAGAGCGAGACGAGGCCGACTACTACTGCGGCACATGG GACGACAGCCTGAACGGCTGGTGTTCGGCGGGGAACTAAGCTGACCGTCTCTA 404A2 VH DVQLVESGGGLVQPGGSLRLSCAASGFTFDISAMSVWRQAPGKLEWVSTISGSAYSTYYADSVKGRFT ISRDNKSTLYLQMNSLRAEDTAVYYCAREIFSDYWGLTLTVSS 405A2 VL (OMC479p1.A2VL) QSVLTQPPSASGTPGQRVTISCSGSTSNIGRESVYWYQQLPGTAPKLLIYSNVQRPSGAPNRFSGSKSG TSASLAISGLQSEADYYCGTWDDSLNGWVFGGGTKLTVL 406A2 HCDR1 GFTFDISAMS 407A2 HCDR2 TISGSAYSTYYADSVKG 408A2 HCDR3 EIFSDY 409A2 LCDR1 SGSTSNIGRESVY 410A2 LCDR2 SNVQRPS 411A2 LCDR3 GTWDDSLNGWV 412H7-767 HC GAGGTGACGCTGGTGGAAAGCGGCGGCGGCGCTCGTGCAGCCTGGCGGATCTCTGCGGCTGAGCTGTGCTGCCAGCGGCTTCACTTTAAATCCTACGCCATGCACCTGGGTAGACAAGCCCCCGGAAAGGCGCTGGAA TGGGTGCCCGCATCGTCTACAGCGGCGGATCTACATACTACGCCGACAGCGTGAAGGCGCGGTTCACTATCAGCAGAGATAATAGCAAGAACACCCCTGTACCTGCAGATGAACAGCCTGAGAGCCGAGGACACCGCC GTGTACTACTGCGCCAAAGTACGACAGAGCTTCTTATTTCTACGATGCCATGGACGTGTGGGGCCAGGGC ACCACTGTACAGTGTCTCAGTAGCACCAAGGCGCTAGCGTGTTCCTGCTGGCGCCCTAGCTCTATAA AGCAAGCGGGGAACCGCGCTCTGGGTGTCTGGTGAAGGACTACTTCCCTGAGCCTGTGACCGTCA AGCTGGAACAGCGGCGCCCTGACCAGCGGCGTTACACATTCGCCGTGTGCTGCAGAGCTCTGGGCTG TACAGCCTGAGCAGCGTGTGACCGTGCCTTCTTCTCTCTGGGCACACAAACATACATCTGCAACGTG AACCAAGCCCAAGTAATACCAAAGTGGATAAGAAGGTGGAACCTAAGTCTTGGCAGAACACACACC TGTCCTCCGTGCCCTGCTCCTGAACCTGgtGGAgctCCAGCGTGTTCCTGTTCCTCCCCCCCCAAACCTAAA	

413	H7-767 LC	GACACCTGATGATCAGCCGGACCCCTGAGGTGACCTGGCTGGTTCGTGCAGCTGTCCCACGAAGATCCT GAGTGAAGTTCAACTGGTACGTGGACGGCGTGGAAGTGCATAATGCCAAGACAAAGCCTAGAGAGAA CAGTAAACAGACACCTATAGAGTGGTGTCCGTGTGACAGTGTGCACACGAGACTGGCTGAACGGCAAG GAATCAAAGTGCAAGGTGTCCAAAGGCCCTCCCGGCCCTATCGAGAAGACCATCAGCAAGGCAAG GGCAACCTAGAGAGCCCCAGGTGTACACCTGCCCTCCAAGCAGAGATGAGCTGACCAAGAACAGGTT AGCCTGACTTGTCTGGTGAAGGCTTCTACCCCTCCGATATCGCCGTGGAATGGAGAGACAACGGCCAG CCTGAGAACAACTACAAGACCACACCTCCAGTGTGGACAGCAGCGCAGCTTCTTCCTGTATAGCAAG CTGACAGTGGACAAGACAGATGGCAGCAGGGCAACGTGTTCACTGCAGCTCATGCACGAGGCCCTG CACACCACCTACACCCAGAAGTCTCTGAGCCTGAGCCCTGGAAGGCCCTGCTTCTAGCAGCACCAAG AAGACCCAGCTGCAGCTGGAACACCTGCTGCTGGCCCTGCAGATGATCCTGAACGGCATCAACAACCTAC AAGAACCCCAAGCTGACCGAGATGCTGACATTTAAGTTCTACATGCCTAAGAAAGCCACCGAGCTGAAG CACCTGCAATGCTTGGAAGAGAGCTGAAACCTCTGGAAGAGGTGCTGAATCTGGCTCAGTCAAAGAAC TTCCACCTTAGACCTAGAGATCTGATCAGCAACATCAACGTGATCCTGCTGGAACCTGAAGGGCAGCGAG ACGACCTTCATGTGCGAGTACGCCGACGAGACAGCCACAATCGTGAGTTCTCTGAACAGATGGATCACC TTCGCCCCAGAGCATCATCTCCACCCCTGACC
414	H7-632 HC CDRs solid underlined Constant region dashed underlined	GAGATCGTGTGATACCCAGTCCCAAGGCACACTGAGCCTGAGCCCGCGGAGCGGGCCACCCCTGAGCTGT AGAGCTAGCCAGAGCATCTCCAGCAGCTTCTTGCCCTGTACACAGCAGAAACCTGGCCAGGCCCTAGA CTGCTGATCTACGACGCCCTCTGATAGAGCTACAGGCATCCCCGACCGGTTTCAGCGGACGGGATCTGGC ACCGACTTACCCCTGACCATCAGCAGACTCGAGCCTGAAGATTTGCCGTGTACTACTGCCAGCAATAC TATGACTGGCCCTCCTCTGTCTTTTGGCGGGGAAACAAAGGTGGAATTAAGCGTACGGTGGCGGCC AGCGTGTTCATCTTCCACCCAGCGACGAGCAGCTGAAGTCCGGCACAGCCAGCGTGGTGTGCCTGCTG AACAACTTCAACCCCGGAGGCCAAGGTGCAGTGGAGGTGGACAAACCCCTGCAGAGCGGCAACAGC CAGGAAGCGTGACCGAGCAGGACAGCAAGGACTCCACCTACAGCCTGAGCAGACCCCTGACCCCTGAGC AAGCCGACTACGAGAAAGCACAGGTGTACGCCCTGCCGAAGTGACCCACCGAGGCCCTGTCCAGCCCCGTG ACCAAGAGCTTCAACCGGGCGGAGTGC EVQLLESGGGLVQPGGSLRLSCAASGFTFKSYAMHWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNKNTLYLQMSLRAEDTAVYCAKYDRASYFYDAMDVMVGQTTVTVSSASTKGPSVFPIAPSSK STSGTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVFPPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKHTCPCPAPELAGAPSVFLFPPKPKDTLMI SRTPEVTCVWVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQINSTYRVVSVLTVLIHQDWLNGKEYCKVSNKALPAPIEKTIKAK GQPREPQVYTLPPSRDELITKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPEVLDSDGSFFLYSK LTVDKSRWQOGNVFSCSYMHEALHNHYTQKSLSPG

415	H7-632 LC CDRs solid underlined Constant region dashed underlined	EIVLTQSPGTLSLSPGERATLSCRASQSISSSFLAWYQQKPGQAPRLLIYDASDRATGIPDRFSGSGG TDFTLTISRLEPEDFAVYQCQYDWPPLSFGGGTVKRTVAAPSVFIFPPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSITYLSSTLTLSKADYEEKHKVIACEVTHQGLSSPV TKSFNRGEC
416	H7-632 VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFKSYAMHWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNKNTLYLQMNLSRAEDTAVYCAKYDRASYFYDAMDVWGQGTITVTVSS
417	H7-632 VL	EIVLTQSPGTLSLSPGERATLSCRASQSISSSFLAWYQQKPGQAPRLLIYDASDRATGIPDRFSGSGG TDFTLTISRLEPEDFAVYQCQYDWPPLSFGGGTVKVEIK
418	H7-632 HCDR1	GTTFKSYAMH
419	H7-632 HCDR2	AIVYSGGSTYYADSVKG
420	H7-632 HCDR3	YDRASYFYDAMDV
421	H7-632 LCDR1	RASQSISSSFLA
422	H7-632 LCDR2	DASDRAT
423	H7-632 LCDR3	QQYYDWPPLS
424	2H7-hIgG4 HC	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNKNTLYLQMNLSRAEDTAVYCAKYTRASYFYDAMDVWGQGTITVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVFSSSLGTTKTYTCNV DHKPSNTKVDKRVESKYGPPCPAPAEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVDSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLTQHWLNQKEYKCKVSNKGLPSSIEKTIISKAKGQP REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPPVLDSDSGSFFLYSRLTV DKSRWQEGNVFSCSVMHENHYTQKSLSLG
425	2H7-hkappa LC	EIVLTQSPGTLSLSPGERATLSCRASQSIKGSFLAWYQQKPGQAPRLLIYDASTRAADIPARFSGSGG TDFTLTISRLEPEDFAVYQCQYDWPPLSFGGGTVKRTVAAPSVFIFPPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSITYLSSTLTLSKADYEEKHKVIACEVTHQGLSSPV TKSFNRGEC
426	C51E6-5-hIgG4 HC	QVQLVQSGSELKPGASVKVCKASGYSLYGTSMHWVRQAPGQGLEWMGYISPFTCRATYYAQGFTGRFV FSLDTSVSTAYLQISLLKAEDTAVYICARDYDYYRYVAMDYWGQGTITVTVSSASTKGPSVFPLAPCSRS TSESTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVFSSSLGTTKTYTCNV HKPSNTKVDKRVESKYGPPCPAPAEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVDSQEDPEVQF

427	C51E6-5-hKappa LC	NWYVDGVEVHNAKTKPREEQFNSTYRVVSULTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPR EPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSGFFLYSRLTVD KSRWQEGNVFSCSVMEALHNHYTQKSLSLGLG EIVLTQSPDVFQSVTPKEKVTITCTASESVPPQFLHWYQQKPDQSPKLLIYASRERASGVPFSRFSGSGSG TDFTLTINSLEAEADAATYYCHQFHRSPITFGGKTLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLIN NFYPPRAKVKWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEEKHKVYACEVTHQGLSSPVT KSENRGEC
428	A2-hIgG4 HC	DVQLVESGGGLVQPGGSLRLSCAASGFTFDISAMSWVRQAPGKGLEWVSTISGSAYSTYYADSVKGRFT ISRDNSSKSTLYLQMNSLRAEDTAVYYCAREIFSDYWGGLTIVTVSSASTKGPSVFFLAPCSRSTSESTA ALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTPSSSLGTKTYTCNVVDHKPSNT KVDKRVESKYGPPCPAPPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSULTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQVYIT LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSGFFLYSRLTVDKSRWQE GNVFCFSVMHEALHNHYTQKSLSLGLG
429	A2-hLambda LC	QSVLTQPPSASGTPGQRVTISCSGSTNIGRESVYWYQQLPGTAPKLLIYSNVQRPSPGAPNRFSGSKSG TSASLAIISGLQSEDEADYYCGTWDDSLNGWFGGKTCLTVLQGPKAAPSVTLFPPSSEELQANKATLV LISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNKNKYAASSYLSTPEQWKSHRSYSCQVTHEGSTVE KTVAPTECS
430	2H7-hIgG4-df- hIL-2 (D20A/R38E) HC hIL-2 in italics	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNSSKNTLYLQMNNLRAEDTAVYYCAKYTRASIFYDAMDVWGQGTITVTVSSASTKGPSVFFLAPCSR STSESTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPAPPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSULTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQ REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSGFFLYSRLTV DKSRWQEGNVFSCSVMEALHNHYTQKSLSLGLKAPTSSTTKTKTLQLEHLLALQMLINGINNYKNP KLTEMLTKFYMPPKKATELKHLCLEELKPLEEVNLNLAQSKNFHLRPRDLISNINIVLELKGSETTF MCEYADETATIVTEFLNRWITFCQSIISTLT
431	H7-632-hIgG1- LAGA-df-hIL-2 (T3A/C125A) HC	EVQLLESGGGLVQPGGSLRLSCAASGFTFKSYAMHWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNSSKNTLYLQMNSLRAEDTAVYYCAKYDRASYFYDAMDVWGQGTITVTVSSASTKGPSVFFLAPSSK STSGGTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKHTCCPPAPPELAGAPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQFNSTYRVVSULTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSGFFLYSK LTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSLSPGKAPASSSTKTKTLQLEHLLALQMLINGINNY KNPKLTRLMTTKFYMPKKATELKHLCLEELKPLEEVNLNLAQSKNFHLRPRDLISNINIVLELKGSE TTFMCEYADETATIVTEFLNRWITFAQSIISTLT

432	C51E6-5-hIgG4-L6-hIL-2 (D20A/R38E) HC Linker in dashed underline hIL-2 in italics	QVQLVQSGSELKPGASVKVSKASGYSLYGTSMHWVRQAPGQGLEWMGYISPFTGRATYAQGFTGRFV FSLDTISVSTAYLQISSLKAEDTAVYICARDYDRIYYAMDYWGQGT'TVTVSSASTKGPSVFPLAPCSR TSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVFSSSLGT'KTYTCNV HKPSNTKVDKRVESKYGPPCPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLT'LVLHQLDNLNGKEYCKKVSNGKGLPSSIEKTIISKAKGQPR EPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDSDGSFFLYSRLTV KSRWQEGNVFSCSVMEALHNHYTQKSLSLGLSGGGGSAPTSSSTKKTKQLQLEHLLALLALQMLINGIN NYKNPKLTEMITFKFYMPKKATELKHLCLEELKPLEEVNLAQSKNFHLRPRDLISININVIVLELKG SETTFMCEYADETATIVFELNRWITFCQSIISTLT
433	A2-hIgG4-df-hIL-2 (D20A/R38E) HC hIL-2 in italics	DVQLVESGGGLVQPGGSLRLSAAAGFTTFDISAMSVVRQAPGKGLEWVSTISGSAYSTYYADSVKGRFT ISRDNKSTLYLQMNLSLRAEDTAVYICAREIFSDYWGGLGLVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVFSSSLGT'KTYTCNV KVDKRVESKYGPPCPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLT'LVLHQLDNLNGKEYCKKVSNGKGLPSSIEKTIISKAKGQPREPQVY LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDSDGSFFLYSRLTVDKSRWQ E GNVFCSCVMHEALHNHYTQKSLSLGLGKAPTSSSTKKTKQLQLEHLLALLALQMLINGINNYKNPKLTEMIT FKFYMPKKATELKHLCLEELKPLEEVNLAQSKNFHLRPRDLISININVIVLELKGSETTFMCEYADE TATIVFELNRWITFCQSIISTLT
434	1H3-hIgG4-df-hIL-2 (D20A/R38E) HC hIL-2 in italics	EVQLVESGGGLVQPGRSLKLSCAVSGFTTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDATYICARHGSGYFDYWGQGMVTVSSASTKGPSVFPLAPCSRSTSES TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVFSSSLGT'KTYTCNV NTHKPSNTKVDKRVESKYGPPCPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWY VDGVEVHNAKTKPREEQFNSTYRVVSVLT'LVLHQLDNLNGKEYCKKVSNGKGLPSSIEKTIISKAKGQPREPQV YTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMEALHNHYTQKSLSLGLGKAPTSSSTKKTKQLQLEHLLALLALQMLINGINNYKNPKLTEM ITFKFYMPKKATELKHLCLEELKPLEEVNLAQSKNFHLRPRDLISININVIVLELKGSETTFMCEYADE TATIVFELNRWITFCQSIISTLT
435	2H7-hIgG4-df-hIL-2 (T3A/D20A/R38E/C125A) HC hIL-2 in italics	EVQLLESGGGLVQPGGSLRLSAAAGFTTFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDNKNTLYLQMNLSLRAEDTAVYICAKYTRASYFDAMDVWGQGT'TVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVFSSSLGT'KTYTCNV DHKPSNTKVDKRVESKYGPPCPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLT'LVLHQLDNLNGKEYCKKVSNGKGLPSSIEKTIISKAKGQ PREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDSDGSFFLYSRLTV DKSRWQEGNVFSCSVMEALHNHYTQKSLSLGLGKAPTSSSTKKTKQLQLEHLLALLALQMLINGINNYKNP KLTEMITFKFYMPKKATELKHLCLEELKPLEEVNLAQSKNFHLRPRDLISININVIVLELKGSETTF MCEYADETATIVFELNRWITFAQSIISTLT

436	hPD-1 extracellular domain	CCAGGATGGTTCTTAGACTCCCGACAGACAGGCCCTGGAAACCCCCCCCACCTTCTCCCGAGCCCTGCTCGTG GTGACCGAAGGGACAAACGCCACCTTACCTGCAGCTTCTCAACACATCGGAGAGCTTCTGCTGCTAAAC TGGTACCGCATGAGCCCCAGCAACAGACGACGAAGCTGGCCGCTTCCCCGAGGACCGCAGCCAGCCC GGCCAGGACTGCCGCTTCCGTTCACACAACCTGCCCAACGGCGGTGACTTCCACATGAGCGTGGTCAAG GCCCGCGCAATGACAGCGGCACCTACCTCTGTGGGCATCTCCTGCCCCCAAGCGCAGATCAAA GAGAGCTGCGGGCAGAGCTCAGGGTGACAGAGAGAAGGCGAGAAAGTGCCACAGCCCCACCCAGCCCC TCACCCAGGCCAGCCGCCAGTCCAA
437	hPD-1 extracellular domain HC	PGWELDSPDRPNPPTFSPALLVTEGDNATFTCSFSNTSEFVLNWMSPSNQTDKLAAPEDRSQP GQDCRFVTQLPNGRDFHMSVVRARRNDSGYLCGAI SLAPKAQIKE SLRAELRV TERRAEVPTAHPSP SPRPAGQFQ
438	OMC.1.B6-hIgG4 HC	EVQLLESGGGLVQPGSLRLSCAASGFTFSSNYMSWVRQAPGKGLEWVSAISSSGGTIFYADSVKGRFT ISRDN SKNTLYIQMNSLRAEDTAVYYCAKHKNNAVYDGM DVWGQGT TTVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVFPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGP REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPPVLDSGDSFFLYSRLTV DKSRWQEGNVFSCSVMH EALHNHYTQKSLSLGLG
439	OMC.1.B6- hLambda IC	QSVLTQPPSASGTPGQRVTISCSGTSNIGRNLVN WYQQLPGTAPKLLIYTI DQRP SGVPDRFSGSKSG TSASLVISGLQSEDEADYYCAAWDGS LNAWFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVC LISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSQCQVTHEGSTVE KTVAPT ECS
440	OMC.2.C6-hIgG4 HC	EVQLLESGGGLVQPGSLRLSCTASGFTFSYEMQWVRQAPGKGLEWVLTITSSSHIFYADSVKGRFT VSRDN SKNTLYIQMNSLRAEDTAVYYCTKDLNSYYGLDVWGQGT TTVTVSSASTKGPSVFPLAPCSRST ESTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVFPSSSLGTKTYTCNV DHK PSNTKVDKRVESKYGPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNW YVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGPREP QVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPPVLDSGDSFFLYSRLTVDKS RWQEGNVFSCSVMH EALHNHYTQKSLSLGLG
441	OMC.2.C6- hLambda IC	QSVMTQPPSASGTPGQRVTISCSGTSNIGNNYVSWYQHLP GTAPKLLIYGN DQRP SGVPDRFSGSKSG TSASLVISGLQSDDEADYYCSWDASLNWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVC LISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSQCQVTHEGSTVE KTVAPT ECS
442	OMC.1.D6-hIgG4 HC	EVQLLESGGGLVQPGSLRLSCAASGFTFSDYYMSWVRQAPGKGLEWVSAISSSGGTIFYADSVKGRFI ISRDN SKNTLYIQMNSLRAEDTAVYYCAKHKNNDVYDAMDVWGQGT TTVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVFPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGP

		REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFFLYSRLLTV DKSRWQEGNVFSCVMHEALHNHYTQKSLSLGLG
443	OMC.1.D6- hLambda IC	QSVLTQPPSASGTPGQRVITISCSGNSNIGRNLVNWYQQLPGTAPKLLIYTVDRPSPGVPDRFSGSKSG TSASLAIISGLASEDEADYYCAAWDSLSNWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLV LISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNKNKYAASSYLSTPEQWKSHRSYSQCQVTHEGSTVE KTVAFTCS
444	D12-hIgG4 HC	DVQLVESGGGLVQPGGSLRLSCAASGFTFDISAMSWVRQAPGKGLIEWVSTISGSAYSTIYADSVKGRFT ISRDNKSTLYLQMNLSRAEDTAVYICAREIFSDYWGGLGLTVTVSSASTKGPSVFLAPCSRSTSESTA ALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYTCNVVDHKPSNT KVDKRVESKYGPPCPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVHLQDHLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQVYIT LPDSQEMTNKQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFFLYSRLLTVDKSRWQE GNVFSCVMHEALHNHYTQKSLSLGLG
445	D12-hLambda IC	QSVLTQPPSASGTPGQRVITISCSGNTSNIGRESVYVYQQLPGTAPKLLIYSNVQRPSPGVPDRFSGSKSG TSASLAIISGLQSEDEADYYCGTWDSDSLNGWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLV LISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNKNKYAASSYLSTPEQWKSHRSYSQCQVTHEGSTVE KTVAFTCS
446	G12-hIgG4 HC	DSLVEGGGLVQPGGSLRLSCAASGFTFDISAMSWVRQAPGKGLIEWVSTISGSAYSTIYADSVKGRFTI SRDNKSTLYLQMNLSRAEDTAVYICAREIFSDYWGGLGLTVTVSSASTKGPSVFLAPCSRSTSESTA LGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYTCNVVDHKPSNTK VDKRVESKYGPPCPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDG EVHNAKTKPREEQFNSTYRVVSVLTVHLQDHLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQVYITL PPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFFLYSRLLTVDKSRWQEG NVFSCVMHEALHNHYTQKSLSLGLG
447	G12-hLambda IC	QSVLTQPPSASGTPGQRVITISCSGNTSNIGRESVYVYQQLPGTAPKLLIYLNQRPSPGVPDRFSGSKSG TSASLAIISGLQSEDEADYYCGTWDSDSLNGWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLV LISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNKNKYAASSYLSTPEQWKSHRSYSQCQVTHEGSTVE KTVAFTCS
448	pCMV6-hygro- HA-cyno-PD-1 (1-185)	aacaaaaataataacgcttaaatccattcgccattcaggctgcgcaactgttgaggaaaggcgatcgg tgcgggcctcttcgtattacccagctggcgaaagggatgtgctgcaaggcgattaaagtgggtaa cgccaggggtttccagtcacgactgtgtaaaacgacgcccagtgccaaagtgcatacatattgaatc aatattggcaattagccataattagtcattggttatataagcataaaatcaattggttatattggccattgc atacgttgatctatatcataatattgacatttataattggtcattgtccaaatagaccgcatgttgac attgattattgactagttattaaatagtaaatcaattacgggggtcattagttcatagcccatatattgaggt tccgcgttacataaactacggtataatggcccgctgctgacccgccccacgacccccgcccattgacgt caataatgacgtatgttcccatagtaacgccaatagggaactttccattgacgtcaatgggtggaggtatt tacggtaaactgcccacttgccagtagcatcaagtgtatcatatgccaaagtcgccccctattgacgtca

