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(54) Title: INTERFERON α 2B VARIANTS

(57) Abstract: The present invention provides a fusion polypeptide comprising a first domain and a second domain, wherein the first domain comprises a polypeptide ligand which binds to a cell surface-associated antigen and the second domain comprises aglycosylated interferon α 2b (IFN α 2b) having a sequence of SEQ ID NO: 1 or SEQ ID NO: 2. The aglycosylated IFN α 2b further comprises one or more amino acid substitutions or deletions which attenuate the activity of the aglycosylated IFN α 2b.



INTERFERON α 2b VARIANTS

FIELD OF INVENTION

[0001] The present invention relates to polypeptides comprising ligands targeted against cell surface antigens and aglycosylated interferon α 2b (IFN α 2b) and the use of these polypeptides in the treatment of cancer.

BACKGROUND OF INVENTION

[0002] Numerous peptide and polypeptide molecules have been described to function by interacting with a receptor on a cell surface, and thereby stimulating, inhibiting, or otherwise modulating a biological response, usually involving signal transduction pathways inside the cell that bears the said receptor. Examples of such molecules include peptide and polypeptide hormones, cytokines, chemokines, growth factors, apoptosis-inducing factors and the like. These molecules can be either soluble or can be attached to the surface of another cell.

[0003] Due to the biological activity of such molecules, some have potential use as therapeutics. Several peptide or polypeptide molecules have been approved by regulatory agencies as therapeutic products, including, for example, human growth hormone, insulin, interferon IFN α 2b, IFN α 2a, IFN β , erythropoietin, G-CSF and GM-CSF. Many of these and other peptides have demonstrated potential in therapeutic applications, but have also exhibited toxicity when administered to human patients. One reason for toxicity is that most of these molecules trigger receptors on a variety of cells, including cells other than those that mediate the therapeutic effect. For example, when IFN α 2b is used to treat multiple myeloma its utility resides, at least in part, in its binding to type I interferon receptors on the myeloma cells, which in turn triggers reduced proliferation and hence limits disease progression. Unfortunately, however, this IFN also binds to numerous other, normal cells within the body, triggering a variety of other cellular responses, some of which are harmful (e.g. flu-like symptoms, neutropenia, depression). A consequence of such “off target” activity of peptides is that many peptides are not suitable as drug candidates. In this context, “off target activity” refers to activity on the peptide's natural

receptor, but on the surface of cells other than those that mediate therapeutically beneficial effects.

[0004] Even though some peptides, such as IFN α 2b, are approved for the treatment of medical conditions, they are poorly tolerated due to their “off target” biological activity. The off-target activity and associated poor tolerability also mean that some of these peptide based drugs cannot be administered at sufficiently high dosages to produce optimal therapeutic effects on the target cells which mediate the therapeutic effect.

[0005] Similarly, it has been known since the mid-1980’s that interferons, in particular IFN α , are able to increase apoptosis and decrease proliferation of certain cancer cells. These biological activities are mediated by type I interferon receptors on the surface of the cancer cells which, when stimulated, initiate various signal transduction pathways leading to reduced proliferation and/or the induction of terminal differentiation or apoptosis. IFN α has been approved by the FDA for the treatment of several cancers including melanoma, renal cell carcinoma, B cell lymphoma, multiple myeloma, chronic myelogenous leukemia (CML) and hairy cell leukemia. A “direct” effect of IFN α on the tumour cells is mediated by the IFN α binding directly to the type I IFN receptor on those cells and stimulating apoptosis, terminal differentiation or reduced proliferation. One “indirect” effect of IFN α on non-cancer cells is to stimulate the immune system, which may produce an additional anti-cancer effect by causing the immune system to reject the tumour.

[0006] Unfortunately, the type I interferon receptor is also present on most non-cancerous cells. Activation of this receptor on such cells by IFN α causes the expression of numerous pro-inflammatory cytokines and chemokines, leading to toxicity. Such toxicity prevents the dosing of IFN α to a subject at levels that exert the maximum anti-proliferative and pro-apoptotic activity on the cancer cells.

[0007] Ozzello *et al.* (Breast Cancer Research and Treatment 25:265-76, 1993) described covalently attaching human IFN α to a tumour-targeting antibody, thereby localizing the direct inhibitory activity of IFN α to the tumour as a way of reducing tumour growth rates, and demonstrated that such conjugates have anti-tumour activity in a xenograft model of a human cancer. The mechanism of the observed anti-cancer activity

was attributed to a direct effect of IFN α on the cancer cells, since the human IFN α used in the experiments did not interact appreciably with the murine type I IFN receptor, which could have lead to an indirect anti-cancer effect. Because of this lack of binding of the human IFN α to the murine cells, however, the authors could not evaluate the toxicity of