	atgacggtaaaatggccgcctggcattatgcccagttacatgacaccttacgggactttcctacttggcagt acatctacgtattagtcacgtctattaccatggtgatcggtgttttggcagttacacaaatggcggtgat agcgtttgactcacgggattttccaagtctccaccctattgacgtcaatggagtttgttttggcacc aaaatcaacgggactttccaaaatgtcgtataaagcagagctcgttttagtaacogtcagaatttttaatacgaactacta tacggtgggaggtctataaagcagagctcgttttagtaacogtcagaatttttaatacgaactacta tagggcgccgggaattcgtgactggatccggtaccgagagagatctcgcgcgagatcgcggcgccg cagatctcaagcttatggacatggcggtgccagcacaactctcggattactattgttatggctcgag gtgcgctgttatcttacgacgtgcctgactacccccaggatggttcttagagtccccagacaggc cctggaacgccccaccttctcccagccctgctcctgtgacogaagggacaaagccacacctcacct gcagcttctccaacgcacgagagcttctgtctaaactggtacaggatgagccagcaacacagcgg acaaagtggccgcttcccggagccgcagccagccggccaggactgcgcttccgtgtcacacgcc tgcccaacggggtgacttccacatgagcgtggtcagggccggcgcaatgacagggcacctacctct gtggggccatctcctggccccaaaggcgagatcaagagagcctcgggcagagctcagggtgacag agagaaggcgagaagtgccacagccccacccagccccctcacccagccagccggccagttccaagccc tgggtgtgtgtcgtggcgctgctggcagcctggtgctgtagtctgggtcctggcgtcatct gctccgcgcgcacaaaggacaatagaagccagcgccacgtgacgcgttaagcgccgcactcgaggt ttaaacggccggcggtcatagctgtttcctgaacagatccccgggtggcactccctgtgacccccctcc cagtcctctcctggcctggaagtggcactccagtcacccagccctgtcctaataaaaattaaagt gcatactttgtcgtgactaggtgctctataatataatgggtggaggggtggtatggagcaagg ggcaagtgggaagacaacctgtagggcctgcgggtctattgggaaccaaagtggatgcagtgccac aatcttggtcactgcaatctccgctcctggttcaagcgattctcctgcctcagcctcccgagttgt tgggattccaggcatgcatgaccaggctcagctaaattttgttttttggtagagacggggtttcacca tattggccaggctggtctccaactcctaatctcagtgatctacccacctggcctcccaaatgctgg gattacaggcgtgaaccactgctccttccctgctctgatttttaaaataactataccagcaggag acgtccagacacagcataggctacctggccatgcccaacoggtgggacatttgagttgcttggtgca ctgtcctctcatgctggttggtccactcagtagatgctgttgaaattgggtacgogggccagcttggtgt ggaatgtgtcagtaggtgtggaagtccccaggctccccagcaggcagaagtatgcaaaagcatgc atctcaatttagtcagcaaccaggtgtggaagtccccaggctccccagcaggcagaagtatgcaagca tgcatctcaatttagtcagcaaccatagtcggccctcaactccgccatccgccccactccgcga gttcgccccattctccgccccatggctgactaaatttttttttatctacagagccgagggccgctcgg cctctgagctattccagaagttagtgaggaggttttttggaggccctaggcttttgcaaaaagctccggg gagcttgatatatccattttcgatctgatcaagagacagctacgacccatgaaaaagcctgaactcaccc cgactctgttgagaagttctgatcgaaaagtgcagacgctctccgacctgatgcagctctcggagg gcgaagaatctcgtgcttcagcttcgatgtaggaggggtggatgtcctcggttaaatagctgcg ccgatgggttctacaaagatcgttatgtttatcgcaacttgcacggcgctcccgattccgggaag tgcttgacattggggaaatttagcgagagcctgacctatgcatctcccgcggtgcacaggggtgcaggt tgcaagacctgcctgaaaccgaaactgcccgtgttctgcaaccgggtcgcggaggccatggatgcaatcg

		cgaattacatgataccccatgttgtgcaaaaaagcggttagtcctcctcggtcctcogatcggtgtcaga agtaagttggcgcagtgattatcaactcatggttatggagcactgcataaattcttactgtcatgcca tccgtaaagatgcttttctgtactggtgagtactcaaccaagtcattctgagaatagtgtatgcggcga ccgagttgctcttgcggcggtcaatacgggataataacgcgcgcacatagcagaactttaaaagtgtc atcattggaaaaacgttcttcggggcgaaaaactctcaagatcttaccgctgttgatccagttcogatg taaccactcgtgcacccaactgatcttcagcatcttttacttccaccagcttctgggtgagcaaaa acaggaggcaaaaatccgcaaaaaagggaataaggcgagacacggaaaatgttgatactactactcttc cttttcaaatattattgaagcatttatcaggttattgtctcatgagcgatacatatttgaatgtatt tagaaaaataaacaatagggttcgcgcacatttccccgaaaaagtcacactgacgcgcctgtagc ggcgattaaagcggcggtgtgtgttacgcgcagcgtgacgcgtacacacttccagcgccttagcg ccgctccttctcgttcttctccttctccttcgcacgctgcggcttcccgtaagctcctaataat cggggctccctttaggttcagatttagtgccttacggcacctgcacccccaaaaaacttgattaggt gatgttcacgtagtgggccatcgccctgatagcgttttttcgcccccttgacgttgaggtccacgttc tttaatagtgactcctgttccaaaactggaacaacacacacccatctcgtgtctattcttttgattta taagggttttgcgatttcggcctattggttaaaaaatgagctgatttaacaaaaatttaacgcgaat ttt
449	Abzlmod-hIgG4 HC	QVQLVQSGSELKPGASVKVCKASGYTFTSYAMHWVRQAPGQGLEWMGYISPFTGRATYYAQFTGRFV FSLDTSVSTAYLIQISLLKAEDAVYYCARDYDYYVYAMDYWGQGTITVTVSSASTKGPSVFPLA PCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVFSSSLG TKTYTCNV DHPKSNTRKVDKRVESKYGPPCPAPAEFLGGPSVFLFPPKPKDTLMISRTPEVTCVWVDVSQED PEVQF NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQPR EPQVYITLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPPVLDSDG SFFLYSRLTV D KSRWQEGNVFSCSVMEALHNHYTQKSLSLGL
450	Abzlmod-hkappa LC	EIVLTQSPDFFQSVTPKEKVTITCRASQSI PPQFLHWYQQKPDQSPKLLIKAASQRASG VPSRFSGSGG TDFTLTINSLEAEDAATYYCHQFHSSPLT FGGGTKLEIKRTVAAPSVFI FPPSDEQLKSG TASVVCLLN NFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTYSLSSTLTLSKADYEEKHKVYACE VTHQGLSSPVT KSFNRGEC
451	Anti-hPD-1 #1-hIgG4-L6-hIL-2 (D20A/R38E) HC Linker in dashed underline hIL-2 in italics	QVQLVESGGGVVQPGRSLRLDCKASGITFSNSGMHWVRQAPGKGLEWVAVIWYDGSKRY YADSVKGRFT ISRDN SKNTLFLQMNSLRAEDAVYYCATNDYWGQGLTVTVSSASTKGPSVFPLA PCSRSTSESTAAL GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVFSSSLG TKTYTCNV DHPKSNTRKVDKRVESKYGPPCPAPAEFLGGPSVFLFPPKPKDTLMISRTPEVTCVWVDVSQED PEVQF VHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQPR EPQVYITLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPPVLDSDG SFFLYSRLTV D KSRWQEGNVFSCSVMEALHNHYTQKSLSLGLKGGGSA PTSSSTKTKTLQLEHLLALQMI LINGINNYKNPKLT EMLTTFKYPKPKKATELKHLCLEELKPLEEVNLQAQSKNFHLRPDRLISININIVLELKG SETTFMCE YADETATIVEFLNRWITFCQSIISTLT

452	Anti-hPD-1 #1-hKappa LC	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLIIYDASNRATGIPARFSGSGGT DFTLTISSLEPEDFAVYCCQSSNWPRFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCCLINN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSITYLSSTLTLSKADYEHKHYACEVTHQGLSSPVTK SFNRGEC
453	OMC.1.B6-hIgG4-L6-hIL-2 (D20A/R38E) HC Linker in dashed underline hIL-2 in italics	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNNYMSWVRQAPGKGLEWVSAISSSGGTIFYADSVKGRFT ISRDN SKNTLYLQMN SLRAEDTAVY YCAKHKNNAVYYDGM DVWGQGT TTVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTTKTYTCNV DHKPSNTKVDKRVESKYGPPCPCPAPEFLGGPSVFLFPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVTHQDWLNGKEYCKKVSNGKGLPSSIEKTI SKAKGQP REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCSVMH EALHNHYTQKSLSLKGSGGGGSAPTSSSTKKTLQLLEHLLALQMI LNGI NNYKNPKLT EMLTTFKFYMPKKAT ELKH LQCLEEEELKPLEEVNL AQSKNFHLRPRDLISNIN VIVLELKG GSETTFMCEYADETATIV EFNLRWITFCQSIISTLT
454	OMC.2.C6-hIgG4-L6-hIL-2 (D20A/R38E) HC Linker in dashed underline hIL-2 in italics	EVQLLESGGGLVQPGGSLRLSCTASGFTFSSEYEMQWVRQAPGKGLEWVLGITSSSSHIFYADSVKGRFT VSRDN SKNTLYLQMN SLRAEDTAVY YCTKDLNSYYGLDVWGQGT TTVTVSSASTKGPSVFPLAPCSRST ESTAAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTTKTYTCNV DHK PSNTKVDKRVESKYGPPCPCPAPEFLGGPSVFLFPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNW YVDGVEVHNAKTKPREEQFNSTYRVVSVLTVTHQDWLNGKEYCKKVSNGKGLPSSIEKTI SKAKGQPREP QVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKS RWQEGNVFSCSVMH EALHNHYTQKSLSLKGSGGGGSAPTSSSTKKTLQLLEHLLALQMI LINGINNY KNPKLT EMLTTFKFYMPKKAT ELKH LQCLEEEELKPLEEVNL AQSKNFHLRPRDLISNIN VIVLELKGSE TTFMCEYADETATIV EFNLRWITFCQSIISTLT
455	OMC.1.D6-hIgG4-L6-hIL-2 (D20A/R38E) HC Linker in dashed underline hIL-2 in italics	EVQLLESGGGLVQPGGSLRLSCAASGFTFSDYYMSWVRQAPGKGLEWVSAISSSGGTIFYADSVKGRFI ISRDN SKNTLYLQMN SLRAEDTAVY YCAKHKNNDVYYDAMD VWGQGT TTVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTTKTYTCNV DHKPSNTKVDKRVESKYGPPCPCPAPEFLGGPSVFLFPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVTHQDWLNGKEYCKKVSNGKGLPSSIEKTI SKAKGQP REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCSVMH EALHNHYTQKSLSLKGSGGGGSAPTSSSTKKTLQLLEHLLALQMI LNGI NNYKNPKLT EMLTTFKFYMPKKAT ELKH LQCLEEEELKPLEEVNL AQSKNFHLRPRDLISNIN VIVLELKG GSETTFMCEYADETATIV EFNLRWITFCQSIISTLT
456	D12-hIgG4-df-hIL-2 (D20A/R38E) HC	DVQLVESGGGLVQPGGSLRLSCAASGFTFDISAMSWVRQAPGKGLEWVSTISGSAYSTYYADSVKGRFT ISRDN SKSTLYLQMN SLRAEDTAVY YCAREIFSDYWGGLT LVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTTKTYTCNV DHKPSNT

	hIL-2 in italics	KVDKRVESKYGPPPCPPCAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQVYIT LPDSQEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE GNVFCSCVMHEALHNHYTQKSLSLGLKAPTSSTTKTQLQLEHLALLAQLQMILNGINNYKNPKLTEMILT FKFYMPKKATELKHLCLEELKPLEEVNLNAQSKNFHLRPRDLISNINIVIVLELKGSETTFMCEYADE TATIVFNLNRMWITFCQSIISTLT
457	G12-hIgG4-df- hIL-2 (D20A/R38E) HC hIL-2 in italics	DSLVEGGGLVQPGGSLRLSCAASGFTFDISAMSWVRQAPGKGLIEWVSTISGSAYSTYYADSVKGRFTI SRDNSKNTLYLQMNLSLRAEDTAVYYCAREIFSDYWGGLGLTVTVSSASTKGPSVFPLAPCSRSTSESTA LGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTTKTYTCNVVDHKPSNTK VDKRVESKYGPPPCPPCAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG EVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQVYITL PPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEG NVFSCVMHEALHNHYTQKSLSLGLKAPTSSTTKTQLQLEHLALLAQLQMILNGINNYKNPKLTEMILTF KFYMPKKATELKHLCLEELKPLEEVNLNAQSKNFHLRPRDLISNINIVIVLELKGSETTFMCEYADET ATIVFNLNRMWITFCQSIISTLT
458	2H7-hIgG4-LE HC	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLIEWVSAIVYSGGSTYYADSVKGRFT ISRDNKNTLYLQMNLSLRAEDTAVYYCAYKTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTTKTYTCNV DHKPSNTKVDKRVESKYGPPPCPPCAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQ REPQVYITLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCVMHEALHNHYTQKSLSLSLG
459	2H7-hIgG4-LAGA HC	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLIEWVSAIVYSGGSTYYADSVKGRFT ISRDNKNTLYLQMNLSLRAEDTAVYYCAYKTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTTKTYTCNV DHKPSNTKVDKRVESKYGPPPCPPCAPEFAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQ REPQVYITLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCVMHEALHNHYTQKSLSLSLG
460	OMC.2-A3- hIgG4/Λ HC	EVQLLESGGGLVQPGGSLRLSCAASGFTFSDYYMSWVRQAPGKGLIEWVSAISSGGTIFYADSVKGRFI ISRDNKNTLYLQMNLSLRAEDTAVYYCAKHKWNDVYDAMDVWGQGTTVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTTKTYTCNV DHKPSNTKVDKRVESKYGPPPCPPCAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQ REPQVYITLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCVMHEALHNHYTQKSLSLSLG

461	OMC476pH7-hIgG4 HC	DMQLVESGGGVVRRPGESLRSLRSTASGFTFSISAMSWVRQAPGKGLEWVSAISGTAYSTYYADSVRGRFT ISRDNKNTLYLQMNSLRAEDTAVYYCAKDNFFDYWGLGLTVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTKTYTCNVVDHKPSNT KVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVDSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVQLHQLDNLNGKEYCKVSNKGLPSSIEKTIISKAKGQPREPQVYIT LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDSGSFFLYSRLTVDKSRWQE GNVFSCVMHEALHNHYTQKSLSLGLG
462	OMC476pB11.H7 LC	QSVMTQPPPSASGTPGQRTVITSCSGVTISGNSVYVYQQLPGTAPKLLIYLNSQRPSPGVPDRFSGSKSG TSASLAI SGLQSEDEADYYCGFWDDSLNWWFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLV LISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNKNKYAASSYLSTPEQWKSHRSYSCQVTHEGSTVE KTVAPTECS
463	OMC476pB11-hIgG4 HC	DVQLVESGGGVVRRPGESLRSLRSTASGFTFSISAMSWVRQAPGKGLEWVSAISGTAYSTYYADSVRGRFT ISRDNKNTLYLQMNSLRAEDTAVYYCAKDNFFDYWGLGLTVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTKTYTCNVVDHKPSNT KVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVDSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVQLHQLDNLNGKEYCKVSNKGLPSSIEKTIISKAKGQPREPQVYIT LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDSGSFFLYSRLTVDKSRWQE GNVFSCVMHEALHNHYTQKSLSLGLG
464	OMC476pG10-hIgG4 HC	DVQLVESGGGVVRRPGESLRSLRSCAASGFTFSIYAMSWVRQAPGEGLEWVSHISASGGSTYYADSVKGRFA ISRDNKNTLYLQMNSLRAEDTAVYYCTTNLGS DYWGLGLTVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTKTYTCNVVDHKPSNT KVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVDSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVQLHQLDNLNGKEYCKVSNKGLPSSIEKTIISKAKGQPREPQVYIT LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDSGSFFLYSRLTVDKSRWQE GNVFSCVMHEALHNHYTQKSLSLGLG
465	OMC476pH10-hIgG4 HC	DVQLVESGGGVVRRPGESLRSLRSCAASGFTFSIYAVSWVRQAPGEGLEWVSHISASGGSTYYADSVKGRFA ISRDNKNTLYLQMNSLRAEDTAVYYCTTNLGS DYWGLGLTVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTKTYTCNVVDHKPSNT KVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVDSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVQLHQLDNLNGKEYCKVSNKGLPSSIEKTIISKAKGQPREPQVYIT LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDSGSFFLYSRLTVDKSRWQE GNVFSCVMHEALHNHYTQKSLSLGLG
466	OMC476pG10.H10 LC	QSVLTQPPPSASGTPGQRTVITSCSGYSIDIGTNYVYVYQQLPGTAPKLLIFATDRRPSGVPDRFSGSKSG TSASLAI SGLQSEDEADYYCGFWDDSLNWWFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLV LISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNKNKYAASSYLSTPEQWKSHRSYSCQVTHEGSTVE KTVAPTECS

467	OMC476pE4- hIG4 HC	DVQLVESGGGVVRRPGESLRSLSCAASGFTFTSDAMGWVRQAPGEGLEWVSLISGGYSTYYADSVKGRFT ISRDN SKNTLYLQMNSLTAEDTAVYYCAKNSLAFFDYWGLGTLVTVSASTKGPSVFPLAPCSRSTSE TAAIGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHK NTKVDKRVESKYGPPCPAPPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSQEDPEVQFNWYV DGEVHNAKTKPREEQFNSTYRVSVLTVLHQDWLNGKEYCKVSNKGLPSSIEKTIISKAGQPREPQV YTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRW QEGNVFCSVMHEALHNHYTQKSLSLGL
468	OMC476pE4 LC	QSVLTQPPSASGTPGQRVTISCSGGSSNIGRESVNWYQQLPGTAPKLLIYSTDRRPSGVPDRFSGSKSG TSASLAI SGLQSEDEADYYCGFWNDNLNGWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVC LISDFYPGA VTAWKADSSPVKAGVETTTPSKQSNKNKYAASSYLSTLPEQWKSHRSYSCQVTHEGSTVE KTVAPTECS
469	J110-hIG1 HC	DVQLQESGGGLVKPQSLSLTCTVTGHSITSDYAWNWI RQFP GDKLEW MGYISYSGYTTYNP SLKSRVS ITRDTSKNQFFLIQINSVTTEDTATYFCARDLDYGPWFAYWQGTLVTVSAASTKGPSVFPLAPSSKSTS GGTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHK PSNTKVDKKVEPKSCDKTHTCPCPAPEL LGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVK FNWYVDGVEVHNAKTKPREEQNSTYRVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQP REPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTV DKSRWQOGNVFCSVMHEALHNHYTQKSLSLSPGK
470	J110-hKappa LC	DIQMTQSPASLSASVGETVTLTCRASENIHNLYAWYQQKQKSPQLLVYNVKT LADGVPSRFSGSGSGT QYSLKINSIQPEDFGSYQCQHFWSPPWTFGGTKVEIKRTVAAPSFI FPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSITYSLSTLTLSKADY EKHKVYACEVTHQGLSSPVTK SFNRGEC
471	2H7-hIG1- LAGA-df-hIL-2 (T3A/D20A/R38E /C125A) HC hIL2 in italics	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAI VYSGSTYYADSVKGRFT ISRDN SKNTLYLQMNNLRAEDTAVYYCAKYTRASYFYDAMDVWGQGT TTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPCPAPELAGAPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDP EVKENWYVDGVEVHNAKTKPREEQNSTYRVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSK LTVDKSRWQOGNVFCSVMHEALHNHYTQKSLSLSPGKAPASSSTKKTLQLEHLLALQMI LINGINNY KNPKLTEM LTFKFYMPKKATELKHLCLEELKPLEEVLNLAQSKNFHLRPRDLISNIN VIVLELKGSE TTFMCEYADETAT IVEFLNRWITFAQSII STLT
472	2H7-hIG4-LE- df-hIL-2 (T3A/D20A/R38E /C125A) HC	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAI VYSGSTYYADSVKGRFT ISRDN SKNTLYLQMNNLRAEDTAVYYCAKYTRASYFYDAMDVWGQGT TTVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNV DHKPSNTKVDKRVESKYGPPCPAPPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQNSTYRVSVLTVLHQDWLNGKEYCKVSNKGLPSSIEKTISKAKGQP REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTV

	hIL-2 in italics	DKSRWQEGNVFSCVMHEALHNHYTQKSLSLGKAPASSSTKKTLQLEHLLALQMI LINGINNYKNP KLTEMLTFKFYMPKKATELKHLCLEELKPLEEVNLQAQSKNFHLRPRDLISININVIVLELKGSETTF MCEYADETATIVEFNLRWITFAQSIIISTLT
473	2H7-hIgG1- LAGA--df-hIL-2 (T3A/D20A/R38E /C125A) HC	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDN SKNTLYLQMN NLR AEDTAVYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYTCNV DHKPSNTKVDKRVESKYGPPCPAPAFAGAPSVFLPPKPKDTLMISRTPEVTCVVDVDSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQP REPQVYITLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCVMHEALHNHYTQKSLSLGKAPASSSTKKTLQLEHLLALQMI LINGINNYKNP KLTEMLTFKFYMPKKATELKHLCLEELKPLEEVNLQAQSKNFHLRPRDLISININVIVLELKGSETTF MCEYADETATIVEFNLRWITFAQSIIISTLT
474	2H7-hIgG1- LAGA-df-hIL-2 (T3A/R38E/I92K /C125A) HC	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDN SKNTLYLQMN NLR AEDTAVYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKHTCTPCPAPELAGAPSVFLPPKPKDTLMISRTPEVTCVVDVDSHEDP EVKENWYVDGVEVHNAKTKPREEQFNSTYRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI SKAK GQPREPQVYITLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPEVLDSDGSFFLYSK LTVDKSRWQGNVFSCVMHEALHNHYTQKSLSLSPGKAPASSSTKKTLQLEHLLLDLQMI LINGINNY KNPKLTEM LTFKFYMPKKATELKHLCLEELKPLEEVNLQAQSKNFHLRPRDLISININVIVLELKGSE TTFMCEYADETATIVEFNLRWITFAQSIIISTLT
475	2H7-hIgG4-LE- df-hIL-2 (T3A/R38E/I92K /C125A) HC	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDN SKNTLYLQMN NLR AEDTAVYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYTCNV DHKPSNTKVDKRVESKYGPPCPAPAFEGGSPVFLPPKPKDTLMISRTPEVTCVVDVDSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQP REPQVYITLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCVMHEALHNHYTQKSLSLGKAPASSSTKKTLQLEHLLLDLQMI LINGINNYKNP KLTEMLTFKFYMPKKATELKHLCLEELKPLEEVNLQAQSKNFHLRPRDLISININVIVLELKGSETTF MCEYADETATIVEFNLRWITFAQSIIISTLT
476	2H7-hIgG4- LAGA-df-hIL-2 (T3A/R38E/I92K /C125A) HC	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDN SKNTLYLQMN NLR AEDTAVYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYTCNV DHKPSNTKVDKRVESKYGPPCPAPAFAGAPSVFLPPKPKDTLMISRTPEVTCVVDVDSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQP REPQVYITLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCVMHEALHNHYTQKSLSLGKAPASSSTKKTLQLEHLLLDLQMI LINGINNYKNP
	hIL-2 in italics	

		<i>KLTEMLTFKFYMPKKA TELKHLCLEELKPLEEVNLAQSKNFHLRPRDLISININVIVLELKGSETTF</i> <i>MCEYADETATIV EFNLRWITFAQSIISTLT</i>
477	2H7-hIgG1- LAGA-df-hIL-2 (T3A/R38E/D84K /C125A) HC hIL-2 in italics	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGSTYYADSVKGRFT ISRDN SKNTLYLQMN NLR AEDTAVYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHCTCPPELAPAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKENWYVDGVEVHNAKTKPRREEQNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIISKAK GQPREPQVYITLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDSGSFFLYSK LTVDKSRWQOGNVFSCSVMH EALHNHYTQKSLSLSPGKAPASSSTKKTQLQLEHLLLDLQMLINGINNY KNPKLT EMLTFKFYMPKKA TELKHLCLEELKPLEEVNLAQSKNFHLRPRKLISININVIVLELKGSE TTFMCEYADETATIV EFNLRWITFAQSIISTLT
478	2H7-hIgG4-LE- df-hIL-2 (T3A/R38E/D84K /C125A) HC hIL-2 in italics	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGSTYYADSVKGRFT ISRDN SKNTLYLQMN NLR AEDTAVYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYTCNV DHKPSNTKVDKR VESKYGPPCPPEAFEGGSPVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQ FNWYVDGVEVHNAKTKPREEQNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQP REPQVYITLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDSGSFFLYSRLTV DKSRWQEGNVFSCSVMH EALHNHYTQKSLSLSPGKAPASSSTKKTQLQLEHLLLDLQMLINGINNYKNP <i>KLTEMLTFKFYMPKKA TELKHLCLEELKPLEEVNLAQSKNFHLRPRKLISININVIVLELKGSETTF</i> <i>MCEYADETATIV EFNLRWITFAQSIISTLT</i>
479	2H7-hIgG4- LAGA-df-hIL-2 (T3A/R38E/D84K /C125A) HC hIL-2 in italics	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGSTYYADSVKGRFT ISRDN SKNTLYLQMN NLR AEDTAVYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYTCNV DHKPSNTKVDKR VESKYGPPCPPEAFAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQ FNWYVDGVEVHNAKTKPREEQNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQP REPQVYITLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDSGSFFLYSRLTV DKSRWQEGNVFSCSVMH EALHNHYTQKSLSLSPGKAPASSSTKKTQLQLEHLLLDLQMLINGINNYKNP <i>KLTEMLTFKFYMPKKA TELKHLCLEELKPLEEVNLAQSKNFHLRPRKLISININVIVLELKGSETTF</i> <i>MCEYADETATIV EFNLRWITFAQSIISTLT</i>
480	1H3-hIgG4-df- hIL-2 (WT) HC hIL-2 in italics	EVQLVESGGGLVQPGGSLRLSKLSCAVSGFTFDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDN AKITLYLQMDSLRSEDATYYCARHGSYFYDWGQGMVTVSSASTKGPSVFPLAPCSRSTSES TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYTCNV DHKPS NTKVDKR VESKYGPPCPPEAFELGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYV DGVEVHNAKTKPREEQNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQV YTLPPEEQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDSGSFFLYSRLTVDKSRW QEGNVFSCSVMH EALHNHYTQKSLSLSPGKAPTSSSTKKTQLQLEHLLLDLQMLINGINNYKNPKLTRM

		<i>LTFFKFMPPKKATELKHLLQCLEELKPLEEVNLNAQSKNFHLRPRDLISNINIVLELKGSETTFMCEYADETATIVFELNRWITFCQSIISTLT</i>
481	1H3-hIgG4-L6-hIL-2 (WT) HC Linker in dashed underline hIL-2 in italics	<i>EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFTISRDNAKITLYIQMDSLRSRSEDATYYCARHSGSYFDYWGQGMVTVSSASTKGPSPFPLAPCSRSTSESTAALGCLVKDYFPEPVTVMNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTTKTYTCNVDPKPSNTKVDKRVESKYGPPCPAPAEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQFPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHREALHNHYTQKSLSLGGGSAPTSSSTKKTKQLQLEHLLLDLQMLINGINNYKNPKLTRMLTFKFYMPKKATELKHLLQCLEELKPLEEVNLNAQSKNFHLRPRDLISNINIVLELKGSETTFMCEYADETATIVFELNRWITFCQSIISTLT</i>
482	1H3-hIgG4 HC	<i>EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFTISRDNAKITLYIQMDSLRSRSEDATYYCARHSGSYFDYWGQGMVTVSSASTKGPSPFPLAPCSRSTSESTAALGCLVKDYFPEPVTVMNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTTKTYTCNVDPKPSNTKVDKRVESKYGPPCPAPAEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQFPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHREALHNHYTQKSLSLIG</i>
483	1H3-hKappa-df-hIL-2 (WT) LC hIL-2 in italics	<i>DTVLTQSPALAVSPGERVTISCRASESVRTGVHWYQQKPGQPQLLIYGASNLESGVPAFSGSGSGTDFTLTIDPVEADDTATYFCQQQWNPDPFTFGSGTKLEIKRTVAAPSVFIAPPDEQLKSGTASVVCCLNNEYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSTYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGECAPTSSSTKKTKQLQLEHLLLDLQMLINGINNYKNPKLTRMLTFKFYMPKKATELKHLLQCLEELKPLEEVNLNAQSKNFHLRPRDLISNINIVLELKGSETTFMCEYADETATIVFELNRWITFCQSIISTLT</i>
484	1H3-hKappa-L6-hIL-2 (WT) LC Linker in dashed underline hIL-2 in italics	<i>DTVLTQSPALAVSPGERVTISCRASESVRTGVHWYQQKPGQPQLLIYGASNLESGVPAFSGSGSGTDFTLTIDPVEADDTATYFCQQQWNPDPFTFGSGTKLEIKRTVAAPSVFIAPPDEQLKSGTASVVCCLNNEYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSTYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGECGGGSAPTSSSTKKTKQLQLEHLLLDLQMLINGINNYKNPKLTRMLTFKFYMPKKATELKHLLQCLEELKPLEEVNLNAQSKNFHLRPRDLISNINIVLELKGSETTFMCEYADETATIVFELNRWITFCQSIISTLT</i>
485	1H3-hIgG4-L6-hIL-2 (D20Y) HC	<i>EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFTISRDNAKITLYIQMDSLRSRSEDATYYCARHSGSYFDYWGQGMVTVSSASTKGPSPFPLAPCSRSTSESTAALGCLVKDYFPEPVTVMNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTTKTYTCNVDPKPSNTKVDKRVESKYGPPCPAPAEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQFPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHREALHNHYTQKSLSLIG</i>

	Linker in dashed underline hIL-2 in italics	DGVEVHNAKTPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQV YTLPPSQEEMTKNQVSLTCLVKGYFSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHAEALHNHYTQKSLSLGLSKGGGSAFTSSSTKKTQLQLEHLLLYLQMLINGINNYKN PKLTRLMTFKFYMPKKATELKHLCLEELKPLEEVNLAQSKNFHLRPRDLISINIVIVLELKGSETT FMCEYADETATIVEFLNRWITFCQSIISTLT
486	1H3-hIgG4-df- hIL-2 (D20Y) HC hIL-2 in italics	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDATYYCARHGSYFDYWGQGMVMTVSSASTKGPSVFPLAPCSRSTSES TAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTTKTYTCNVDHKPS NTKVDKRVESKYGPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYV DGVEVHNAKTPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQV YTLPPSQEEMTKNQVSLTCLVKGYFSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHAEALHNHYTQKSLSLGLSKAPTSSTKKTQLQLEHLLLYLQMLINGINNYKNPKLTRL MTFKFYMPKKATELKHLCLEELKPLEEVNLAQSKNFHLRPRDLISINIVIVLELKGSETTFMCEYA DETATIVEFLNRWITFCQSIISTLT
487	1H3-hIgG1-df- hIL-2 (D20Y) HC hIL-2 in italics	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDATYYCARHGSYFDYWGQGMVMTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTTQTYICNVNHKPS NTKVDKVEPKSCDKHTCCPPAPELIGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGYFSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHAEALHNHYTQKSLSLSPGKAPTSSSTKKTQLQLEHLLLYLQMLINGINNYKNPKL TRMLTFKYMPKKATELKHLCLEELKPLEEVNLAQSKNFHLRPRDLISINIVIVLELKGSETTFMC EYADETATIVEFLNRWITFCQSIISTLT
488	1H3-hIgG4-L6- hIL-2 (D20A/R38P) HC Linker in dashed underline hIL-2 in italics	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDATYYCARHGSYFDYWGQGMVMTVSSASTKGPSVFPLAPCSRSTSES TAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTTKTYTCNVDHKPS NTKVDKRVESKYGPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYV DGVEVHNAKTPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQV YTLPPSQEEMTKNQVSLTCLVKGYFSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHAEALHNHYTQKSLSLGLSKGGGSAFTSSSTKKTQLQLEHLLLYLQMLINGINNYKN PKLTPMLTFKYMPKKATELKHLCLEELKPLEEVNLAQSKNFHLRPRDLISINIVIVLELKGSETT FMCEYADETATIVEFLNRWITFCQSIISTLT
489	1H3-hIgG4-L6- hIL-2 (D20A/R38S) HC	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDATYYCARHGSYFDYWGQGMVMTVSSASTKGPSVFPLAPCSRSTSES TAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTTKTYTCNVDHKPS

	Linker in dashed underline hIL-2 in italics	NTKVDKRVESKYGPPCPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQV YTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHREALHNHYTEQSLSLGKSGGGGSAPTSSSTKKTKQLQLEHLLALQMLINGINNYKN PKLTQMLTTFKPYMPKKATELKHLCLEEEELKPLEEVNLQAQSKNFHLRPRDLISINNVIVLELKGSETT FMCEYADETATIVFELNRWITFCQSIISTLT
490	1H3-hIgG4-L6- hIL-2 (D20A/R38D) HC Linker in dashed underline hIL-2 in italics	EVQLVESGGGLVQPGRSRLKLSCAVSGFTFSDYAMAWRQAPKPKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDATYYCARHSGSYFDYWGQGMVTVSSASTKGPSVFPLAPCSRSTSE TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTTKTYTCNVDHKPS NTKVDKRVESKYGPPCPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQV YTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHREALHNHYTEQSLSLGKSGGGGSAPTSSSTKKTKQLQLEHLLALQMLINGINNYKN PKLTQMLTTFKPYMPKKATELKHLCLEEEELKPLEEVNLQAQSKNFHLRPRDLISINNVIVLELKGSETT FMCEYADETATIVFELNRWITFCQSIISTLT
491	1H3-hIgG4-L6- hIL-2 (D20A/R38Q/E95 A) HC Linker in dashed underline hIL-2 in italics	EVQLVESGGGLVQPGRSRLKLSCAVSGFTFSDYAMAWRQAPKPKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDATYYCARHSGSYFDYWGQGMVTVSSASTKGPSVFPLAPCSRSTSE TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTTKTYTCNVDHKPS NTKVDKRVESKYGPPCPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQV YTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHREALHNHYTEQSLSLGKSGGGGSAPTSSSTKKTKQLQLEHLLALQMLINGINNYKN PKLTQMLTTFKPYMPKKATELKHLCLEEEELKPLEEVNLQAQSKNFHLRPRDLISINNVIVLALKGSETT FMCEYADETATIVFELNRWITFCQSIISTLT
492	1H3-hIgG4-L6- hIL-2 (D20A/F42H/E95 A) HC Linker in dashed underline	EVQLVESGGGLVQPGRSRLKLSCAVSGFTFSDYAMAWRQAPKPKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDATYYCARHSGSYFDYWGQGMVTVSSASTKGPSVFPLAPCSRSTSE TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTTKTYTCNVDHKPS NTKVDKRVESKYGPPCPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQV YTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSVMHREALHNHYTEQSLSLGKSGGGGSAPTSSSTKKTKQLQLEHLLALQMLINGINNYKN PKLTRMLTHKFYMPKKATELKHLCLEEEELKPLEEVNLQAQSKNFHLRPRDLISINNVIVLALKGSETT FMCEYADETATIVFELNRWITFCQSIISTLT

	hIL-2 in italics	
493	1H3-hIgG4-L6- hIL-2 (R38D/I92D) HC Linker in dashed underline hIL-2 in italics	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDATYYCARHGSYFDYWGQGMVTVSSASTKGPSVFPEPLAPCSRSTSES TAALGCLVKDYFPEPTVSMNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTKTITCNVDHKPS NTKVDKRVESKYGPPCPAPAEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQV YTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSSEFFLYSRLTVDKSRW QEGNVFSCSVMEALHNHYTQKSLSLGLKSGGGGSAPTSSSTKKTKQLQLEHLLLDLQMIINGINNYKN PKLTDMLTFFKYPMPKKATELKHLCLEELKPLEEVNLNLAQSKNFHLRPRDLISININVDVLELKGSETT FMCEYADETATIVFEFLNRWITFCQSIISTLT
494	1H3-hIgG4-L6- hIL-2 (R38E/I92D) HC Linker in dashed underline hIL-2 in italics	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDATYYCARHGSYFDYWGQGMVTVSSASTKGPSVFPEPLAPCSRSTSES TAALGCLVKDYFPEPTVSMNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTKTITCNVDHKPS NTKVDKRVESKYGPPCPAPAEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQV YTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSSEFFLYSRLTVDKSRW QEGNVFSCSVMEALHNHYTQKSLSLGLKSGGGGSAPTSSSTKKTKQLQLEHLLLDLQMIINGINNYKN PKLTDMLTFFKYPMPKKATELKHLCLEELKPLEEVNLNLAQSKNFHLRPRDLISININVDVLELKGSETT FMCEYADETATIVFEFLNRWITFCQSIISTLT
495	1H3-hIgG4-L6- hIL-2 (F42H/I92D) HC Linker in dashed underline hIL-2 in italics	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDATYYCARHGSYFDYWGQGMVTVSSASTKGPSVFPEPLAPCSRSTSES TAALGCLVKDYFPEPTVSMNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTKTITCNVDHKPS NTKVDKRVESKYGPPCPAPAEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQV YTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSSEFFLYSRLTVDKSRW QEGNVFSCSVMEALHNHYTQKSLSLGLKSGGGGSAPTSSSTKKTKQLQLEHLLLDLQMIINGINNYKN PKLTDMLTFFKYPMPKKATELKHLCLEELKPLEEVNLNLAQSKNFHLRPRDLISININVDVLELKGSETT FMCEYADETATIVFEFLNRWITFCQSIISTLT
496	1H3-hIgG4-L6- hIL-2 (D20A/R38E) HC	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDATYYCARHGSYFDYWGQGMVTVSSASTKGPSVFPEPLAPCSRSTSES TAALGCLVKDYFPEPTVSMNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTKTITCNVDHKPS NTKVDKRVESKYGPPCPAPAEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQV

	Linker in dashed underline hIL-2 in italics	YTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPPVLDSGSEFFLYSRLTVDKSRW QEGNVFSCSVMHREALHNHYTQKSLSLGLKSGGGGSAPTSSSTKKTLQLEHLLALQMLINGINNYKN PKLTEMLTFFKYPMPKKATELKHLCLEELKPLEEVLNLAQSKNFHLRPRDLISINNVIVLELKGSETT FMCEYADETATIVFELNRWITFAQSIISTLT
497	1H3-hIgG4-L6- hIL-2 (T3A/D20A/R38E) HC Linker in dashed underline hIL-2 in italics	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDATYYCARHSGSYFDYWGQGMVTVSSASTKGPSVFPLAPCSRSTSE TAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTTKTYTCNVDHKPS NTKVDKRVESKYGPPCPAPPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYV DGEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQV YTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPPVLDSGSEFFLYSRLTVDKSRW QEGNVFSCSVMHREALHNHYTQKSLSLGLKSGGGGSAPTSSSTKKTLQLEHLLALQMLINGINNYKN PKLTEMLTFFKYPMPKKATELKHLCLEELKPLEEVLNLAQSKNFHLRPRDLISINNVIVLELKGSETT FMCEYADETATIVFELNRWITFAQSIISTLT
498	1H3-hIgG4-L6- hIL-2 (D20A/R38E/C12 5A) HC Linker in dashed underline hIL-2 in italics	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDATYYCARHSGSYFDYWGQGMVTVSSASTKGPSVFPLAPCSRSTSE TAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTTKTYTCNVDHKPS NTKVDKRVESKYGPPCPAPPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYV DGEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQV YTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPPVLDSGSEFFLYSRLTVDKSRW QEGNVFSCSVMHREALHNHYTQKSLSLGLKSGGGGSAPTSSSTKKTLQLEHLLALQMLINGINNYKN PKLTEMLTFFKYPMPKKATELKHLCLEELKPLEEVLNLAQSKNFHLRPRDLISINNVIVLELKGSETT FMCEYADETATIVFELNRWITFAQSIISTLT
499	1H3-hIgG4-L6- hIL-2 (T3A/D20A/R38E /C125A) HC Linker in dashed underline	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDATYYCARHSGSYFDYWGQGMVTVSSASTKGPSVFPLAPCSRSTSE TAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTTKTYTCNVDHKPS NTKVDKRVESKYGPPCPAPPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYV DGEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQV YTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPPVLDSGSEFFLYSRLTVDKSRW QEGNVFSCSVMHREALHNHYTQKSLSLGLKSGGGGSAPTSSSTKKTLQLEHLLALQMLINGINNYKN PKLTEMLTFFKYPMPKKATELKHLCLEELKPLEEVLNLAQSKNFHLRPRDLISINNVIVLELKGSETT FMCEYADETATIVFELNRWITFAQSIISTLT

	hIL-2 in italics	
500	1H3-hIgG1-L6- hIL-2 (D20A/R38E) HC Linker in dashed underline hIL-2 in italics	EVQLVESGGGLVQPGRSLLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDATYYCARHSGSYFDYWGQGMVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPTVSMNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGPPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDK SRWQOGNVFSCVMHEALHNHYTQKSLSLSPGKSGGGSAPTSSSTKKTQLQLEHLLIALQMIILINGINN YKNPKLTEMILTFFYMPKKATELKHLCLEELKPLEEVNLNAQSKNFHLRPRDLISNINNVIVLELKG ETTFMCEYADETATIVFELNRWITFCQSIISTLT
501	1H3-hIgG1-L6- hIL-2 (T3A/D20A/R38E) HC Linker in dashed underline hIL-2 in italics	EVQLVESGGGLVQPGRSLLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDATYYCARHSGSYFDYWGQGMVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPTVSMNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGPPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDK SRWQOGNVFSCVMHEALHNHYTQKSLSLSPGKSGGGSAPTSSSTKKTQLQLEHLLIALQMIILINGINN YKNPKLTEMILTFFYMPKKATELKHLCLEELKPLEEVNLNAQSKNFHLRPRDLISNINNVIVLELKG ETTFMCEYADETATIVFELNRWITFCQSIISTLT
502	1H3-hIgG1-L6- hIL-2 (D20A/R38E/C12 5A) HC Linker in dashed underline hIL-2 in italics	EVQLVESGGGLVQPGRSLLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDATYYCARHSGSYFDYWGQGMVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPTVSMNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGPPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDK SRWQOGNVFSCVMHEALHNHYTQKSLSLSPGKSGGGSAPTSSSTKKTQLQLEHLLIALQMIILINGINN YKNPKLTEMILTFFYMPKKATELKHLCLEELKPLEEVNLNAQSKNFHLRPRDLISNINNVIVLELKG ETTFMCEYADETATIVFELNRWITFCQSIISTLT
503	1H3-hkappa-df- hIL-2 (D20A/R38E) LC	DTVLTQSPALAVSPGERVTISCRASESVRTGVHWYQQKPGQPKLLIYGASNLESQVPAFSGSGSGTD FTLTIDPVEADDTATYFCQQSWNDPFTFGSGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNE YPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTYSLSLTITLTSKADYEEKHKVYACEVTHQGLSSPVTKS

	hIL-2 in italics	FNRGECAPTSSSTKKTQLQLEHLLALLQMLINGINNYKNPKLTEMILTFFKYMPPKKATELKHLCLEEL KPLEEVNLNAQSKNFHLRPRDLISNINIVLELKGSETTFMCEYADETATIVFELNRWITFCQSIISTLT
504	1H3-hKappa-L6- hIL-2 (D20A/R38E) LC Linker in dashed underline hIL-2 in italics	DTVLTQSPALAVSPGERVTISRASESVRTGVHWYQQKFCQQPKLLIYGASNLESGVPAFSGSGSGTD FTLTIDPEADDATATYFCQQSWNDPFTFGSGTKLEIKRTVAAPSVFIFFPSDEQLKSGTASVVCLLNNE YPREAKVQWKVDNALQSGNSQESVTEQDSKDSYLSLSITITLSKADYEKHKVYACEVTHQGLSSPVTKS FNRGECGGGGSAPTSSSTKKTQLQLEHLLALLQMLINGINNYKNPKLTEMILTFFKYMPPKKATELKHLC CLEELKPLEEVNLNAQSKNFHLRPRDLISNINIVLELKGSETTFMCEYADETATIVFELNRWITFCQ SIISTLT
505	OMC476pB11- hIgG4-df-hIL-2 (D20A/R38E) HC hIL-2 in italics	DVQLVESGGGVVRPGESLRSLSCASGFTFSISAMSWVRQAPGKGLEWVSAISGTAYSTYYADSVRGRFT ISRDNSKNTLYLQMNSLRAEDTAVYCAKDNFFDYWGLGLTLVTSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPTVSMNSGALTSGVHTFPAVLQSSGLYSLSSVTPSSSLGTKTYTCNVDPKPSNT KVDKRVESKYGPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQVYT LPDSQEMTNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQE GNVFCSMVEALHNHYTQKSLSLGLKAPTSSTSTKKTQLQLEHLLALLQMLINGINNYKNPKLTEMILT FKFYMPPKKATELKHLCLEELKPLEEVNLNAQSKNFHLRPRDLISNINIVLELKGSETTFMCEYADE TATIVFELNRWITFCQSIISTLT
506	OMC476pE4- hIgG4-df-hIL-2 (D20A/R38E) HC hIL-2 in italics	DVQLVESGGGVVRPGESLRSLSCASGFTFSTDAMGWVRQAPGEGLEWVSLISGSGYSTYYADSVKGRFT ISRDNSKNTLYLQMNSLTAEADTAVYCAKNSLAFFDYWGLGLTLVTSSASTKGPSVFPLAPCSRSTSES TAALGCLVKDYFPEPTVSMNSGALTSGVHTFPAVLQSSGLYSLSSVTPSSSLGTKTYTCNVDPKPS NTKVDKRVESKYGPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVQEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQV YTLPPSQEEMTNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRW QEGNVFSCSMVEALHNHYTQKSLSLGLKAPTSSTSTKKTQLQLEHLLALLQMLINGINNYKNPKLTEM LTFKFYMPPKKATELKHLCLEELKPLEEVNLNAQSKNFHLRPRDLISNINIVLELKGSETTFMCEYADE TATIVFELNRWITFCQSIISTLT
507	OMC476pG10- hIgG4-df-hIL-2 (D20A/R38E) HC hIL-2 in italics	DVQLVESGGGVVRPGESLRSLSCASGFTFSIYAMSWVRQAPGEGLEWVSHISAGSGYSTYYADSVKGRFA ISRDNSKNTLYLQMNSLRAEDTAVYCTTNLGSYWGGLTLVTSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPTVSMNSGALTSGVHTFPAVLQSSGLYSLSSVTPSSSLGTKTYTCNVDPKPSNT KVDKRVESKYGPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQVYT LPDSQEMTNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQE

508	OMC476pH10- hIgG4-df-hIL-2 (D20A/R38E) HC hIL-2 in italics	GNVFSCVMHEALHNHYTQKSLSLGKAPTSSSTKKTLQLEHLLALQMLNGINNKNPKLTEMILT FKFYMPKKATELKHLLQCLEEELKPLEEVNLNAQSKNFHLRPRDLISNINIVLELKGSETTFMCEYADE TATIVEFLNRWITFCQSIISTLT DVQLVESGGGLVQPGGSLRLSCAASGFTTFDIYAVSWVRQAPGKGLEWVSHISASGGSTYYADSVKGRFA ISRDNSKNTLYLQMNSLRAEDTAVYCYCTTNLGS DYWGLGLTVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVMNSGALTSGVHTFPAVLQSSGLYSLSSVTPSSSLGTKTTCNVVDHKPSNT KVDKRVESKYGPPCPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVDSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQVYT LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFLYSRLTVDKSRWQE GNVFSCVMHEALHNHYTQKSLSLGKAPTSSSTKKTLQLEHLLALQMLNGINNKNPKLTEMILT FKFYMPKKATELKHLLQCLEEELKPLEEVNLNAQSKNFHLRPRDLISNINIVLELKGSETTFMCEYADE TATIVEFLNRWITFCQSIISTLT
509	A2-hIgG4-df- hIL-2 (D20A/F42A) HC hIL-2 in italics	DVQLVESGGGLVQPGGSLRLSCAASGFTTFDISAMSWVRQAPGKGLEWVSTISGSAYSTYYADSVKGRFT ISRDNSKNTLYLQMNSLRAEDTAVYCYAREIFSDYWGLGLTVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVMNSGALTSGVHTFPAVLQSSGLYSLSSVTPSSSLGTKTTCNVVDHKPSNT KVDKRVESKYGPPCPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVDSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQVYT LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFLYSRLTVDKSRWQE GNVFSCVMHEALHNHYTQKSLSLGKAPTSSSTKKTLQLEHLLALQMLNGINNKNPKLTEMILT AKFYMPKKATELKHLLQCLEEELKPLEEVNLNAQSKNFHLRPRDLISNINIVLELKGSETTFMCEYADE TATIVEFLNRWITFCQSIISTLT
510	A2-hIgG4-df- hIL-2 (D20A/F42S) HC hIL-2 in italics	DVQLVESGGGLVQPGGSLRLSCAASGFTTFDISAMSWVRQAPGKGLEWVSTISGSAYSTYYADSVKGRFT ISRDNSKNTLYLQMNSLRAEDTAVYCYAREIFSDYWGLGLTVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVMNSGALTSGVHTFPAVLQSSGLYSLSSVTPSSSLGTKTTCNVVDHKPSNT KVDKRVESKYGPPCPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVDSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQVYT LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFLYSRLTVDKSRWQE GNVFSCVMHEALHNHYTQKSLSLGKAPTSSSTKKTLQLEHLLALQMLNGINNKNPKLTEMILT SKFYMPKKATELKHLLQCLEEELKPLEEVNLNAQSKNFHLRPRDLISNINIVLELKGSETTFMCEYADE TATIVEFLNRWITFCQSIISTLT
511	A2-hIgG4-df- hIL-2 (D20S/R38E) HC hIL-2 in italics	DVQLVESGGGLVQPGGSLRLSCAASGFTTFDISAMSWVRQAPGKGLEWVSTISGSAYSTYYADSVKGRFT ISRDNSKNTLYLQMNSLRAEDTAVYCYAREIFSDYWGLGLTVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVMNSGALTSGVHTFPAVLQSSGLYSLSSVTPSSSLGTKTTCNVVDHKPSNT KVDKRVESKYGPPCPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVDSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQVYT LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFLYSRLTVDKSRWQE GNVFSCVMHEALHNHYTQKSLSLGKAPTSSSTKKTLQLEHLLALQMLNGINNKNPKLTEMILT

		<i>FKFYMPKKATELKHLCLEEEELKPLEEVNLNAQSKNFHLRPRDLISNINIVLELKGSETTFMCEYADE</i> <i>TATIVEFLNRWITFCQSIISTLT</i>
512	A2-hIgG4-df-hIL-2 (F42A/N88R) HC hIL-2 in italics	DVQLVESGGGLVQPGGSLRLSCAASGFTTFDISAMSWVRQAPGKGLEWVSTISGSAYSTYYADSVKGRFT ISRDNKSTLYLQMNSLRAEDTAVYYCAREIFSDYWGLGLTLVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTPSSSLGTCTYTCNVVDHKPSNT KVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVQLHQQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQVY LPDSQEMTNQVSLTCLVKGYFSPDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQE GNVFCSCVMHEALHNHYTQKSLSLGLKAPTSSSTKKTKQLQLEHLLLDLQMLINGINNYKNPKLTRLT AKFYMPKKATELKHLCLEEEELKPLEEVNLNAQSKNFHLRPRDLISNINIVLELKGSETTFMCEYADE <i>TATIVEFLNRWITFCQSIISTLT</i>
513	A2-hIgG4-df-hIL-2 (F42I/I92D) HC hIL-2 in italics	DVQLVESGGGLVQPGGSLRLSCAASGFTTFDISAMSWVRQAPGKGLEWVSTISGSAYSTYYADSVKGRFT ISRDNKSTLYLQMNSLRAEDTAVYYCAREIFSDYWGLGLTLVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTPSSSLGTCTYTCNVVDHKPSNT KVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVQLHQQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQVY LPDSQEMTNQVSLTCLVKGYFSPDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQE GNVFCSCVMHEALHNHYTQKSLSLGLKAPTSSSTKKTKQLQLEHLLLDLQMLINGINNYKNPKLTRLT IKFYMPKKATELKHLCLEEEELKPLEEVNLNAQSKNFHLRPRDLISNINIVLELKGSETTFMCEYADE <i>TATIVEFLNRWITFCQSIISTLT</i>
514	A2-hIgG4-df-hIL-2 (F42Q/I92D) HC hIL-2 in italics	DVQLVESGGGLVQPGGSLRLSCAASGFTTFDISAMSWVRQAPGKGLEWVSTISGSAYSTYYADSVKGRFT ISRDNKSTLYLQMNSLRAEDTAVYYCAREIFSDYWGLGLTLVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTPSSSLGTCTYTCNVVDHKPSNT KVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVQLHQQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQVY LPDSQEMTNQVSLTCLVKGYFSPDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQE GNVFCSCVMHEALHNHYTQKSLSLGLKAPTSSSTKKTKQLQLEHLLLDLQMLINGINNYKNPKLTRLT QKFYMPKKATELKHLCLEEEELKPLEEVNLNAQSKNFHLRPRDLISNINIVLELKGSETTFMCEYADE <i>TATIVEFLNRWITFCQSIISTLT</i>
515	A2-hIgG4-df-hIL-2 (F42T/I92D) HC hIL-2 in italics	DVQLVESGGGLVQPGGSLRLSCAASGFTTFDISAMSWVRQAPGKGLEWVSTISGSAYSTYYADSVKGRFT ISRDNKSTLYLQMNSLRAEDTAVYYCAREIFSDYWGLGLTLVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTPSSSLGTCTYTCNVVDHKPSNT KVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVQLHQQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQVY LPDSQEMTNQVSLTCLVKGYFSPDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQE GNVFCSCVMHEALHNHYTQKSLSLGLKAPTSSSTKKTKQLQLEHLLLDLQMLINGINNYKNPKLTRLT

		<i>TKFYMPKKATELKHLCLEEEELKPLEEVNLNAQSKNFHLRPRDLISNINVDVLELKGSETTFMCEYADE</i> <i>TATIVEFLNRWITFCQSIISTLT</i>
516	A2-hIgG4-df-hIL-2 (F42W/I92D) HC hIL-2 in italics	DVQLVESGGGLVQPGGSLRLSCAASGFTTFDISAMSWVRQAPGKGLEWVSTISGSAYSTYYADSVKGRFT ISRDNKSTLYLQMNSLRAEDTAVYYCAREIFSDYWGLGLTLVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTPSSSLGTKTYTCNVVDHKPSNT KVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSIVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQVYT LPDSQEDMTKNQVSLTCLVKGYFPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE GNVFSCVMHEALHNHYTQKSLSLGLKAPTSSTKKTQLQLEHLLLDLQMLINGINNYKNPKLTEMILT WKFYMPKKATELKHLCLEEEELKPLEEVNLNAQSKNFHLRPRDLISNINVDVLELKGSETTFMCEYADE <i>TATIVEFLNRWITFCQSIISTLT</i>
517	A2-hIgG4-df-hIL-2 (R38E/D84K) HC hIL-2 in italics	DVQLVESGGGLVQPGGSLRLSCAASGFTTFDISAMSWVRQAPGKGLEWVSTISGSAYSTYYADSVKGRFT ISRDNKSTLYLQMNSLRAEDTAVYYCAREIFSDYWGLGLTLVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTPSSSLGTKTYTCNVVDHKPSNT KVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSIVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQVYT LPDSQEDMTKNQVSLTCLVKGYFPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE GNVFSCVMHEALHNHYTQKSLSLGLKAPTSSTKKTQLQLEHLLLDLQMLINGINNYKNPKLTEMILT FKFYMPKKATELKHLCLEEEELKPLEEVNLNAQSKNFHLRPRDLISNINVDVLELKGSETTFMCEYADE <i>TATIVEFLNRWITFCQSIISTLT</i>
518	A2-hIgG4-df-hIL-2 (R38E/I92K) HC hIL-2 in italics	DVQLVESGGGLVQPGGSLRLSCAASGFTTFDISAMSWVRQAPGKGLEWVSTISGSAYSTYYADSVKGRFT ISRDNKSTLYLQMNSLRAEDTAVYYCAREIFSDYWGLGLTLVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTPSSSLGTKTYTCNVVDHKPSNT KVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSIVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQVYT LPDSQEDMTKNQVSLTCLVKGYFPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE GNVFSCVMHEALHNHYTQKSLSLGLKAPTSSTKKTQLQLEHLLLDLQMLINGINNYKNPKLTEMILT FKFYMPKKATELKHLCLEEEELKPLEEVNLNAQSKNFHLRPRDLISNINVDVLELKGSETTFMCEYADE <i>TATIVEFLNRWITFCQSIISTLT</i>
519	C51E6-5-hIgG4-df-hIL-2 (D20A/R38E) HC hIL-2 in italics	QVQLVQSGSELKPGASVKVSKASGYSLYGTSMHWVRQAPGQGLEWMGYISPFTGRATYAQGGFTGRFV FSLDFTSVSTAYLQISSLKAEDTAVYYCARDYDYYRYAMDYWGQGTITVTVSSASTKGPSVFPLAPCSR TSESTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTPSSSLGTKTYTCNV HKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQF NWYVDGVEVHNAKTKPREEQFNSTYRVVSIVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPR EPQVYTLPPSQEEMTKNQVSLTCLVKGYFPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVD KSRWQEGNVFSCVMHEALHNHYTQKSLSLGLKAPTSSTKKTQLQLEHLLLDLQMLINGINNYKNPK

		<i>LTEM LTFK F Y M P K K A T E L K H L Q C L E E L K P L E E V L N L A Q S K N F H L R P R D L I S N I N V I V L E L K G S E T T F M</i> <i>C E Y A D E T A T I V E F L N R W I T F A Q S I I S T L T</i>
520	C51E6-5-hIgG4- LE-df-hIL-2 (T3A/D20A/R38E /C125A) HC hIL-2 in italics	QVQLVQSGSELEKPKGASVKVKSCKASGYSLYGTSMHWVRQAPGQGLEWMGYISPFTGRATYAQGTGRFV FSLDTSVSTAYLQISSLKAEDTAVYCARDYDYRYYYAMDYWGQGT'TVTVSSASTKGPSVFPLAPCSRS TSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVFSSSLGT'KTYTCNVD HKPSNTKVDKRVESKYGPPCPAPPEFEGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSDQEDPEVQF NWYVDGVEVHNAKTKPREEQNTSYRVVSVLT'LVLHQLDWLNGKEYCKVKSNKGLPSSIEKTIISKAKGQPR EPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVD KSRWQEGNVFSCSVMH EALHNHYTQKSLSLGLKAPASSSTKKTQLQLEHLLALQMLINGINNYKNPK <i>LTEM LTFK F Y M P K K A T E L K H L Q C L E E L K P L E E V L N L A Q S K N F H L R P R D L I S N I N V I V L E L K G S E T T F M</i> <i>C E Y A D E T A T I V E F L N R W I T F A Q S I I S T L T</i>
521	C51E6-5-hIgG4- LAGA-df-hIL-2 (T3A/D20A/R38E /C125A) HC hIL-2 in italics	QVQLVQSGSELEKPKGASVKVKSCKASGYSLYGTSMHWVRQAPGQGLEWMGYISPFTGRATYAQGTGRFV FSLDTSVSTAYLQISSLKAEDTAVYCARDYDYRYYYAMDYWGQGT'TVTVSSASTKGPSVFPLAPCSRS TSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVFSSSLGT'KTYTCNVD HKPSNTKVDKRVESKYGPPCPAPPEFAGAPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSDQEDPEVQF NWYVDGVEVHNAKTKPREEQNTSYRVVSVLT'LVLHQLDWLNGKEYCKVKSNKGLPSSIEKTIISKAKGQPR EPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVD KSRWQEGNVFSCSVMH EALHNHYTQKSLSLGLKAPASSSTKKTQLQLEHLLALQMLINGINNYKNPK <i>LTEM LTFK F Y M P K K A T E L K H L Q C L E E L K P L E E V L N L A Q S K N F H L R P R D L I S N I N V I V L E L K G S E T T F M</i> <i>C E Y A D E T A T I V E F L N R W I T F A Q S I I S T L T</i>
522	1H3-hIgG1- LAGA-L6-hIL-2 (T3A/D20A/R38E /C125A)	EVQLVESGGGLVQPGSRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDATYICARHGSGYFDYWGQGVMTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVFSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELAGAPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQXNTSYRVVSVLT'LVLHQLDWLNGKEYCKVKSNKALPAIEKTIISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMH EALHNHYTQKSLSLSPGKSGGGGSA PASSTKKTQLQLEHLLALQMLINGINN YKNPKLT EMLT FKFYMPKKATELKH LQCLEEEELKPLEEV LNL A Q S K N F H L R P R D L I S N I N V I V L E L K G S ETTFMCEYADETATIV EFLNRWITFAQSIISTLT
523	2A3-hkappa LC	EIVLTQSPGTLSLSPGERATLSCRASQSIGRSFLAWYQQKPGQAPRLLIYDASTRAADIPARFSGSGSG TDFTLTISSELEPEDFAVYCYQQYDWPPLPSPFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSITYSLSSLTLSKADYEEKHKVYACEVTHQGLSSPV TKSFNRGEC
524	1H9-hIgG4-df- hIL-2 (D20A/R38E) HC	EVQLLESGGGLVQPGSLRLSCVSGGFNLKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDN SKNTLYLQMNSLRAEDTAVYICAKYTRGSYFYDAMDVWGQGT'TVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVFSSSLGT'KTYTCNV DHKPSNTKVDKRVESKYGPPCPAPPEFLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSDQEDPEVQ

	hIL-2 in italics	FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQP REPQVYITLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCVMHEALHNYTQKSLSLGLKAPTSSTTKTQLQLEHLLALLQMIINGINNYKNP <i>KLTEMLTFKFMPPKKATELKHLQCLEEEELKPLEEVNLQSKNFHLRPRDLISNINNVIVLELKGSETTF</i> <i>MCEYADETATIVFELNRWITFCQSIISTLT</i>
525	1H9-hkappa LC	EIVLTQSPGTLSLSPGERATLSCRASQSIGRSFLAWYQKPGQAPRLLIYDASTRAADIPDRFSGSGG TDFTLTINRLEPEDFAVYCYQYDWPPLTFGGGTVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSITYLSSTLTLSKADYEEKHKVIYACEVTHQGLSSPV TKSENRGEC
526	1D5-hIgG4-df-hIL-2 (D20A/R38E) HC hIL-2 in italics	EVQLLESGGGLVQPGGSLRLSCVGSQFNFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDN SKNTLYLQMNSLRAEDTAVYCYAKYTRGSYFYDAMDVWGQGTITVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVFSSSLGTCTYTCNV DHKPSNTKVDKRVESKYGPPCPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQP REPQVYITLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCVMHEALHNYTQKSLSLGLKAPTSSTTKTQLQLEHLLALLQMIINGINNYKNP <i>KLTEMLTFKFMPPKKATELKHLQCLEEEELKPLEEVNLQSKNFHLRPRDLISNINNVIVLELKGSETTF</i> <i>MCEYADETATIVFELNRWITFCQSIISTLT</i>
527	1D5-hkappa LC	EIVLTQSPGTLSLSPGERATLSCRASQSIGRSFLAWYQKPGQAPRLLIYDASTRAADIPDRFSGSGG TEFTLTISLQSEDFAVYCYQYDWPPLTFGGGTVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSITYLSSTLTLSKADYEEKHKVIYACEVTHQGLSSPV TKSENRGEC
528	1D5-hIgG4-LE-df-hIL-2 (T3A/D20A/R38E/C125A) HC hIL-2 in italics	EVQLLESGGGLVQPGGSLRLSCVGSQFNFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDN SKNTLYLQMNSLRAEDTAVYCYAKYTRGSYFYDAMDVWGQGTITVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVFSSSLGTCTYTCNV DHKPSNTKVDKRVESKYGPPCPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQP REPQVYITLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCVMHEALHNYTQKSLSLGLKAPASSTTKTQLQLEHLLALLQMIINGINNYKNP <i>KLTEMLTFKFMPPKKATELKHLQCLEEEELKPLEEVNLQSKNFHLRPRDLISNINNVIVLELKGSETTF</i> <i>MCEYADETATIVFELNRWITFCQSIISTLT</i>
529	1D5-hIgG4-LAGA-df-hIL-2 (T3A/D20A/R38E/C125A) HC	EVQLLESGGGLVQPGGSLRLSCVGSQFNFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDN SKNTLYLQMNSLRAEDTAVYCYAKYTRGSYFYDAMDVWGQGTITVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVFSSSLGTCTYTCNV DHKPSNTKVDKRVESKYGPPCPCPAPEFAGAPSVFLFPPKPKDTLMISRTPEVTCVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQP REPQVYITLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTV

	hIL-2 in italics	DKSRWQEGNVFSCVMHEALHNHYTQKSLSLSGKAPASSSTKKTLQLEHLLALQMIILNGINNYKNP KLTEMLTFKFYMPKKATELKHLCLEEEELKPLEEVNLQAQSKNFHLRPRDLISNINVIVLELKGSETTF MCEYADETATIVEFLNRWITFAQSIIISTLT
530	2H7-hIgG1-df- hIL-2 (T3A/D20A/R38E /C125A) HC hIL-2 in italics	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDN SKNTLYLQMN NLR AEDTAVYCAKYTRASYFYDAMD VWGGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKHTCCPPAPELGGPSVFLFPPKPKDITLMISRTPEVTCVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYITLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDSGSFFLYSK LTVDKSRWQQGNVFSCVMHEALHNHYTQKSLSLSPGKAPASSSTKKTLQLEHLLALQMIILNGINNY KNPKLTEM LTFKFYMPKKATELKHLCLEEEELKPLEEVNLQAQSKNFHLRPRDLISNINVIVLELKGSE TTFMCEYADETATIVEFLNRWITFAQSIIISTLT
531	2H7-hIgG1-LE- df-hIL-2 (T3A/D20A/R38E /C125A) HC hIL-2 in italics	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDN SKNTLYLQMN NLR AEDTAVYCAKYTRASYFYDAMD VWGGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKHTCCPPAPELGGPSVFLFPPKPKDITLMISRTPEVTCVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYITLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDSGSFFLYSK LTVDKSRWQQGNVFSCVMHEALHNHYTQKSLSLSPGKAPASSSTKKTLQLEHLLALQMIILNGINNY KNPKLTEM LTFKFYMPKKATELKHLCLEEEELKPLEEVNLQAQSKNFHLRPRDLISNINVIVLELKGSE TTFMCEYADETATIVEFLNRWITFAQSIIISTLT
532	H7-767 HC	EVQLLESGGGLVQPGGSLRLSCAASGFTFKSYAMHWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDN SKNTLYLQMN NLR AEDTAVYCAKYDRASYFYDAMD VWGGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKHTCCPPAPELAGAPSVFLFPPKPKDITLMISRTPEVTCVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYITLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDSGSFFLYSK LTVDKSRWQQGNVFSCVMHEALHNHYTQKSLSLSPGKAPASSSTKKTLQLEHLLALQMIILNGINNY KNPKLTEM LTFKFYMPKKATELKHLCLEEEELKPLEEVNLQAQSKNFHLRPRDLISNINVIVLELKGSE TTFMCEYADETATIVEFLNRWITFAQSIIISTLT
533	2H7-hIgG1-LE- df-hIL-2 (T3A/R38E/D84K /C125A) HC hIL-2 in italics	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDN SKNTLYLQMN NLR AEDTAVYCAKYTRASYFYDAMD VWGGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKHTCCPPAPELGGPSVFLFPPKPKDITLMISRTPEVTCVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYITLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDSGSFFLYSK LTVDKSRWQQGNVFSCVMHEALHNHYTQKSLSLSPGKAPASSSTKKTLQLEHLLALQMIILNGINNY

		<i>KNPKLTEMLTFFKPYMPKKATELKHQLQCLEELKPLEEVNLAQSKNFHLRPRKLISININVIVLELKGSE</i> <i>TTFMCEYADETATIVEFLNRWITFAQSIISTLT</i>
534	2H7-hIgG4-df-hIL-2 (T3A/R38E/D84K/C125A) HC hIL-2 in italics	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDN SKNTLYIQMNNLRAEDTAVYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVFPPSSSLGTQTYICNV DHKPSNTKVDKRVESKYGPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVDSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLTQHQLWNGKEYCKVSNKGLPSSIEKTI SKAKGQP REPQVYITLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCVMHEALHNHYTQKSLSLSPGKAPASSSTKKTKQLQLEHLLLDLQMLINGINNYKNP <i>KLTEMLTFFKPYMPKKATELKHQLQCLEELKPLEEVNLAQSKNFHLRPRKLISININVIVLELKGSETTF</i> <i>MCEYADETATIVEFLNRWITFAQSIISTLT</i>
535	2H7-hIgG1-df-hIL-2 (T3A/R38E/I92K/C125A) HC hIL-2 in italics	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDN SKNTLYIQMNNLRAEDTAVYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVFPPSSSLGTQTYICNV NHKPSNTKVDKRVESKYGPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVDSHEDP EVKFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLTQHQLWNGKEYCKVSNKALPAPIEKTI SKAK GQPREPQVYITLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSK LTVDKSRWQGNVFSCVMHEALHNHYTQKSLSLSPGKAPASSSTKKTKQLQLEHLLLDLQMLINGINNY <i>KNPKLTEMLTFFKPYMPKKATELKHQLQCLEELKPLEEVNLAQSKNFHLRPRDLISININVIVLELKGSE</i> <i>TTFMCEYADETATIVEFLNRWITFAQSIISTLT</i>
536	2H7-hIgG1-LE-df-hIL-2 (T3A/R38E/I92K/C125A) HC hIL-2 in italics	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDN SKNTLYIQMNNLRAEDTAVYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVFPPSSSLGTQTYICNV NHKPSNTKVDKRVESKYGPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVDSHEDP EVKFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLTQHQLWNGKEYCKVSNKALPAPIEKTI SKAK GQPREPQVYITLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSK LTVDKSRWQGNVFSCVMHEALHNHYTQKSLSLSPGKAPASSSTKKTKQLQLEHLLLDLQMLINGINNY <i>KNPKLTEMLTFFKPYMPKKATELKHQLQCLEELKPLEEVNLAQSKNFHLRPRDLISININVIVLELKGSE</i> <i>TTFMCEYADETATIVEFLNRWITFAQSIISTLT</i>
537	2H7-hIgG4-df-hIL-2 (T3A/R38E/I92K/C125A) HC hIL-2 in italics	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGGSTYYADSVKGRFT ISRDN SKNTLYIQMNNLRAEDTAVYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVFPPSSSLGTQTYICNV DHKPSNTKVDKRVESKYGPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVDSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLTQHQLWNGKEYCKVSNKGLPSSIEKTI SKAKGQP REPQVYITLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCVMHEALHNHYTQKSLSLSPGKAPASSSTKKTKQLQLEHLLLDLQMLINGINNYKNP

		<i>KLTEMLTFKFYMPKKA TELKHLOCLEEELKPLEEVNLAQSKNFHLRPRDLISININVKVLELKGSETTF</i> <i>MCEYADETATIVEFLNRWITFAQSIISTLT</i> EVQLLESGGGLVQPGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGSTYYADSVKGRFT I SRDNSKNTLYLQMNLRRAEDTAVYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVFPPKPKDTLMISRTPEVTCVVDVSHEDP NHKPSNTKVDKKVEPKSCDKHTCCPPAPELAGAPSVFLFPPKPKDTLMI SRTPEVTCVVDVSHEDP EVKENWYVDGVEVHNAKTKPRREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDSGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKAPASSSTKKTKQLQLEHLLLDLQMIILNGINNY <i>KNPKLTEMILTFKFYMPKKA TELKHLOCLEEELKPLEEVNLAQSKNFHLRPRDLISININVI VLELKGSE</i> <i>TTFMCEYADETATIVEFLNRWITFAQSIISTLT</i>
538	2H7-hIgG1- LAGA-df-hIL2 (T3A/D20S/R38E /C125A) HC hIL-2 in italics	EVQLLESGGGLVQPGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGSTYYADSVKGRFT I SRDNSKNTLYLQMNLRRAEDTAVYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVFPPKPKDTLMI SRTPEVTCVVDVSHEDP NHKPSNTKVDKKVEPKSCDKHTCCPPAPELAGAPSVFLFPPKPKDTLMI SRTPEVTCVVDVSHEDP EVKENWYVDGVEVHNAKTKPRREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDSGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKAPASSSTKKTKQLQLEHLLLDLQMIILNGINNY <i>KNPKLTEMILTFKFYMPKKA TELKHLOCLEEELKPLEEVNLAQSKNFHLRPRDLISININVI VLELKGSE</i> <i>TTFMCEYADETATIVEFLNRWITFAQSIISTLT</i>
539	2H7-hIgG1- LAGA-df-hIL2 (T3A/R38E/D84F /C125A) HC hIL-2 in italics	EVQLLESGGGLVQPGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGSTYYADSVKGRFT I SRDNSKNTLYLQMNLRRAEDTAVYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVFPPKPKDTLMI SRTPEVTCVVDVSHEDP NHKPSNTKVDKKVEPKSCDKHTCCPPAPELAGAPSVFLFPPKPKDTLMI SRTPEVTCVVDVSHEDP EVKENWYVDGVEVHNAKTKPRREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDSGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKAPASSSTKKTKQLQLEHLLLDLQMIILNGINNY <i>KNPKLTEMILTFKFYMPKKA TELKHLOCLEEELKPLEEVNLAQSKNFHLRPRDLISININVI VLELKGSE</i> <i>TTFMCEYADETATIVEFLNRWITFAQSIISTLT</i>
540	2H7-hIgG1- LAGA-df-hIL2 (T3A/R38E/I92R /C125A) HC hIL-2 in italics	EVQLLESGGGLVQPGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGSTYYADSVKGRFT I SRDNSKNTLYLQMNLRRAEDTAVYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVFPPKPKDTLMI SRTPEVTCVVDVSHEDP NHKPSNTKVDKKVEPKSCDKHTCCPPAPELAGAPSVFLFPPKPKDTLMI SRTPEVTCVVDVSHEDP EVKENWYVDGVEVHNAKTKPRREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDSGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKAPASSSTKKTKQLQLEHLLLDLQMIILNGINNY <i>KNPKLTEMILTFKFYMPKKA TELKHLOCLEEELKPLEEVNLAQSKNFHLRPRDLISININVI VLELKGSE</i> <i>TTFMCEYADETATIVEFLNRWITFAQSIISTLT</i>
541	2H7-hIgG1- LAGA-df-hIL2 (T3A/R38E/I92E /C125A) HC hIL-2 in italics	EVQLLESGGGLVQPGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGSTYYADSVKGRFT I SRDNSKNTLYLQMNLRRAEDTAVYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVFPPKPKDTLMI SRTPEVTCVVDVSHEDP NHKPSNTKVDKKVEPKSCDKHTCCPPAPELAGAPSVFLFPPKPKDTLMI SRTPEVTCVVDVSHEDP EVKENWYVDGVEVHNAKTKPRREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDSGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKAPASSSTKKTKQLQLEHLLLDLQMIILNGINNY

		KNPKLTEMILTFFKPYMPKKATELKHLOCLEEEELKPLEEVNLNLAQSKNFHLRPRDLISNINVEVLELKGSE TTFMCEYADETATIVEFNLNRWITFAQSIISTLT
542	2H7-hIgG1- LAGA-df-hIL2 (T3A/R38E/I92S /C125A) HC hIL-2 in italics	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGSTYYADSVKGRFT ISRDN SKNTLYLQMN NLR AEDTAVYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVFPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKHTCCPPAPELAGAPSVFLFPPKPKDTLMI SRTPEVTCVVDVSHEDP EVKENWYVDGVEVHNAKTKPRREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDSGSFFLYSK LTVDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLSPGKAPASSSTKKTKQLQLEHLLLDLQMLINGINNY KNPKLTEMILTFFKPYMPKKATELKHLOCLEEEELKPLEEVNLNLAQSKNFHLRPRDLISNINVEVLELKGSE TTFMCEYADETATIVEFNLNRWITFAQSIISTLT
543	2H7-hIgG1- LAGA-df-hIL2 (T3A/R38E/I92D /C125A) HC hIL-2 in italics	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGSTYYADSVKGRFT ISRDN SKNTLYLQMN NLR AEDTAVYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVFPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKHTCCPPAPELAGAPSVFLFPPKPKDTLMI SRTPEVTCVVDVSHEDP EVKENWYVDGVEVHNAKTKPRREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDSGSFFLYSK LTVDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLSPGKAPASSSTKKTKQLQLEHLLLDLQMLINGINNY KNPKLTEMILTFFKPYMPKKATELKHLOCLEEEELKPLEEVNLNLAQSKNFHLRPRDLISNINVEVLELKGSE TTFMCEYADETATIVEFNLNRWITFAQSIISTLT
544	2H7-hIgG1- LAGA-df-hIL2 (T3A/H16E/R38E /C125A) HC hIL-2 in italics	EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYCMTWVRQAPGKGLEWVSAIVYSGSTYYADSVKGRFT ISRDN SKNTLYLQMN NLR AEDTAVYCAKYTRASYFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVFPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKHTCCPPAPELAGAPSVFLFPPKPKDTLMI SRTPEVTCVVDVSHEDP EVKENWYVDGVEVHNAKTKPRREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDSGSFFLYSK LTVDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLSPGKAPASSSTKKTKQLQLEHLLLDLQMLINGINNY KNPKLTEMILTFFKPYMPKKATELKHLOCLEEEELKPLEEVNLNLAQSKNFHLRPRDLISNINVEVLELKGSE TTFMCEYADETATIVEFNLNRWITFAQSIISTLT
545	1H3-hIgG1-L6- hIL-2 (T3A/D20A/R38E /C125A) HC Linker in dashed underline	EVQLVESGGGLVQPGRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDN AKITLYLQMDSLRSEDATYICARHGSYFYDWQGQVMVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVFPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKHTCCPPAPELAGAPSVFLFPPKPKDTLMI SRTPEVTCVVDVSHEDPEVKFN WYVDGVEVHNAKTKPRREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDSGSFFLYSKLTVDK SRWQQGNVFSCSVMH EALHNHYTQKSLSLSPGKSGGGGSAPASSSTKKTKQLQLEHLLLDLQMLINGINNY

	hIL-2 in italics	YKNPKLT TEMLT FKFYMPKKATELKH LQCL EEELKPLEEVNL AQSKNFHLRPRDL ISNIN VIVLEL KGS ETTFMCEYADETAT IVEFLNRWIT FAQSIISTLT
546	1H3-hIgG1- LAGA-df-hIL-2 (T3A/D20A/R38E /C125A) HC	EVQLVESGGGLVQ GRSLK LSCAVSGFTTSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQ MDSLR SE DATYYCAR HGSGYFDYWGQGMVTVSSASTKGPSVFPLAPSSKSTSGG TAA LGCLVKDY FPEPVTVMNSGALTSGVHTFPAVLQSSGLYSLSSVTV VPSSSLGTQTY ICNVNHKPS NTKVDKKVEPKSCDK TH TPCPAP ELAGAP SFLFPKP DKDTLMI SRTPEVTCVVVDV SHEDPE VKEN WYVDGVEVHNAKTKPREEQ YNSTYRV SVLT VLV HQD WLNGKEY KCKVSNKALPAPIEKTI ISKAKGQ PRE PQVY TLPP SRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TT PPVLDSDGSFFLYSKLTVDK SRWQ QGNVF SCSMHEALHNHYTQKSLSLSPGKAPASS TKTQLQL LEHLL LALQML INGINNYKNPKL TEMLTFKYMPKKATELKH LQCL EEELKPLEEVNL AQSKNFHLRPRDL ISNIN VIVLEL KGSETTFMC EYADETAT IVEFLNRWIT FAQSIISTLT
547	C51E6-5- hIgG4/k-LE HC	QVQLVQSGSE L KKPGASVKVSCKASGYSLYGTSMHWVRQAPGQGLEWMGYISPTFTGRATYAQ GTGRFV FSLDTSVSTAYLQISSLKAEDTAVYYCARDYD RYYY AMDYWGQ TTVT VSSASTKGPSVFPLAPCSRS TSESTAALGCLVKDYFPEPVTVMNSGALTSGVHTFPAVLQSSGLYSLSSVTV VPSSSLGT KTYTCNVD HKPSNTKVDKRVESKYGPPCPAPEFEGGSPSF FLFPKP DKDTLMI SRTPEVTCVVVDV SQEDPEVQF NWYVDGVEVHNAKTKPREEQ FNSTYRV SVLT VLV HQD WLNGKEY KCKVSNKGLPSSIEKTI ISKAKGQ PR EPQVY TLPP SQEE MTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYK TT PPVLDSDGSFFLYSRLTVD KSRWQEGNVFSCSMHEALHNHYTQKSLSLSLG
548	C51E6-5- hIgG4/k-LAGA HC	QVQLVQSGSE L KKPGASVKVSCKASGYSLYGTSMHWVRQAPGQGLEWMGYISPTFTGRATYAQ GTGRFV FSLDTSVSTAYLQISSLKAEDTAVYYCARDYD RYYY AMDYWGQ TTVT VSSASTKGPSVFPLAPCSRS TSESTAALGCLVKDYFPEPVTVMNSGALTSGVHTFPAVLQSSGLYSLSSVTV VPSSSLGT KTYTCNVD HKPSNTKVDKRVESKYGPPCPAPEFAGAPSV FLFPKP DKDTLMI SRTPEVTCVVVDV SQEDPEVQF NWYVDGVEVHNAKTKPREEQ FNSTYRV SVLT VLV HQD WLNGKEY KCKVSNKGLPSSIEKTI ISKAKGQ PR EPQVY TLPP SQEE MTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYK TT PPVLDSDGSFFLYSRLTVD KSRWQEGNVFSCSMHEALHNHYTQKSLSLSLG
549	C51E6-5- hIgG4/k-LEPG HC	QVQLVQSGSE L KKPGASVKVSCKASGYSLYGTSMHWVRQAPGQGLEWMGYISPTFTGRATYAQ GTGRFV FSLDTSVSTAYLQISSLKAEDTAVYYCARDYD RYYY AMDYWGQ TTVT VSSASTKGPSVFPLAPCSRS TSESTAALGCLVKDYFPEPVTVMNSGALTSGVHTFPAVLQSSGLYSLSSVTV VPSSSLGT KTYTCNVD HKPSNTKVDKRVESKYGPPCPAPEFEGGSPSF FLFPKP DKDTLMI SRTPEVTCVVVDV SQEDPEVQF NWYVDGVEVHNAKTKPREEQ FNSTYRV SVLT VLV HQD WLNGKEY KCKVSNKGLGSSIEKTI ISKAKGQ PR EPQVY TLPP SQEE MTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYK TT PPVLDSDGSFFLYSRLTVD KSRWQEGNVFSCSMHEALHNHYTQKSLSLSLG
550	C51E6-5- hIgG4/k-df- hIL-2	QVQLVQSGSE L KKPGASVKVSCKASGYSLYGTSMHWVRQAPGQGLEWMGYISPTFTGRATYAQ GTGRFV FSLDTSVSTAYLQISSLKAEDTAVYYCARDYD RYYY AMDYWGQ TTVT VSSASTKGPSVFPLAPCSRS TSESTAALGCLVKDYFPEPVTVMNSGALTSGVHTFPAVLQSSGLYSLSSVTV VPSSSLGT KTYTCNVD HKPSNTKVDKRVESKYGPPCPAPEFLGGSPSF FLFPKP DKDTLMI SRTPEVTCVVVDV SQEDPEVQF

	(T3A/D20A/R38E /C125A) HC hIL-2 in italics	NWYVDGVEVHNAKTKPREEQNFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPR EPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVD KSRWQEGNVFSCSVMHAEALHNHYTQKSLSLGLKAPASSSTKTKTQLEHLLALLQMLINGINNYKNPK LTEMLETKFYMPPKKA TELKHLQCLEEEELKPLEEVNLAQSKNFHLRPRDLISININVLVLELKGSETTFM CEYADETATIVEFLNRWITFAQSIISTLT
551	C51E6-5- hIgG4/k-LEPG- hIL-2 (T3A/D20A/R38E /C125A) HC hIL-2 in italics	QVQLVQSGSELKPKGASVKVCKASKASYSLYGTSMHWVRQAPGQGLEWVMGYISPTFTGRATYAQGTGRFV FSLDTISVSTAYLQISSLKAEDTAVYCYARDYRYYYAMDYWGQTTVTTVSSASTKGPSVFPLAPCSR TSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTKTYTCNV HKPSNTKVDKRVESKYGPPCPAPAFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF NWYVDGVEVHNAKTKPREEQNFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLGSSIEKTIISKAKGQPR EPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTV KSRWQEGNVFSCSVMHAEALHNHYTQKSLSLGLKAPASSSTKTKTQLEHLLALLQMLINGINNYKNPK LTEMLETKFYMPPKKA TELKHLQCLEEEELKPLEEVNLAQSKNFHLRPRDLISININVLVLELKGSETTFM CEYADETATIVEFLNRWITFAQSIISTLT
552	A2-hIgG4/k-LE HC	DVQLVESGGGLVQPGGSLRLSCAASGFTFDISAMSWVRQAPGKGLEWVSTISGSAYSTYYADSVKGRFT ISRDNLSKSTLYLQMNLSRAEDTAVYCYAREIFSDYWGGLGLTVTVSSASTKGPSVFPLAPCSRSTSE ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTKTYTCNV KVDKRVESKYGPPCPAPAFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQNFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQVY LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQ E GNVFSCSVMHAEALHNHYTQKSLSLSLG
553	A2-hIgG4/k- LAGA HC	DVQLVESGGGLVQPGGSLRLSCAASGFTFDISAMSWVRQAPGKGLEWVSTISGSAYSTYYADSVKGRFT ISRDNLSKSTLYLQMNLSRAEDTAVYCYAREIFSDYWGGLGLTVTVSSASTKGPSVFPLAPCSRSTSE ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTKTYTCNV KVDKRVESKYGPPCPAPAFAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQNFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQVY LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQ E GNVFSCSVMHAEALHNHYTQKSLSLSLG
554	A2-hIgG4/k- LEPG HC	DVQLVESGGGLVQPGGSLRLSCAASGFTFDISAMSWVRQAPGKGLEWVSTISGSAYSTYYADSVKGRFT ISRDNLSKSTLYLQMNLSRAEDTAVYCYAREIFSDYWGGLGLTVTVSSASTKGPSVFPLAPCSRSTSE ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTKTYTCNV KVDKRVESKYGPPCPAPAFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQNFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLGSSIEKTIISKAKGQPREPQVY LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQ E GNVFSCSVMHAEALHNHYTQKSLSLSLG
555	A2-hIgG4/k-df- hIL-2	DVQLVESGGGLVQPGGSLRLSCAASGFTFDISAMSWVRQAPGKGLEWVSTISGSAYSTYYADSVKGRFT ISRDNLSKSTLYLQMNLSRAEDTAVYCYAREIFSDYWGGLGLTVTVSSASTKGPSVFPLAPCSRSTSE

	(T3A/D20A/R38E /C125A) HC hIL-2 in italics	ALGCLVKDYFPEPVTVMNSGALTSGVHTTTPAVLQSSGLYSLSSVTVFPSSSLGTKTYTCNVVDHKPSNT KVDKRVESKYGPPCPPEFPGPSVFLFPPKPKDTLMISRTPEVTCVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQVYIT LPDSQEMTNKVLSLTLCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE GNVFSCVMHEALHNHYTQKSLSLGLKAPASSTKKTQLEHLLALLQMLINGINNYKNPKLITEMLT FKFYMPKKA TELKHLCLEEEELKPLEEVNLQAQSKNFHLRPRDLISININVIIVLELKGSETTFMCEYADE TATIVEFLNRWITFAQSIISTLT
556	A2-hIgG4/k-LE- df-hIL-2 (T3A/D20A/R38E /C125A) HC hIL-2 in italics	DVQLVESGGGLVQPGGSLRLSCAASGFTTFDI SAMSVMWRQAPGKGLEWVSTISGSAYSTYYADSVKGRFT ISRDNKSTLYLQMNSLRAEDTAVYYCAREIFSDYWGGLTGLTVTVSSASTKGPSVFLAPCSRSTSESTA ALGCLVKDYFPEPVTVMNSGALTSGVHTTTPAVLQSSGLYSLSSVTVFPSSSLGTKTYTCNVVDHKPSNT KVDKRVESKYGPPCPPEFPGPSVFLFPPKPKDTLMISRTPEVTCVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQVYIT LPDSQEMTNKVLSLTLCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE GNVFSCVMHEALHNHYTQKSLSLGLKAPASSTKKTQLEHLLALLQMLINGINNYKNPKLITEMLT FKFYMPKKA TELKHLCLEEEELKPLEEVNLQAQSKNFHLRPRDLISININVIIVLELKGSETTFMCEYADE TATIVEFLNRWITFAQSIISTLT
557	A2-hIgG4/k- LAGA-df-hIL-2 (T3A/D20A/R38E /C125A) HC hIL-2 in italics	DVQLVESGGGLVQPGGSLRLSCAASGFTTFDI SAMSVMWRQAPGKGLEWVSTISGSAYSTYYADSVKGRFT ISRDNKSTLYLQMNSLRAEDTAVYYCAREIFSDYWGGLTGLTVTVSSASTKGPSVFLAPCSRSTSESTA ALGCLVKDYFPEPVTVMNSGALTSGVHTTTPAVLQSSGLYSLSSVTVFPSSSLGTKTYTCNVVDHKPSNT KVDKRVESKYGPPCPPEFPGAPSVFLFPPKPKDTLMISRTPEVTCVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQVYIT LPDSQEMTNKVLSLTLCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE GNVFSCVMHEALHNHYTQKSLSLGLKAPASSTKKTQLEHLLALLQMLINGINNYKNPKLITEMLT FKFYMPKKA TELKHLCLEEEELKPLEEVNLQAQSKNFHLRPRDLISININVIIVLELKGSETTFMCEYADE TATIVEFLNRWITFAQSIISTLT
558	A2-hIgG4/k- LEPG-df-hIL-2 (T3A/D20A/R38E /C125A) HC hIL-2 in italics	DVQLVESGGGLVQPGGSLRLSCAASGFTTFDI SAMSVMWRQAPGKGLEWVSTISGSAYSTYYADSVKGRFT ISRDNKSTLYLQMNSLRAEDTAVYYCAREIFSDYWGGLTGLTVTVSSASTKGPSVFLAPCSRSTSESTA ALGCLVKDYFPEPVTVMNSGALTSGVHTTTPAVLQSSGLYSLSSVTVFPSSSLGTKTYTCNVVDHKPSNT KVDKRVESKYGPPCPPEFPGPSVFLFPPKPKDTLMISRTPEVTCVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLGSSIEKTIISKAKGQPREPQVYIT LPDSQEMTNKVLSLTLCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE GNVFSCVMHEALHNHYTQKSLSLGLKAPASSTKKTQLEHLLALLQMLINGINNYKNPKLITEMLT FKFYMPKKA TELKHLCLEEEELKPLEEVNLQAQSKNFHLRPRDLISININVIIVLELKGSETTFMCEYADE TATIVEFLNRWITFAQSIISTLT
559	Anti-hPD-1 #1 HC	QVQLVESGGGVQVQPGSRSLRLDCKASGITFSNSGMHWWRQAPGKGLEWAVIWIYDGSKRYIYADSVKGRFT ISRDNKNTLFLQMNSLRAEDTAVYYCATNDYWGQGLTVTVSSASTKGPSVFLAPCSRSTSESTAAL GCLVKDYFPEPVTVMNSGALTSGVHTTTPAVLQSSGLYSLSSVTVFPSSSLGTKTYTCNVVDHKPSNTKV

		DKRVE\$KYGPPPCPPAPEFLGGPSVFLFPPKPKDITLMI\$RTPEVTCVVVDVSDQEDPEVQFNWYVDGVE VHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI\$KAKGQPREPQVYITLP PSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFFLY\$RLTIVDKSRWQEGN VFSC\$VMHEALHNHYTQKSLSL\$LG
560	Anti-CD20- hIgG1/k HC	QVQLQQPGAELVKPGASVKMSCKASGYTFTSYNMHWVKQTPGRGLEWIGAIYPGN\$GDTSYNQKFKGKAT LTADKSSSTAYMQLSSLTSEDSAVYYCARSTYYGGDWYFNVWGAGTTVTV\$AASTKGPSVFPLAPSSKS TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL\$SVVTVFSSSLGTQTYICNVN HKPSNTKVDKKVEPKSCDKTHTCPPCPAPELGGPSVFLFPPKPKDITLMI\$RTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV\$SNKALPAPIEKTISKAKG QPREPQVYITLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFFLY\$SKL TVDKSRWQQGNVFSC\$VMHEALHNHYTQKSLSL\$SPGK
561	Anti-CD20- hIgG1/k-IAGA HC	QVQLQQPGAELVKPGASVKMSCKASGYTFTSYNMHWVKQTPGRGLEWIGAIYPGN\$GDTSYNQKFKGKAT LTADKSSSTAYMQLSSLTSEDSAVYYCARSTYYGGDWYFNVWGAGTTVTV\$AASTKGPSVFPLAPSSKS TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL\$SVVTVFSSSLGTQTYICNVN HKPSNTKVDKKVEPKSCDKTHTCPPCPAPELAGAPSVFLFPPKPKDITLMI\$RTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV\$SNKALPAPIEKTISKAKG QPREPQVYITLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFFLY\$SKL TVDKSRWQQGNVFSC\$VMHEALHNHYTQKSLSL\$SPG
562	Anti-CD20- hKappa LC	QIVLSQSPAIL\$ASPGEKVITTCRASSSVSYIHW\$FQQKPGSSPKPWIYAT\$NLASGVPVRFSGSGSGTS YSLTISRVEAEADAATYYCQQWTSNPPTFGG\$TKLEIKRTVAAPSVFIFPP\$DEQLKSGTASVVCCLLNFE YP\$REAKVQWKVDNALQSGNSQESVTEQ\$DKSDSTYSL\$STLTLSKADY\$EKHKVYACEVTHQ\$GLSSPVTKS FNRGEC
563	1H3-hIgG1- LAGA-df-hIL-2 (T3A/C125A) HC hIL-2 in italics	EVQLVESGGGLVQPG\$RLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYD\$SRITYYRDSVKGRFT ISRDNAKITLYLQMD\$SLRSEDATYYCARHSGSYFDYWGQGVMTVSSASTKGPSVFPLAPSSK\$TSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL\$SVVTVFSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELAGAPSVFLFPPKPKDITLMI\$RTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV\$SNKALPAPIEKTISKAKGQPRE PQVYITLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFFLY\$SKLTVDK SRWQQGNVFSC\$VMHEALHNHYTQKSLSL\$SPGKAPASS\$TKTQL\$LEHLLLDLQ\$MILNGINNYKNPKL TRMLT\$FKFMPKKATEL\$KHLQCL\$EELKPLEEVNLAQ\$KNFHLRPRDLISINIVL\$ELK\$SETTFMC EYADETATIV\$EFLNRWITFAQ\$SIITLT
564	anti-mPD-1 RMP1-14 mIgG2b-N297A HC	EVQLQESGPGLVKPSQ\$SLTFC\$SVTGY\$ITSSYRWNIWRKFP\$GNRLEW\$MGYINSAGISNYP\$SLKRRIS ITRDT\$KNQFFLQVNSVTTEDATYYCARSDNMGITTPTYWGQGT\$LVTVSSAKITTPSVYPLAPGCGDT TGSSVTLGCLVKGYFPE\$SVTVTWNSG\$LS\$SSVHTFPALLQ\$GLYTMS\$SSVTVPS\$STWPSQT\$VTC\$VAHP AS\$T\$TVDK\$KLEPSGPI\$TINPCPCKECK\$KCPAPNLEGGPSVFIFPPNIKDVLMI\$SLTPKVT\$CVVVDVS EDDPDVQ\$ISW\$FVNNEVHTAQ\$TQTHREDYASTIRVV\$STLPIQH\$QDWM\$SGKEFKCKVNNKDL\$PSP\$IER\$T\$I

		SKI KGLVRAPQVY ILPPPAEQLSRKDVSLTCLVVGFPNGDISVEWTSNGHTEENYKDTAPVLDS DGSYF IYSKLNMTSKWEKTD SFSCNVRHEGLKNYYLKKTISRSPGK
565	anti-mPD-1 RMP1-14 mIgG2b-N297A- L6-hIL-2 (F42K/Y45R/V69 R) HC linker in dashed underline hIL-2 in italics	EVQLQESGPGLVKPSQSLSLTCSVTGYSTSSYRWNIWKFPNGRLEWMGYINSAGISNYPNPSLKRRI S ITRDTSKNQFFLQVNSVTTEDAATYYCARSDNMGTTPFTYWGQGLTVTVSSAKTTPPSVYPLAPGCGDT TGSSVTIGCLVKGYFPESVTVTWNSGSLSSSVHTFPALLQSGLYTMSSSVTVPSSTWPSQTVTCSVAHP ASSTTVDDKKLEPSGPISTINPCPCKECHKCPAPNLEGPSVFI FPPNIKDVLMI SLTPKVT CVVVDVS EDDPDVQISW FVNNVEVHTAQTHREDYASTIRVVSTLPIQH QDWMGKEFKCKVNNKDLPSPIERTI SKI KGLVRAPQVY ILPPPAEQLSRKDVSLTCLVVGFPNGDISVEWTSNGHTEENYKDTAPVLDS DGSYF IYSKLNMTSKWEKTD SFSCNVRHEGLKNYYLKKTISRSPKSGGGGSA PTSSSTKKTLQLEHLLLDL QMLINGINNYKNPKLTRMLTKKFRMPKKATELKHLCLEELKPLEERLNLAQSKNPHLRPRDLISNIN VIVLELKGSETTEMCEYADETATIVEFNLRWITFCQSIISTLT
566	anti-mPD-1 RMP1-14 mKappa LC	DIVMTQGTLPNPVPSGESVSTCRSSKSLLYSDGKTYLNWYLQRPQSPQLLIYWMSTRASGVSDRFSG SGSGTDFTLKISGVEAEDVGIY CQQGLEFPTFGGKTLELKRADAAPT VSI FPPSSEQLTSGGASVVC FLNFPK DINVKWKIDGSE RQNGVLNSWTDQDSKDSY SMSSTLT LT KDEYERHNSYTC EATHKTS PIVKS FNRNEC
567	anti-mPD-1 RMP1-30 mIgG2b-N297A HC	EVQLVESGGGLVQPGRSLKLSCAASGFTFGDYSMAWVRQAPKRGLEWVANI IYDGSRTFYRDSVKGRFT ISRDNAKPTLYLQMDSLRPEDATY YCATHNYPGYAMEAWGQGSTVTVSSAKTTPPSVYPLAPGCGDTT GSSVTIGCLVKGYFPESVTVTWNSGSLSSSVHTFPALLQSGLYTMSSSVTVPSSTWPSQTVTCSVAHPA SSTTVDDKKLEPSGPISTINPCPCKECHKCPAPNLEGPSVFI FPPNIKDVLMI SLTPKVT CVVVDVSE DDPDVQISW FVNNVEVHTAQTHREDYASTIRVVSTLPIQH QDWMGKEFKCKVNNKDLPSPIERTIS KI KGLVRAPQVY ILPPPAEQLSRKDVSLTCLVVGFPNGDISVEWTSNGHTEENYKDTAPVLDS DGSYFI YSKLNMTSKWEKTD SFSCNVRHEGLKNYYLKKTISRSPGK
568	anti-mPD-1 RMP1-30 mKappa LC	DTVLTQSPALPVS LGQRVNI SCRATKSVSRYVHWYQQKSGQQPRLLIYTTSNLESGVPSPRFSGSGGTD FTLTIDPVEADDIANYYCQQSNEIPYTFGAGTKLELKRADAAPT VSI FPPSSEQLTSGGASVVCFLNPF YPKDINVKWKIDGSE RQNGVLNSWTDQDSKDSY SMSSTLT LT KDEYERHNSYTC EATHKTSPIVKS FNRNEC
569	anti-mPD-1 RMP1-30 mIgG2b-N297A- L6-hIL-2 (F42K/Y45R/V69 R) HC	EVQLVESGGGLVQPGRSLKLSCAASGFTFGDYSMAWVRQAPKRGLEWVANI IYDGSRTFYRDSVKGRFT ISRDNAKPTLYLQMDSLRPEDATY YCATHNYPGYAMEAWGQGSTVTVSSAKTTPPSVYPLAPGCGDTT GSSVTIGCLVKGYFPESVTVTWNSGSLSSSVHTFPALLQSGLYTMSSSVTVPSSTWPSQTVTCSVAHPA SSTTVDDKKLEPSGPISTINPCPCKECHKCPAPNLEGPSVFI FPPNIKDVLMI SLTPKVT CVVVDVSE DDPDVQISW FVNNVEVHTAQTHREDYASTIRVVSTLPIQH QDWMGKEFKCKVNNKDLPSPIERTIS KI KGLVRAPQVY ILPPPAEQLSRKDVSLTCLVVGFPNGDISVEWTSNGHTEENYKDTAPVLDS DGSYFI YSKLNMTSKWEKTD SFSCNVRHEGLKNYYLKKTISRSPKSGGGGSA PTSSSTKKTLQLEHLLLDLQ

	linker in dashed underline hIL-2 in italics	MILNGINNYKNPKLTRMLTKKFMPPKKATELKHLCLEELKPLEErLNLAQSKNFHLRPRDLISNINV IVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
570	anti-KLH-C3- mIgG2b-N297A- L6-hIL-2 (F42K/Y45R/V69 R) HC linker in dashed underline hIL-2 in italics	EVQLVSGGGGLVQPGGSLKLSCAASGFTFSDFYMAWRQAPTKGLEWVASISTGGGNTHYRDSVKGRFT ISRDNASTLYLQMDSLRSEETATYYCARLLSTISTPFDYWQGVIVTVSSAKTTPPSVYPLAPGCGDT TGSSVTLGCLVKGYFPESTVTWNSGSLSSSVHTFPALLQSLGYTMSSTVTPSSTWPSQTVTCSVAHP ASSTVVDKKLEPSGPISTINCPCKECKCPAPNLEGPVSFIFPPNIKDVLMIISLTPKVTCVVVDVS EDDPDVQISWVFNNEVHTAQTHREDYASTIRVVSITLPIQHQDMMSGKEFKCKVNNKDLPSPIERTI SKIKGLVRAPQVYILPPPAEQLSRKDVSLTCLVGFNPGDISVEWTSNGHTEENYKDTAPVLDSDGSYF IYSKLNMTSKWEKTDSCNVRHEGLKNYYLKKTISRSPKSGGGGSAPTSSSTKKTKQLQLEHLLLDL QMI L N G I N N Y K N P K L T R M L T K K F M P P K K A T E L K H L Q C L E E L K P L E E r L N L A Q S K N F H L R P R D L I S N I N V I V L E L K G S E T T F M C E Y A D E T A T I V E F L N R W I T F C Q S I I S T L T
571	KLH-C3-mKappa LC	DVVLIQSPITLTVTPGETVLSLRASHSVGTNLHWYQQRTNESPSLLIKYSSHSSTGIPSRFSATGSGT DFTLNISNVEFDDVASYFCQQSQKWPLTFGSGTKLEIKRADAAPTVSIFPPSSEQLTSGGASVVCFLNN FYPKDINVVKWKIDGSEKQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCSEATHKSTSTSPIVK SFNRNEC
572	2D12-hIgG1-L6- hIL-2 HC linker in dashed underline hIL-2 in italics	EVQLQSSGPGLVKPGASVKISCKTSGYTFTEYTMHWKQSHGKSLEWIGGINPNNGGTTYNQKFKGKAT LTVDKSSSTAYMELRSLTSQDSAVYCARDYRYRGHYAMDYWGQGTSVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPTVTSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKHTCCPAPPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI SKAK GQPREPQVYITLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPEVLDSDGSEFFLYSK LTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGKSGGGGSAPTSSSTKKTKQLQLEHLLLDLQMI L N G I N N Y K N P K L T R M L T K K F M P P K K A T E L K H L Q C L E E L K P L E E r L N L A Q S K N F H L R P R D L I S N I N V I V L E L K G S E T T F M C E Y A D E T A T I V E F L N R W I T F C Q S I I S T L T
573	2D12-hkappa LC	QIVLTQSPA IMSASPEKVTMTCSVSSSVRFMHWYQQKSGTSPKRWIYDTSKLASGVPARFSGSGSGTS YSLTISSEAEADAATYYCQQWSSNPPTFGGGTKLKIKKTVAAPSVFI FPPSDEQLKSGTASVVCLLNMF YPREAKVQWKVDNALQSGNSQESVTEQDSKDSITYSLSSITLTLSKADY EKHKVYACEVTHQGLSSPVTKS FNRGEC
574	hIL-2 F42A/Y45A/L72G	APTSSSTKKTKQLQLEHLLLDLQMLNGINNYKNPKLTRMLT AKF AMPKKATELKHLCLEELKPLEEV LN G AQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT

575	hIL-2 H16A/F42A	APTSSTKKTLQLEALLLDLQMLINGINNYKNPKLTRMLTAKFYMPKKATELKHLQCLEEELKPLEEV LNLAQSKNHLRPDLISININIVLELKGSETTFMCEYADETATIVFELNRWITFCQSIISTLT
576	1H9-hIgG4 HC	EVQLLESGGGLVQPGGSLRLSCVSGGFNLKDYCMTWVRAQPGKGLEWVSAIVYSGSTYYADSVKGRFT ISRDNKNTLYLQMNSLRAEDAVYYCAKYTRGSYFYDAMDVWGQTTVTYSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTTKTYTCNV DHKPSNTKVDKRVESKYGPPCPAPEFLGGPSVFLFPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIKAKGQP REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDSGSFFLYSRLTV DKSRWQEGNVFSCVMHEALHNHYTQKSLSLGLG
577	1D5-hIgG4 HC	EVQLLESGGGLVQPGGSLRLSCVSGGFNLKDYCMTWVRAQPGKGLEWVSAIVYSGSTYYADSVKGRFT ISRDNKNTLYLQMNSLRAEDAVYYCAKYTRGSYFYDAMDVWGQTTVTYSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTTKTYTCNV DHKPSNTKVDKRVESKYGPPCPAPEFLGGPSVFLFPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIKAKGQP REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDSGSFFLYSRLTV DKSRWQEGNVFSCVMHEALHNHYTQKSLSLGLG
578	Anti-hPD-1 #2 HC	QVQLVQSGVEVKKPGASVKVSKASGYFTFTNYYMWVRAQPGQGLEWMGGINPSNGGTNFEKFKNRVT LTTDSTTTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWQGTTVTVSSASTKGPSVFPLAPCSRST SESTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTTKTYTCNV KPSNTKVDKRVESKYGPPCPAPEFLGGPSVFLFPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFN WYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIKAKGQPRE PQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDSGSFFLYSRLTVDK SRWQEGNVFSCVMHEALHNHYTQKSLSLGLG
579	Anti-hPD-1 #2 LC	EIVLTQSPATLSLSPGERATLSCRASKGVSTSGYSYLHWYQQKPGQAPRLLIYLASYLESQVPAFSGS GSGTDFTLT ISSLEPEDFAVYYCQHSRDPLPTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSITYSLSSLTLSKADYEEKHKVYACEVTHQGLSS PVTKSFNRGEC
580	human PD-1 receptor lentiviral vector	gtcgacggatcgggagatctccgatcccatgtggtgacatctcagtagtaaatctgctctgatgccgcat agttaagccagtatctgctccctgctgtgtgtggaggtcgctgagtagtcgcgagcaaaatttaag ctacaacaaggcaagcttgaccgacaaattgcatgaagaatctgcttagggtagcggttttgcgctgc ttcgcgatgtacggccagatatacgcttgacattgattgactagttattagtagtaataatcaatta cgggtcattagttcatagccatataatggaggtccggttacataaactacgtagtaaatgccccgctg gctgacgcgccccagacccccccattgacgtcaaatagcagtagtatttccccatagtaaacgcaatag ggactttccattgacgtcaatgggtggagtatttacggtaaactgccacttggcagtagcatcaagtgt atcatatgccaaagtacgccccctattgacgtcaatgacggtaaatgccccgctggcattatgcccagt acatgaccttatgggactttccctacttggcagtagatcacgtattgctacgtcgtattaccatggtga tcgggttttggcagtagcatcaatggcggtggatagcggttgactcacggtgatttcccaagtctccacc

	ccattgacgtcaatgggagtttgggttttggcaccacaaatcaacgggactttccaaaatgctgtaacaact ccgcccattgacgcaaatggcggttaggcgtgtacggtgggaggtctatatagaagcgcggttttggcc tgtactgggtctctctggttagaccagatctgagcctgggagctctctggtaactagggaaacccactg cttaagcctcaataaagcttgcttgagtgcttcaagtagtggtgcccgtctgttggtgtagctctggt aactagagatccctcagacccttttagtcagtggtgaaatctctagcagtggtgcccgaacaggact tgaaagcgaagggaaccagaggagctctctgacgaggactcggttgctgaagcgcacggcaa gaggcgaggggcgagcttggttagtacgcccacaaattttgactagcggaggttagaaggagagatg ggtgcgagagcgtcagttattaaagcgggagaaattagatcgcgatgggaaaaaattcggttaaggccag ggggaagaaaaaataataattaaaacatatagtagggcaagcagcagtagaagcagattcgagttta atcctggcctgttagaaacatcagaaggctgtagacaaatactggacagctacacccatcccttcaga caggatcagaagaacttagatcattatataataatcagtagcaacccctctattgtgcatcaaggatag agataaaagacacccaaggaagctttagacaagatagaggaaagacaaaacaaaagtaagaccaccgcac agcaagcggccgctgatcttcagaccctggaggagagatagagggaacaattggagaagtgaattatat aaataaaagttagtaaaaattgaaccattaggagtagcaccacccaaggcacaagagaagagtggtgcag agagaaaaagagcagtggaataggagcttcttcttgggttcttgggagcagcaggaagcactatg ggcgagcgtcaatgacgtgacggttacaggccagacaattattgtctggtatagtgacgacgagaac aatttgctgagggtctattgagcgcaacagcatctgttgcaactcacagctcctgggcatcaagcagctc caggcaagaatcctggctgtgaaagatacctaaaggtcaacagctcctggggttggggttgcctct ggaaaaactcattgcaccactgctgtgcttggaatgctagttggagtaataaatctctggaacagatt tggaatcacacgacctggatggagtggaagagaaatgaacaaatcacacaagcttaatacactcctta attgaagaatcgaaaaccagcaagaaagaatgaacaaagaattattggaattagataaaatgggcaagt ttgtggaattggtttaacataacaaaattggctggtgatatataaaattattcataatgtagtaggagc ttggtaggtttaagaatagtttttctgctgacttctctatagtgatagagtaggaggtgatatccca ttatcgtttcagaccaccccccaccccgaggggaccgcagagcccgaaagggaatagaagaagaggt ggagagagacagagacagatccattcgattagtgacggatcggcactgctggtgccaattctgcag acaaatggcagtatccatcccaattttaaaagaaaagggggttgggggtacagtgaggggaaag aatagtagacataaatagcaacagacatacaaaactaaagaattacaaaaacaaaattcaaaaa ttttcggtttattacagggacagcagagatccagtttggttaattaaagtaattcgtagtaggtctt gaaaggagtgggaattggctccggtgccgtcagtgggcagagcgacatgccacagtccccgagaa gttggggggagggtcgcaattgatccggtgcctagagaagtggtgctgggggttaactgggaaagtga tgtcgtgtagtggctccgcttttcccgagggtggggagaaaccgtatataagtgtagtagtgcggt gaacgttcttttcgcaacgggttgccgcagaaacacagcagcgttctagagcgtgccaccatgca gatccacagggccctggccagtgctgtggcggtgtcacaaactgggtggcgccaggtggttctt agactcccagacagggccctggaacccccccaccttccccagccctgctcgtggtgaccgaaggga caacgcaccttcacctgcagcttctccacacatcgagagcttctgctaaactggtaccgcagtag ccccagcaaccagagacagtgccgcttccccaggaccgagcagccggccaggtgactgccc cttcggtgtcacacaactgcccaacggcgctgacttccacatgagcgtggtcagggcccgccgaatga

	cagcggcaacctacctgtgtggggccatctccctggcccccaaggcgagatcaaaagagagcctgcgggc agagctcagggtgacagagagaaggcgagaaagtgcacacagccccacccagccccctcaccagggccagc cgccaggtccaaaacctgggtgtgtgtcgtggcgccgtgctggcgagcctggtgctgtagtctg ggtcctggcgtcatctgctccggcgccgacagagggacaataaggagccagcgccagccagccccct gaaggaggacccctcagccgtgctgtctctgttgactatgggagctggattccagtgcgaga gaagacccggagcccccgctgcccgtgtccctgagcagcggagtgcacccattgtcttccctag cggaatgggcaacctcatcccgcgcgcgagggctagctgacggcctggagtgccagccactgag gcctaggatggacactgctcttggccccctgagccccctcctcccccccccaacgttactggcc gaagccgcttgaataaggccggtgtcgtttgtctatatgtatttccaccatatggccgtcttttg gcaatgtgagggcccgaaacctggccctgtctcttgacgagcattcctaggggtcttccccctcgc ccaaagggaatgcaaggtctgtgaatgtcgtgaaggagcagttcctctggaagctcttgaagacaaa caacgtctgtagcagacctttgcaggcagcggaacccccccacccctggcagacgtcctctcgggccaaa agccacgtgtataagatacacctgcaaaaggcggcacaaacccacgtgccagtttgagtgagtagttg tggaagagtc aaatggctcctcotaagcgtattcaacaaggggctgaaggatgccagaaggtacccc attgtatgggatctgatctggggcctcgtgcacatgctttacatgtgttagtgaggttaaaaaaac gtctagggccccccgaaccacgggacgtggttttcttgaaaaaacacagatgataatatggccacaatg accagttacaaagccacggtggcctcgccaccccgacgagcgtccccagggccgtacgcacccctgcgc gcccgttcgacgactaccccgccacgcgcacacccgtcgatcggacccacacatcgagcgggtcacc gagctcaagaactcttctcacgcgcgtcgggctcgacatcggcaaggtgtgggtcgcggacgagcgc gcccgtggcgtctggaacacgcggagagcgtcgagcggggggcgtgttcgocgagatcggccgcg cgcatggccgagttgagcgttcccggtcggcgcgacgacacagatggaaggcctcctggcgccgac cgcccaaggagcccggtgttctggccacccgtcgaggtctcgcccgacacccagggcaagggtctg ggcagcgccgtcgtgctccccgagtgaggcgccgagcgcggggtcccgccttccctggagacc tccgcgccccgcaacctccctctacgagcggctcgggttaccgtcacccgcgacgtcgaggtgcc gaaggacgcgcacctggtgcatgacccgcaagcccggtgcctgaacggttaagtgcacaatcaacct ctggaatacaaaaatttgtgaagattgactggtattcttaactatgttgcctctttacgctatgtga tacgtgctttaatgcctttgtatcatgctattgcttcccgatggcttccatttctcctcctgtat aaatccctggtgctgctcttttatgaggagtgtggcccggtgtcaggcaacgtggcgtggtgcact gtgttgctgacgcaacccccactggtggggcattgcccacacctgtcagctccttccgggacttc gcttccccctccctattgcaagcggaactcagccgcctgcctgcccgtgctggacagggct cggtgttgggcaactgacaattccgtggtgtgtcggggaaatcatcgtccttcttggctgctgcgc tgtgttgccacctggattctgcggggacgtccttctgtagctccttggccctcaatccagcgac cttccctcccgccgtcgtccggctcgtcggcctcttccgcgtctcgccctcgccctcagacagt cggatcctcctttgggcgcctccccgcgtcgactttaagaccaatgacttaacaggcagctgtagatc ttagccactttttaaagaaaagggggagctggaagggttaattcactcccaagagacaagatctgc ttttgcttgactgggtcctctgtgttagaccagatctgagcctggagcgtctcttggttaactagga accactgcttaagcctcaataaagcttgcccttgagtgcttcaagtagtgtgtgcccgctctgtgtgtg

		tcgctcaagctgggtgtgtgcacgaaccccccgcttcagcccgaccgctgcgccttatccggtaaacta tcgtcttgagtcacaaccccgtaagacacgacttatcgcaactggcagcagccactggtaacaggattag cagagcagggtatgtaggcgggtctacagagttcttgaagtgggtgcctaactacggtctacactagaag aacagtatttggtatctgcgctctgctgaagccagttaccttcggaaaaagagttggtagctcttgatc cggaacaaacaccccgctgtagcgggtggttttttttttgcagcagcagagattacgcgcagaaaaa aggatctcaagaagatcctttgatctttctacgggtgctgacgctcagtggaacgaaaaactcacgtta agggattttggtcatgagattatcaaaaaggatcttcacctagatcccttttaattaaaaatgaagttt taaatcaatctaaagtatatatgagtaaacttggtctgacagttaccaatcttaactcagtgaggcacc tatctcagcgatctgtctatttcggtccatccatagttgcctgactccccgctgctgtagataactacgat acgggaggggttaccatctggcccgctgctgcaatgataccgcgagacccacgctcaccggctccaga tttatcagcaataaacacgagccggaagggccgagcgagaagtggtcctgcaactttatccgcctc catccagtcctattaatgttgcgggaagctagagtaagtagtgcgcagttaatagtttgcgcaacgt tgttgccattgctacaggcatcgttggtgtcacgctcgttggttggtatggcttcattcagctccggttc ccaacgatcaaggcgagttacatgacccccatgttgcaaaaaagcggtagctccttcggtccctc gacgttgtcagaagtaagttggccgagtggttatcactcatggttatggcagcactgcataattctct tactgtcatgccatccgtaagatgcttttctgtgactggtgagtactcaaccaagtcattctgagaata gtgtatggcgcgaccgagttgctcttgcggcgctcaatacgggataataacggccacacatagcagaac tttaaaagtgtctcatcttggaacacgttcttcggggcgaaaaactctcaaggtattaccgctgttgag atccagttcgatgtaacccactcgtgcacccaactgatcttcagcatcttttactttcaccagcgttc tggtgagcaaaaaacaggaagcaaaatgccgcaaaaaagggaataaggcgacacgggaatgttgaat actcatactctctcttttcaatatattgaagcatttatcagggttattgtctctcatgagcggatacat atttgaatgtatttagaaaaataaaaaaatagggggttcgcgcgcacatttccccgaaaaagtgccacctga c
581	hIL-2 V69R	APTSSSTKKTQLQLEHLLLDLQMLNGINNYKNPKLTRMLTFKFYMPKKATELKHLCLEELKPLEER LNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVFELNRWITFCQSIISTLT
582	H7-02-hIgG1- LAGA-df-hIL-2 (T3A/D20A/R38E /C125A) HC	EVQLLESGGGLVQPGSLRLSCAASGFTFKSYAMTWVRQAPGKGLEWVSAIVYSGSTYYADSVKGRFT ISRDNKNTLYLQMNSLRAEDTAVYYCAKYTRASFYDAMDVWGQGTTVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVFSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKHTPCPPAPELAGAPSVFLFPPKPKDTLMI SRTPEVTCVWVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVHLQDNLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGKAPASSTKKTQLQLEHLLALQMLINGINNY KNPKLTEMLTTFKFYMPKKATELKHLCLEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSE TTFMCEYADETATIVFELNRWITFAQSIISTLT
583	H7-02-hKappa LC	EIVLTQSPGTLSLSPGERATFSCRASQSISSSFLAWYQOKPGQAPRLLIYDASTRATGIPDRFSGSGG TDFTLTISRLEPEDFAVYYCQQYYDWPPLSFGGGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL

		NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSTLSSTLTLSKADYEHKHKVYACEVTHQGLSSPV TKSENRGEC
584	hPD-L1	MRIFAVFIEMTYWHLLNAFTVVPKDLVVEYGSNMTECKFPVEKQLDLAALIVYWEDEKNNIIQFVH GEEDLKVQHSSYRQARLLKDQLSLGNAALQITDVKLQDAGVYRCMI SYGGADYKRITVVKVNAFYNKIN QRILVVDPVITSEHETCQAEQYKAEVITWSSDHQVLSKGTTTTNSKREEKLFNVTSTLRINTTTNEIF YCTFRRLDPEENHTAELVIPLELPAHPNERTHLVILGAILLCGLVALTFIFRLRKRMMMDVKKCGIQD TNSKKQSDTHLEET
585	KLH-C3-hIgG4 HC	EVQLVSGGGLVQPGGSLKLSCAASGFTTFSDFYMAWVRQAPTKGLEWVASISTGGNTHYRDSVKGRFT ISRDNAKSTLYLQMDSLRSEETATYCARLLSTISTPFDYWGQGVIVTVSSASTKGPVFPFLAPCSRST SESTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYTCNVDH KPSNTKVDKRVESKYGPPCPAPAEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVKFN WYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQPRE PQVYITLPPSQEEMTKNQVSLTCLLVKGFPYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDK SRWQEGNVFSCSVMEALHNHYTQKSLSLGLK
586	KLH-C3-hKap α LC	DVVLIQSPPTLSVTPGETVSLSCRASHSVGTNLHWYQQRTNESPSLLIKYSSHSSTSGIPSRFSATGSGT DFTLNISNVEFDDVASYFCQQSQKWPLTFGSGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCCLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSTLSSTLTLSKADYEHKHKVYACEVTHQGLSSPVTK SFNRGEC
587	1H3-hIgG1-L6- hCD25 (1-164) - L20-hIL-2 (E15A) HC	EVQLVESGGGLVQGRSLKLSCAVSGFTTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDATYICARHGSGYFDYWGQGMVTVSSASTKGPVFPFLAPSSKSTSGG TAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELIGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYITLPPSRDELTKNQVSLTCLLVKGFPYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMEALHNHYTQKSLSLSPGKSGGGSELCDDDPPEIPHATFKAMAYKEGTMNCEC KRGFRRIKSGSLYMLCTGNSSHSWDNQCCQCTSSATRNTHKQVTPQPEEQKERKITEMQSPMPVDQAS LPGHCREPPPWENEATERIYHFVVGQMVYYQCVQGYRALHGPAAESVCKMTHGKTRWTQPQLICTSGGG GSGGGSGGGSGGSAPTSSSTTKTQLQLAHLALLDQMLINGINNYKNPKLTMLTFKFYMPKKATEL KHLQCLEFEELKPLEEVNLQAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATIVFEFLNRWI TFCQSIISTLT
588	1H3-hIgG1-L6- hCD25 (1-164) - L20-hIL-2 (D20I) HC	EVQLVESGGGLVQGRSLKLSCAVSGFTTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDATYICARHGSGYFDYWGQGMVTVSSASTKGPVFPFLAPSSKSTSGG TAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELIGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYITLPPSRDELTKNQVSLTCLLVKGFPYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMEALHNHYTQKSLSLSPGKSGGGSELCDDDPPEIPHATFKAMAYKEGTMNCEC

		KRGFRRIKSGSLYMLCTGNSSHSWDNQCCQTSSATRNNTKQVTPQPEEQKERKTEMQSPMQPVDQAS LPGHCREPPPWENEATERIYHFVVGQMVYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTSGGG SGGGSGGGSGGGSAPTSSTTKKTQLQLEHLLILQMLINGINNYKNPKLTRMLTFKFYMPKKATEL KHLQCLEEELKPLEEVNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATATIVEFLNRWI TFCQSIISTLT
589	1H3-hIgG1-L6- hCD25 (1-164) - L20-hIL-2 (D20S) HC	EVQLVESGGGLVQPRSLKLSCAVSGGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDLSRSEDATYICARHSGSYFDYWGQGMVMTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPS NTKVDKKEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDLNKGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDK SRWQOGNVFSCVMHEALHNHYTQKSLSLSPGKSGGGSELCDDDPPEIPHATFKAMAYKEGTMLNCEC KRGFRRIKSGSLYMLCTGNSSHSWDNQCCQTSSATRNNTKQVTPQPEEQKERKTEMQSPMQPVDQAS LPGHCREPPPWENEATERIYHFVVGQMVYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTSGGG SGGGSGGGSGGGSAPTSSTTKKTQLQLEHLLILQMLINGINNYKNPKLTRMLTFKFYMPKKATEL KHLQCLEEELKPLEEVNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATATIVEFLNRWI TFCQSIISTLT
590	1H3-hIgG1-L6- hCD25 (1-164) - L20-hIL-2 (D20H) HC	EVQLVESGGGLVQPRSLKLSCAVSGGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDLSRSEDATYICARHSGSYFDYWGQGMVMTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPS NTKVDKKEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDLNKGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDK SRWQOGNVFSCVMHEALHNHYTQKSLSLSPGKSGGGSELCDDDPPEIPHATFKAMAYKEGTMLNCEC KRGFRRIKSGSLYMLCTGNSSHSWDNQCCQTSSATRNNTKQVTPQPEEQKERKTEMQSPMQPVDQAS LPGHCREPPPWENEATERIYHFVVGQMVYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQLICTSGGG SGGGSGGGSGGGSAPTSSTTKKTQLQLEHLLILQMLINGINNYKNPKLTRMLTFKFYMPKKATEL KHLQCLEEELKPLEEVNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATATIVEFLNRWI TFCQSIISTLT
591	1H3-hIgG1-L6- hCD25 (1-164) - L20-hIL-2 (D20W) HC	EVQLVESGGGLVQPRSLKLSCAVSGGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDLSRSEDATYICARHSGSYFDYWGQGMVMTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPS NTKVDKKEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDLNKGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDK SRWQOGNVFSCVMHEALHNHYTQKSLSLSPGKSGGGSELCDDDPPEIPHATFKAMAYKEGTMLNCEC KRGFRRIKSGSLYMLCTGNSSHSWDNQCCQTSSATRNNTKQVTPQPEEQKERKTEMQSPMQPVDQAS

592	1H3-hIgG1-L6-hCD25 (1-164) -L20-hIL-2 (D20Y) HC	LPGHCREPPPWENEATERIYHFVVGQMVVYQCQGYRALHRGPAESVCKMTHGKTRWTQPQLICTSGGG GSGGGSGGGSGGSAPTSSTTKTQLQLEHLLWLQMLINGINNYKNPKLTRMLTFKFYMPKKATEL KHLQCLEEELKPLEEVNLQAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVFEFLNRWI TFCQSIISTLT EVQLVESGGGLVQPGSRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDATYICARHSGSYFDYWGQGMVTVSSASTKGPVFPPLAPSSKSTSGG TAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELGGPSVFLFPPKPKDITIMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDK SRWQOGNVFSCVMHEALHNHYTQKSLSLSPGKSGGGSELCDDDPPEIPHATFKAMAYKEGTMLNCEC KRGFRRIKSGSLYMLCTGNSSHSWDNQCQCTSSATRNTHKQVTPQEEQKERKTEMQSPMQPVDQAS LPGHCREPPPWENEATERIYHFVVGQMVVYQCQGYRALHRGPAESVCKMTHGKTRWTQPQLICTSGGG GSGGGSGGGSGGSAPTSSTTKTQLQLEHLLWLQMLINGINNYKNPKLTRMLTFKFYMPKKATEL KHLQCLEEELKPLEEVNLQAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVFEFLNRWI TFCQSIISTLT EVQLVESGGGLVQPGSRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDATYICARHSGSYFDYWGQGMVTVSSASTKGPVFPPLAPSSKSTSGG TAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELGGPSVFLFPPKPKDITIMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDK SRWQOGNVFSCVMHEALHNHYTQKSLSLSPGKSGGGSELCDDDPPEIPHATFKAMAYKEGTMLNCEC KRGFRRIKSGSLYMLCTGNSSHSWDNQCQCTSSATRNTHKQVTPQEEQKERKTEMQSPMQPVDQAS LPGHCREPPPWENEATERIYHFVVGQMVVYQCQGYRALHRGPAESVCKMTHGKTRWTQPQLICTSGGG GSGGGSGGGSGGSAPTSSTTKTQLQLEHLLWLQMLINGINNYKNPKLTRMLTFKFYMPKKATEL KHLQCLEEELKPLEEVNLQAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVFEFLNRWI TFCQSIISTLT EVQLVESGGGLVQPGSRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDATYICARHSGSYFDYWGQGMVTVSSASTKGPVFPPLAPSSKSTSGG TAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELGGPSVFLFPPKPKDITIMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDK SRWQOGNVFSCVMHEALHNHYTQKSLSLSPGKSGGGSELCDDDPPEIPHATFKAMAYKEGTMLNCEC KRGFRRIKSGSLYMLCTGNSSHSWDNQCQCTSSATRNTHKQVTPQEEQKERKTEMQSPMQPVDQAS LPGHCREPPPWENEATERIYHFVVGQMVVYQCQGYRALHRGPAESVCKMTHGKTRWTQPQLICTSGGG
593	1H3-hIgG1-L6-hCD25 (1-164) -L20-hIL-2 (D20R) HC	LPGHCREPPPWENEATERIYHFVVGQMVVYQCQGYRALHRGPAESVCKMTHGKTRWTQPQLICTSGGG GSGGGSGGGSGGSAPTSSTTKTQLQLEHLLWLQMLINGINNYKNPKLTRMLTFKFYMPKKATEL KHLQCLEEELKPLEEVNLQAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVFEFLNRWI TFCQSIISTLT EVQLVESGGGLVQPGSRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDATYICARHSGSYFDYWGQGMVTVSSASTKGPVFPPLAPSSKSTSGG TAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELGGPSVFLFPPKPKDITIMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDK SRWQOGNVFSCVMHEALHNHYTQKSLSLSPGKSGGGSELCDDDPPEIPHATFKAMAYKEGTMLNCEC KRGFRRIKSGSLYMLCTGNSSHSWDNQCQCTSSATRNTHKQVTPQEEQKERKTEMQSPMQPVDQAS LPGHCREPPPWENEATERIYHFVVGQMVVYQCQGYRALHRGPAESVCKMTHGKTRWTQPQLICTSGGG GSGGGSGGGSGGSAPTSSTTKTQLQLEHLLWLQMLINGINNYKNPKLTRMLTFKFYMPKKATEL KHLQCLEEELKPLEEVNLQAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVFEFLNRWI TFCQSIISTLT EVQLVESGGGLVQPGSRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDATYICARHSGSYFDYWGQGMVTVSSASTKGPVFPPLAPSSKSTSGG TAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELGGPSVFLFPPKPKDITIMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDK SRWQOGNVFSCVMHEALHNHYTQKSLSLSPGKSGGGSELCDDDPPEIPHATFKAMAYKEGTMLNCEC KRGFRRIKSGSLYMLCTGNSSHSWDNQCQCTSSATRNTHKQVTPQEEQKERKTEMQSPMQPVDQAS LPGHCREPPPWENEATERIYHFVVGQMVVYQCQGYRALHRGPAESVCKMTHGKTRWTQPQLICTSGGG
594	1H3-hIgG1-L6-hCD25 (1-164) -L20-hIL-2 (D20F) HC	LPGHCREPPPWENEATERIYHFVVGQMVVYQCQGYRALHRGPAESVCKMTHGKTRWTQPQLICTSGGG GSGGGSGGGSGGSAPTSSTTKTQLQLEHLLWLQMLINGINNYKNPKLTRMLTFKFYMPKKATEL KHLQCLEEELKPLEEVNLQAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVFEFLNRWI TFCQSIISTLT EVQLVESGGGLVQPGSRSLKLSCAVSGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDATYICARHSGSYFDYWGQGMVTVSSASTKGPVFPPLAPSSKSTSGG TAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELGGPSVFLFPPKPKDITIMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDK SRWQOGNVFSCVMHEALHNHYTQKSLSLSPGKSGGGSELCDDDPPEIPHATFKAMAYKEGTMLNCEC KRGFRRIKSGSLYMLCTGNSSHSWDNQCQCTSSATRNTHKQVTPQEEQKERKTEMQSPMQPVDQAS LPGHCREPPPWENEATERIYHFVVGQMVVYQCQGYRALHRGPAESVCKMTHGKTRWTQPQLICTSGGG

[illegible]

		KHLQCLEEEELKPLEEVNLQAQSKNFHLRPRDLISYINVIVLELKGSETTFMCEYADETATATIVEFLNRWI TFCQSIISTLT
598	1H3-hIgG1-L6- hCD25 (1-164) - L20-hIL-2 (N88D) HC	EVQLVESGGGLVQPGRSILKLSCAVSGGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDATYYCARHSGSYFDYWGQGMVTVSSASTKGPSVFPEPLAPSSKSTSGG TAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDK SRWQOQNVFSCVMHEALHNHYTQKSLSLSPGKSGGGSELCDDDPPEIPHATFKAMAYKEGTMNCEC KRGFRRIKSGSLYMLCTGNSSHSWDNQCCTSSATRNTTKQVTPQPEEQKERKKTTEMQSPMQPVDQAS LPGHCREPPPWENEATERIYHFVVGQMVVYQCQGYRALHRGPAESVCKMTHGKTRWTQPQLICTSGGG GSGGGSGGGSGGGGSAPTSSSTKKTQLQLEHLLLDLQMLINGINNYKNPKLTRMLTFKFYMPKKATEL KHLQCLEEEELKPLEEVNLQAQSKNFHLRPRDLISDINVIVLELKGSETTFMCEYADETATATIVEFLNRWI TFCQSIISTLT
599	1H3-hIgG1-L6- hCD25 (1-164) - L20-hIL-2 (N88R) HC	EVQLVESGGGLVQPGRSILKLSCAVSGGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDATYYCARHSGSYFDYWGQGMVTVSSASTKGPSVFPEPLAPSSKSTSGG TAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDK SRWQOQNVFSCVMHEALHNHYTQKSLSLSPGKSGGGSELCDDDPPEIPHATFKAMAYKEGTMNCEC KRGFRRIKSGSLYMLCTGNSSHSWDNQCCTSSATRNTTKQVTPQPEEQKERKKTTEMQSPMQPVDQAS LPGHCREPPPWENEATERIYHFVVGQMVVYQCQGYRALHRGPAESVCKMTHGKTRWTQPQLICTSGGG GSGGGSGGGSGGGGSAPTSSSTKKTQLQLEHLLLDLQMLINGINNYKNPKLTRMLTFKFYMPKKATEL KHLQCLEEEELKPLEEVNLQAQSKNFHLRPRDLISRINVIVLELKGSETTFMCEYADETATATIVEFLNRWI TFCQSIISTLT
600	1H3-hIgG1-L6- hCD25 (1-164) - L20-hIL-2 (N88E) HC	EVQLVESGGGLVQPGRSILKLSCAVSGGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDATYYCARHSGSYFDYWGQGMVTVSSASTKGPSVFPEPLAPSSKSTSGG TAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDK SRWQOQNVFSCVMHEALHNHYTQKSLSLSPGKSGGGSELCDDDPPEIPHATFKAMAYKEGTMNCEC KRGFRRIKSGSLYMLCTGNSSHSWDNQCCTSSATRNTTKQVTPQPEEQKERKKTTEMQSPMQPVDQAS LPGHCREPPPWENEATERIYHFVVGQMVVYQCQGYRALHRGPAESVCKMTHGKTRWTQPQLICTSGGG GSGGGSGGGSGGGGSAPTSSSTKKTQLQLEHLLLDLQMLINGINNYKNPKLTRMLTFKFYMPKKATEL KHLQCLEEEELKPLEEVNLQAQSKNFHLRPRDLISRINVIVLELKGSETTFMCEYADETATATIVEFLNRWI TFCQSIISTLT

		KHLQCLEEEELKPLEEVNLQAQSKNFHLRPRDLISEINVIVLELKGSETTFMCEYADETATATIVEFLNRWI TFCQSIISTLT
601	1H3-hIgG1-L6- hCD25 (1-164) - L20-hIL-2 (N88F) HC	EVQLVESGGGLVQPGRSILKLSCAVSGGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDATYYCARHSGSYFDYWGQGMVTVSSASTKGPVFPFLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDK SRWQOGNVFSCVMHEALHNHYTQKSLSLSPGKSGGGSELCDDDPPEIPHATFKAMAYKEGTMNCEC KRGFRRIKSGSLYMLCTGNSSHSWDNQCCTSSATRNTTKQVTPQPEEQKERKITEMQSPMQPVDQAS LPGHCREPPPWENEATERIYHFVVGQMVVYQCQGYRALHRGPAESVCKMTHGKTRWTQPQLICTSGGG GSGGGSGGGSGGGGSAPTSSSTKKTQLQLEHLLLDLQMLINGINNYKNPKLTRMLTFKFYMPKKATEL KHLQCLEEEELKPLEEVNLQAQSKNFHLRPRDLISFINVIVLELKGSETTFMCEYADETATATIVEFLNRWI TFCQSIISTLT
602	1H3-hIgG1-L6- hCD25 (1-164) - L20-hIL-2 (N88I) HC	EVQLVESGGGLVQPGRSILKLSCAVSGGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDATYYCARHSGSYFDYWGQGMVTVSSASTKGPVFPFLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDK SRWQOGNVFSCVMHEALHNHYTQKSLSLSPGKSGGGSELCDDDPPEIPHATFKAMAYKEGTMNCEC KRGFRRIKSGSLYMLCTGNSSHSWDNQCCTSSATRNTTKQVTPQPEEQKERKITEMQSPMQPVDQAS LPGHCREPPPWENEATERIYHFVVGQMVVYQCQGYRALHRGPAESVCKMTHGKTRWTQPQLICTSGGG GSGGGSGGGSGGGGSAPTSSSTKKTQLQLEHLLLDLQMLINGINNYKNPKLTRMLTFKFYMPKKATEL KHLQCLEEEELKPLEEVNLQAQSKNFHLRPRDLISFINVIVLELKGSETTFMCEYADETATATIVEFLNRWI TFCQSIISTLT
603	1H3-hIgG1-L6- hCD25 (1-164) - L20-hIL-2 (I92A) HC	EVQLVESGGGLVQPGRSILKLSCAVSGGFTFSDYAMAWVRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDATYYCARHSGSYFDYWGQGMVTVSSASTKGPVFPFLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDK SRWQOGNVFSCVMHEALHNHYTQKSLSLSPGKSGGGSELCDDDPPEIPHATFKAMAYKEGTMNCEC KRGFRRIKSGSLYMLCTGNSSHSWDNQCCTSSATRNTTKQVTPQPEEQKERKITEMQSPMQPVDQAS LPGHCREPPPWENEATERIYHFVVGQMVVYQCQGYRALHRGPAESVCKMTHGKTRWTQPQLICTSGGG GSGGGSGGGSGGGGSAPTSSSTKKTQLQLEHLLLDLQMLINGINNYKNPKLTRMLTFKFYMPKKATEL KHLQCLEEEELKPLEEVNLQAQSKNFHLRPRDLISFINVIVLELKGSETTFMCEYADETATATIVEFLNRWI TFCQSIISTLT

		KHLQCLEEEELKPLEEVNLQAQSKNFHLRPRDLISNINVAVLELKGSETTFMCEYADETATATIVEFLNRWI TFCQSIISTLT
604	1H3-hIgG1-L6- hCD25 (1-164) - L20-hIL-2 (E95A) HC	EVQLVESGGGLVQPGRSILKLSCAVSGFTFSDYAMAWRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDATYYCARHSGSYFDYWGQGMVTVSSASTKGPSVFPPLAPSSKSTSGG TAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPS NTKVDKKEVPKSCDKTHTCPPCPAPELIGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDLNKGKEYCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDK SRWQQGNVSCSVMHEALHNHYTQKSLSLSPGKSGGSGSELCDDDPPEIPHATFKAMAYKEGTMLNCEC KRGFRRIKSGSLYMLCTGNSSHSWDNQCCTSSATRNTTKQVTPQPEEQKERKITEMQSPMQPVDQAS LPGHCREPPPWENEATERIYHFVVGQMVYYQCVQGYRALHGRPAAESVCKMTHGKTRWTQPQLICTSGGG GSGGGSGGGSGGGGSAPTSSSTKKTQLQLEHLLLDLQMLINGINNYKNPKLTRMLTFKFYMPKKATEL KHLQCLEEEELKPLEEVNLQAQSKNFHLRPRDLISNINVIIVLALKGSETTFMCEYADETATATIVEFLNRWI TFCQSIISTLT
605	1H3-hIgG1-L6- hCD25 (1-164) - L20-hIL-2 (E95K) HC	EVQLVESGGGLVQPGRSILKLSCAVSGFTFSDYAMAWRQAPKKGLEWVATISYDGSRTYYRDSVKGRFT ISRDNAKITLYLQMDSLRSEDATYYCARHSGSYFDYWGQGMVTVSSASTKGPSVFPPLAPSSKSTSGG TAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPS NTKVDKKEVPKSCDKTHTCPPCPAPELIGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDLNKGKEYCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDK SRWQQGNVSCSVMHEALHNHYTQKSLSLSPGKSGGSGSELCDDDPPEIPHATFKAMAYKEGTMLNCEC KRGFRRIKSGSLYMLCTGNSSHSWDNQCCTSSATRNTTKQVTPQPEEQKERKITEMQSPMQPVDQAS LPGHCREPPPWENEATERIYHFVVGQMVYYQCVQGYRALHGRPAAESVCKMTHGKTRWTQPQLICTSGGG GSGGGSGGGSGGGGSAPTSSSTKKTQLQLEHLLLDLQMLINGINNYKNPKLTRMLTFKFYMPKKATEL KHLQCLEEEELKPLEEVNLQAQSKNFHLRPRDLISNINVIIVLALKGSETTFMCEYADETATATIVEFLNRWI TFCQSIISTLT
606	hIL-2 D20R/R38E	APTSSTKKTQLQLEHLLLRQLQMLINGINNYKNPKLT EM LTFKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATATIVEFLNRWITFCQSIISTLT
607	hIL-2 D20N/R38E	APTSSTKKTQLQLEHLLLNQLQMLINGINNYKNPKLT EM LTFKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATATIVEFLNRWITFCQSIISTLT
608	hIL-2 D20Q/R38E	APTSSTKKTQLQLEHLLLQLQMLINGINNYKNPKLT EM LTFKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATATIVEFLNRWITFCQSIISTLT
609	hIL-2 D20E/R38E	APTSSTKKTQLQLEHLLLELQMLINGINNYKNPKLT EM LTFKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVIIVLELKGSETTFMCEYADETATATIVEFLNRWITFCQSIISTLT

610	hIL-2 D20G/R38E	APTSSSTKKTQQLQLEHLLLL GL QMI L NGINNYKNPKLT EM LTKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVI V LELKGSETTFMCEYADETAT I VEFLNRWITFCQSIISTLT
611	hIL-2 D20I/R38E	APTSSSTKKTQQLQLEHLLLL IL QMI L NGINNYKNPKLT EM LTKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVI V LELKGSETTFMCEYADETAT I VEFLNRWITFCQSIISTLT
612	hIL-2 D20L/R38E	APTSSSTKKTQQLQLEHLLLL LL QMI L NGINNYKNPKLT EM LTKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVI V LELKGSETTFMCEYADETAT I VEFLNRWITFCQSIISTLT
613	hIL-2 D20K/R38E	APTSSSTKKTQQLQLEHLLLL KL QMI L NGINNYKNPKLT EM LTKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVI V LELKGSETTFMCEYADETAT I VEFLNRWITFCQSIISTLT
614	hIL-2 D20M/R38E	APTSSSTKKTQQLQLEHLL LLML QMI L NGINNYKNPKLT EM LTKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVI V LELKGSETTFMCEYADETAT I VEFLNRWITFCQSIISTLT
615	hIL-2 D20F/R38E	APTSSSTKKTQQLQLEHLLLL FL QMI L NGINNYKNPKLT EM LTKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVI V LELKGSETTFMCEYADETAT I VEFLNRWITFCQSIISTLT
616	hIL-2 D20P/R38E	APTSSSTKKTQQLQLEHLLLL PL QMI L NGINNYKNPKLT EM LTKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVI V LELKGSETTFMCEYADETAT I VEFLNRWITFCQSIISTLT
617	hIL-2 D20T/R38E	APTSSSTKKTQQLQLEHLLLL TL QMI L NGINNYKNPKLT EM LTKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVI V LELKGSETTFMCEYADETAT I VEFLNRWITFCQSIISTLT
618	hIL-2 D20W/R38E	APTSSSTKKTQQLQLEHLLLL WL QMI L NGINNYKNPKLT EM LTKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVI V LELKGSETTFMCEYADETAT I VEFLNRWITFCQSIISTLT
619	hIL-2 D20Y/R38E	APTSSSTKKTQQLQLEHLLLL YL QMI L NGINNYKNPKLT EM LTKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVI V LELKGSETTFMCEYADETAT I VEFLNRWITFCQSIISTLT
620	hIL-2 D20V/R38E	APTSSSTKKTQQLQLEHLLLL VL QMI L NGINNYKNPKLT EM LTKFYMPKKATELKHLCLEEEELKPLEEV LNLAQSKNFHLRPRDLISNINVI V LELKGSETTFMCEYADETAT I VEFLNRWITFCQSIISTLT
621	hIL-2 F42K/Y45R/V69R	APTSSSTKKTQQLQLEHLLLLD L QMI L NGINNYKNPKLT RM LTKKFRMPKKATELKHLCLEEEELKPLEER LNLAQSKNFHLRPRDLISNINVI V LELKGSETTFMCEYADETAT I VEFLNRWITFCQSIISTLT

EMBODIMENTS

[0231] The following list of embodiments is intended to complement, rather than displace or supersede, the previous descriptions.

Embodiment 1. A method of treating a cancer in a subject, the method comprising administering to the subject:

(A) an anti-human PD-1 (hPD-1) antibody-modified human interleukin-2 (hIL-2) immunoconjugate comprising:

a modified hIL-2 protein comprising a D20A, D20S, D20Q, D20M, D20I, D20V, D20N, D20G, D20T, or D20E substitution at amino acid position 20 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345 and an R38E substitution at amino acid position 38 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345; and

an anti-hPD-1 antibody, or antigen-binding fragment thereof, that immunospecifically binds to hPD-1, wherein the antibody or antigen-binding fragment thereof comprises:

(i) a heavy chain complementarity determining region 1 (CDR1) comprising the amino acid sequence of SEQ ID NO: 418, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 419, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 420, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 421, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 422, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 423;

(ii) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 386, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 387, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 388, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 389, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 390, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 391;

- (iii) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 396, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 397, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 398, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 399, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 400, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 401; or
 - (iv) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 406, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 407, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 408, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 409, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 410, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 411; and
- (B) an antagonistic anti-PD-1 antibody that binds PD-1 in the presence of the immunoconjugate.

Embodiment 2. The method of embodiment 1, wherein the antagonistic anti-PD-1 antibody is nivolumab, pembrolizumab, cemiplimab, dostarlimab, or retifanlimab.

Embodiment 3. The method of embodiment 1 or 2, wherein the modified hIL-2 protein comprises the amino acid sequence of any one of SEQ ID NOs: 149, 307, 607-611, 614, 617, or 620.

Embodiment 4. The method of any one of the previous embodiments, wherein the modified hIL-2 protein comprises a D20A substitution relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345 and a R38E substitution relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345.

Embodiment 5. The method of embodiment 4, wherein the modified hIL-2 protein comprises the amino acid sequence of SEQ ID NO: 149.

Embodiment 6. The method of any one of the previous embodiments, wherein the modified hIL-2 protein further comprises a deletion or substitution at amino acid position 3 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345.

Embodiment 7. The method of embodiment 6, wherein the substitution at amino acid position 3 of the modified hIL-2 protein is T3A.

Embodiment 8. The method of embodiment 7, wherein the modified hIL-2 protein comprises the amino acid sequence of SEQ ID NO: 216.

Embodiment 9. The method of embodiment 6, wherein the modified hIL-2 protein comprises the amino acid sequence of SEQ ID NO: 218.

Embodiment 10. The method of any one of the previous embodiments, wherein the modified hIL-2 protein further comprises a deletion or substitution at amino acid position 125 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345.

Embodiment 11. The method of embodiment 10, wherein the substitution at amino acid position 125 is C125A.

Embodiment 12. The method of embodiment 11, wherein the modified hIL-2 protein comprises the amino acid sequence of SEQ ID NO: 215, 217, or 219.

Embodiment 13. The method of embodiment 12, wherein the modified hIL-2 protein comprises the amino acid sequence of SEQ ID NO: 217.

Embodiment 14. The method of any one of the previous embodiments, wherein the modified hIL-2 protein is fused to the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate at the N-terminus of an antibody light chain, the C-terminus of an antibody light chain, the N-terminus of an antibody heavy chain, the C-terminus of an antibody heavy

chain, the N-terminus of the antigen-binding fragment, or the C-terminus of the antigen-binding fragment.

Embodiment 15. The method of any one of the previous embodiments, wherein the modified hIL-2 protein is directly fused by a peptide bond to the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate.

Embodiment 16. The method of embodiment 15, wherein the modified hIL-2 protein is directly fused by a peptide bond to the C-terminal amino acid residue of the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate.

Embodiment 17. The method of any one of embodiments 1-14, wherein the modified hIL-2 protein is fused to the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate through a linker.

Embodiment 18. The method of any one of the previous embodiments, wherein the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate comprises:

- a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 416 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 417;
- b) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 384 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 385;
- c) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 394 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 395; or
- d) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 404 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 405.

Embodiment 19. The method of any one of the previous embodiments, wherein the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate comprises an IgG1 heavy chain constant region.

Embodiment 20. The method of embodiment 19, wherein the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate comprises an L235A substitution and a G237A substitution, according to EU numbering.

Embodiment 21. The method of any one of the previous embodiments, wherein the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate comprises:

- a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 414 and a light chain comprising the amino acid sequence of SEQ ID NO: 415;
- b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 424 and a light chain comprising the amino acid sequence of SEQ ID NO: 425;
- c) a heavy chain comprising the amino acid sequence of SEQ ID NO: 426 and a light chain comprising the amino acid sequence of SEQ ID NO: 427; or
- d) a heavy chain comprising the amino acid sequence of SEQ ID NO: 428 and a light chain comprising the amino acid sequence of SEQ ID NO: 429.

Embodiment 22. The method of embodiment 21, wherein the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 414 and a light chain comprising the amino acid sequence of SEQ ID NO: 415.

Embodiment 23. The method of any one of the previous embodiments, wherein the immunoconjugate comprises:

- a light chain comprising the amino acid sequence of SEQ ID NO: 415; and
- a heavy chain-modified hIL-2 protein fusion comprising the amino acid sequence of SEQ ID NO: 532.

Embodiment 24. The method of any one of the previous embodiments, wherein the antagonistic anti-PD-1 antibody and the immunoconjugate are administered to the subject together in a mixture, concurrently as single agents, or sequentially as single agents in any order.

Embodiment 25. The method of embodiment 24, comprising:

- administering the immunoconjugate prior to administering the antagonistic anti-PD-1 antibody;

- administering the antagonistic anti-PD-1 antibody prior to administering the immunoconjugate; or

- administering the immunoconjugate at substantially the same time as administering the antagonistic anti-PD-1 antibody.

Embodiment 26. The method of any one of the previous embodiments, wherein the cancer is melanoma, Merkel cell carcinoma, non-small cell lung carcinoma, renal cell carcinoma, triple negative breast cancer, squamous cell carcinoma of the head/neck, hepatocellular carcinoma, or microsatellite instability-high tumors or tumors with deficient DNA mismatch repair.

Embodiment 27. A method of treating a renal cell carcinoma, a triple negative breast cancer, a squamous cell carcinoma of the head/neck, a Merkel cell carcinoma, a hepatocellular carcinoma, or a microsatellite instability-high tumor or tumor with deficient DNA mismatch repair in a subject, the method comprising administering to the subject:

- an anti-human PD-1 (hPD-1) antibody-modified human interleukin-2 (hIL-2) immunoconjugate comprising:

- a modified hIL-2 protein comprising a D20A, D20S, D20Q, D20M, D20I, D20V, D20N, D20G, D20T, or D20E substitution at amino acid position 20 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345 and an R38E substitution at amino acid position 38 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345; and

- an anti-hPD-1 antibody, or antigen-binding fragment thereof, that immunospecifically binds to hPD-1, wherein the antibody or antigen-binding fragment thereof comprises:

- (i) a heavy chain complementarity determining region 1 (CDR1) comprising the amino acid sequence of SEQ ID NO: 418, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 419, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 420, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 421, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 422, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 423;
- (ii) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 386, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 387, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 388, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 389, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 390, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 391;
- (iii) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 396, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 397, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 398, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 399, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 400, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 401; or
- (iv) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 406, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 407, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 408, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 409, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 410, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 411.

Embodiment 28. The method of embodiment 27, wherein the modified hIL-2 protein comprises the amino acid sequence of any one of SEQ ID NOs: 149, 307, 607-611, 614, 617, or 620.

Embodiment 29. The method of embodiment 27 or 28, wherein the modified hIL-2 protein comprises a D20A substitution relative to the non-modified hIL-2 amino acid sequence of SEQ

ID NO: 345 and a R38E substitution relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345.

Embodiment 30. The method of embodiment 29, wherein the modified hIL-2 protein comprises the amino acid sequence of SEQ ID NO: 149.

Embodiment 31. The method of any one of embodiments 27-30, wherein the modified hIL-2 protein further comprises a deletion or substitution at amino acid position 3 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345.

Embodiment 32. The method of embodiment 31, wherein the substitution at amino acid position 3 of the modified hIL-2 protein is T3A.

Embodiment 33. The method of embodiment 32, wherein the modified hIL-2 protein comprises the amino acid sequence of SEQ ID NO: 216.

Embodiment 34. The method of embodiment 31, wherein the modified hIL-2 protein comprises the amino acid sequence of SEQ ID NO: 218.

Embodiment 35. The method of any one of embodiments 27-34, wherein the modified hIL-2 protein further comprises a deletion or substitution at amino acid position 125 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345.

Embodiment 36. The method of embodiment 35, wherein the substitution at amino acid position 125 is C125A.

Embodiment 37. The method of embodiment 36, wherein the modified hIL-2 protein comprises the amino acid sequence of SEQ ID NO: 215, 217, or 219.

Embodiment 38. The method of embodiment 37, wherein the modified hIL-2 protein comprises the amino acid sequence of SEQ ID NO: 217.

Embodiment 39. The method of any one of embodiments 27-38, wherein the modified hIL-2 protein is fused to the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate at the N-terminus of an antibody light chain, the C-terminus of an antibody light chain, the N-terminus of an antibody heavy chain, the C-terminus of an antibody heavy chain, the N-terminus of the antigen-binding fragment, or the C-terminus of the antigen-binding fragment.

Embodiment 40. The method of any one of embodiments 27-39, wherein the modified hIL-2 protein is directly fused by a peptide bond to the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate.

Embodiment 41. The method of embodiment 40, wherein the modified hIL-2 protein is directly fused by a peptide bond to the C-terminal amino acid residue of the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate.

Embodiment 42. The method of any one of embodiments 27-39, wherein the modified hIL-2 protein is fused to the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate through a linker.

Embodiment 43. The method of any one of embodiments 27-42, wherein the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate comprises:

- a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 416 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 417;
- b) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 384 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 385;
- c) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 394 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 395; or

d) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 404 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 405.

Embodiment 44. The method of any one of embodiments 27-43, wherein the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate comprises an IgG1 heavy chain constant region.

Embodiment 45. The method of embodiment 44, wherein the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate comprises an L235A substitution and a G237A substitution, according to EU numbering.

Embodiment 46. The method of any one of embodiments 27-45, wherein the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate comprises:

- a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 414 and a light chain comprising the amino acid sequence of SEQ ID NO: 415;
- b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 424 and a light chain comprising the amino acid sequence of SEQ ID NO: 425;
- c) a heavy chain comprising the amino acid sequence of SEQ ID NO: 426 and a light chain comprising the amino acid sequence of SEQ ID NO: 427; or
- d) a heavy chain comprising the amino acid sequence of SEQ ID NO: 428 and a light chain comprising the amino acid sequence of SEQ ID NO: 429.

Embodiment 47. The method of embodiment 46, wherein the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 414 and a light chain comprising the amino acid sequence of SEQ ID NO: 415.

Embodiment 48. The method of any one of embodiments 27-47, wherein the immunoconjugate comprises:

- a light chain comprising the amino acid sequence of SEQ ID NO: 415; and

a heavy chain-modified hIL-2 protein fusion comprising the amino acid sequence of SEQ ID NO: 532.

Embodiment 49. Use of

(A) an anti-hPD-1 antibody-modified human interleukin-2 (hIL-2) immunoconjugate comprising:

a modified hIL-2 protein comprising a D20A, D20S, D20Q, D20M, D20I, D20V, D20N, D20G, D20T, or D20E substitution at amino acid position 20 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345 and an R38E substitution at amino acid position 38 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345; and

an anti-hPD-1 antibody, or antigen-binding fragment thereof, that immunospecifically binds to hPD-1, wherein the antibody or antigen-binding fragment thereof comprises:

(i) a heavy chain complementarity determining region 1 (CDR1) comprising the amino acid sequence of SEQ ID NO: 418, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 419, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 420, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 421, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 422, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 423;

(ii) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 386, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 387, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 388, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 389, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 390, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 391;

(iii) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 396, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 397, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 398, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 399, a light chain CDR2 comprising the amino acid

sequence of SEQ ID NO: 400, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 401; or

(iv) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 406, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 407, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 408, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 409, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 410, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 411; and

(B) an antagonistic anti-PD-1 antibody that binds PD-1 in the presence of the immunoconjugate
for the treatment of cancer.

What is claimed:

1. A method of treating a cancer in a subject, the method comprising administering to the subject:

(A) an anti-human PD-1 (hPD-1) antibody-modified human interleukin-2 (hIL-2) immunoconjugate comprising:

a modified hIL-2 protein comprising a D20A, D20S, D20Q, D20M, D20I, D20V, D20N, D20G, D20T, or D20E substitution at amino acid position 20 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345 and an R38E substitution at amino acid position 38 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345; and

an anti-hPD-1 antibody, or antigen-binding fragment thereof, that immunospecifically binds to hPD-1, wherein the antibody or antigen-binding fragment thereof comprises:

- (i) a heavy chain complementarity determining region 1 (CDR1) comprising the amino acid sequence of SEQ ID NO: 418, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 419, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 420, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 421, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 422, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 423;
- (ii) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 386, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 387, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 388, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 389, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 390, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 391;
- (iii) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 396, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 397, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 398, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 399, a

light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 400, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 401; or

(iv) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 406, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 407, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 408, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 409, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 410, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 411; and

(B) an antagonistic anti-PD-1 antibody that binds PD-1 in the presence of the immunoconjugate.

2. The method of claim 1, wherein the antagonistic anti-PD-1 antibody is nivolumab, pembrolizumab, cemiplimab, dostarlimab, or retifanlimab.

3. The method of claim 1 or 2, wherein the modified hIL-2 protein comprises the amino acid sequence of any one of SEQ ID NOs: 149, 307, 607-611, 614, 617, or 620.

4. The method of any one of the previous claims, wherein the modified hIL-2 protein comprises a D20A substitution relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345 and a R38E substitution relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345.

5. The method of claim 4, wherein the modified hIL-2 protein comprises the amino acid sequence of SEQ ID NO: 149.

6. The method of any one of the previous claims, wherein the modified hIL-2 protein further comprises a deletion or substitution at amino acid position 3 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345.

7. The method of claim 6, wherein the substitution at amino acid position 3 of the modified hIL-2 protein is T3A.

8. The method of claim 7, wherein the modified hIL-2 protein comprises the amino acid sequence of SEQ ID NO: 216.
9. The method of claim 6, wherein the modified hIL-2 protein comprises the amino acid sequence of SEQ ID NO: 218.
10. The method of any one of the previous claims, wherein the modified hIL-2 protein further comprises a deletion or substitution at amino acid position 125 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345.
11. The method of claim 10, wherein the substitution at amino acid position 125 is C125A.
12. The method of claim 11, wherein the modified hIL-2 protein comprises the amino acid sequence of SEQ ID NO: 215, 217, or 219.
13. The method of claim 12, wherein the modified hIL-2 protein comprises the amino acid sequence of SEQ ID NO: 217.
14. The method of any one of the previous claims, wherein the modified hIL-2 protein is fused to the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate at the N-terminus of an antibody light chain, the C-terminus of an antibody light chain, the N-terminus of an antibody heavy chain, the C-terminus of an antibody heavy chain, the N-terminus of the antigen-binding fragment, or the C-terminus of the antigen-binding fragment.
15. The method of any one of the previous claims, wherein the modified hIL-2 protein is directly fused by a peptide bond to the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate.

16. The method of claim 15, wherein the modified hIL-2 protein is directly fused by a peptide bond to the C-terminal amino acid residue of the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate.

17. The method of any one of claims 1-14, wherein the modified hIL-2 protein is fused to the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate through a linker.

18. The method of any one of the previous claims, wherein the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate comprises:

- a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 416 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 417;
- b) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 384 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 385;
- c) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 394 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 395; or
- d) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 404 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 405.

19. The method of any one of the previous claims, wherein the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate comprises an IgG1 heavy chain constant region.

20. The method of claim 19, wherein the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate comprises an L235A substitution and a G237A substitution, according to EU numbering.

21. The method of any one of the previous claims, wherein the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate comprises:

- a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 414 and a light chain comprising the amino acid sequence of SEQ ID NO: 415;
- b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 424 and a light chain comprising the amino acid sequence of SEQ ID NO: 425;
- c) a heavy chain comprising the amino acid sequence of SEQ ID NO: 426 and a light chain comprising the amino acid sequence of SEQ ID NO: 427; or
- d) a heavy chain comprising the amino acid sequence of SEQ ID NO: 428 and a light chain comprising the amino acid sequence of SEQ ID NO: 429.

22. The method of claim 21, wherein the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 414 and a light chain comprising the amino acid sequence of SEQ ID NO: 415.

23. The method of any one of the previous claims, wherein the immunoconjugate comprises:
a light chain comprising the amino acid sequence of SEQ ID NO: 415; and
a heavy chain-modified hIL-2 protein fusion comprising the amino acid sequence of SEQ ID NO: 532.

24. The method of any one of the previous claims, wherein the antagonistic anti-PD-1 antibody and the immunoconjugate are administered to the subject together in a mixture, concurrently as single agents, or sequentially as single agents in any order.

25. The method of claim 24, comprising:
administering the immunoconjugate prior to administering the antagonistic anti-PD-1 antibody;
administering the antagonistic anti-PD-1 antibody prior to administering the immunoconjugate; or

administering the immunoconjugate at substantially the same time as administering the antagonistic anti-PD-1 antibody.

26. The method of any one of the previous claims, wherein the cancer is melanoma, Merkel cell carcinoma, non-small cell lung carcinoma, renal cell carcinoma, triple negative breast cancer, squamous cell carcinoma of the head/neck, hepatocellular carcinoma, or microsatellite instability-high tumors or tumors with deficient DNA mismatch repair.

27. A method of treating a renal cell carcinoma, a triple negative breast cancer, a squamous cell carcinoma of the head/neck, a Merkel cell carcinoma, a hepatocellular carcinoma, or a microsatellite instability-high tumor or tumor with deficient DNA mismatch repair in a subject, the method comprising administering to the subject:

an anti-human PD-1 (hPD-1) antibody-modified human interleukin-2 (hIL-2) immunoconjugate comprising:

a modified hIL-2 protein comprising a D20A, D20S, D20Q, D20M, D20I, D20V, D20N, D20G, D20T, or D20E substitution at amino acid position 20 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345 and an R38E substitution at amino acid position 38 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345; and

an anti-hPD-1 antibody, or antigen-binding fragment thereof, that immunospecifically binds to hPD-1, wherein the antibody or antigen-binding fragment thereof comprises:

- (i) a heavy chain complementarity determining region 1 (CDR1) comprising the amino acid sequence of SEQ ID NO: 418, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 419, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 420, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 421, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 422, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 423;
- (ii) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 386, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 387, a

- heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 388, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 389, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 390, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 391;
- (iii) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 396, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 397, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 398, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 399, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 400, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 401; or
- (iv) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 406, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 407, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 408, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 409, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 410, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 411.

28. The method of claim 27, wherein the modified hIL-2 protein comprises the amino acid sequence of any one of SEQ ID NOs: 149, 307, 607-611, 614, 617, or 620.

29. The method of claim 27 or 28, wherein the modified hIL-2 protein comprises a D20A substitution relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345 and a R38E substitution relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345.

30. The method of claim 29, wherein the modified hIL-2 protein comprises the amino acid sequence of SEQ ID NO: 149.

31. The method of any one of claims 27-30, wherein the modified hIL-2 protein further comprises a deletion or substitution at amino acid position 3 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345.

32. The method of claim 31, wherein the substitution at amino acid position 3 of the modified hIL-2 protein is T3A.
33. The method of claim 32, wherein the modified hIL-2 protein comprises the amino acid sequence of SEQ ID NO: 216.
34. The method of claim 31, wherein the modified hIL-2 protein comprises the amino acid sequence of SEQ ID NO: 218.
35. The method of any one of claims 27-34, wherein the modified hIL-2 protein further comprises a deletion or substitution at amino acid position 125 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345.
36. The method of claim 35, wherein the substitution at amino acid position 125 is C125A.
37. The method of claim 36, wherein the modified hIL-2 protein comprises the amino acid sequence of SEQ ID NO: 215, 217, or 219.
38. The method of claim 37, wherein the modified hIL-2 protein comprises the amino acid sequence of SEQ ID NO: 217.
39. The method of any one of claims 27-38, wherein the modified hIL-2 protein is fused to the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate at the N-terminus of an antibody light chain, the C-terminus of an antibody light chain, the N-terminus of an antibody heavy chain, the C-terminus of an antibody heavy chain, the N-terminus of the antigen-binding fragment, or the C-terminus of the antigen-binding fragment.
40. The method of any one of claims 27-39, wherein the modified hIL-2 protein is directly fused by a peptide bond to the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate.

41. The method of claim 40, wherein the modified hIL-2 protein is directly fused by a peptide bond to the C-terminal amino acid residue of the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate.
42. The method of any one of claims 27-39, wherein the modified hIL-2 protein is fused to the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate through a linker.
43. The method of any one of claims 27-42, wherein the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate comprises:
- a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 416 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 417;
 - b) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 384 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 385;
 - c) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 394 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 395; or
 - d) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 404 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 405.
44. The method of any one of claims 27-43, wherein the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate comprises an IgG1 heavy chain constant region.
45. The method of claim 44, wherein the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate comprises an L235A substitution and a G237A substitution, according to EU numbering.

46. The method of any one of claims 27-45, wherein the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate comprises:

- a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 414 and a light chain comprising the amino acid sequence of SEQ ID NO: 415;
- b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 424 and a light chain comprising the amino acid sequence of SEQ ID NO: 425;
- c) a heavy chain comprising the amino acid sequence of SEQ ID NO: 426 and a light chain comprising the amino acid sequence of SEQ ID NO: 427; or
- d) a heavy chain comprising the amino acid sequence of SEQ ID NO: 428 and a light chain comprising the amino acid sequence of SEQ ID NO: 429.

47. The method of claim 46, wherein the anti-hPD-1 antibody, or antigen-binding fragment thereof, portion of the immunoconjugate comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 414 and a light chain comprising the amino acid sequence of SEQ ID NO: 415.

48. The method of any one of claims 27-47, wherein the immunoconjugate comprises:
a light chain comprising the amino acid sequence of SEQ ID NO: 415; and
a heavy chain-modified hIL-2 protein fusion comprising the amino acid sequence of SEQ ID NO: 532.

49. Use of

(A) an anti-hPD-1 antibody-modified human interleukin-2 (hIL-2) immunoconjugate comprising:

a modified hIL-2 protein comprising a D20A, D20S, D20Q, D20M, D20I, D20V, D20N, D20G, D20T, or D20E substitution at amino acid position 20 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345 and an R38E substitution at amino acid position 38 relative to the non-modified hIL-2 amino acid sequence of SEQ ID NO: 345; and

an anti-hPD-1 antibody, or antigen-binding fragment thereof, that immunospecifically binds to hPD-1, wherein the antibody or antigen-binding fragment thereof comprises:

- (i) a heavy chain complementarity determining region 1 (CDR1) comprising the amino acid sequence of SEQ ID NO: 418, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 419, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 420, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 421, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 422, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 423;
- (ii) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 386, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 387, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 388, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 389, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 390, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 391;
- (iii) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 396, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 397, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 398, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 399, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 400, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 401; or
- (iv) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 406, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 407, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 408, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 409, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 410, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 411; and

(B) an antagonistic anti-PD-1 antibody that binds PD-1 in the presence of the immunoconjugate for the treatment of cancer.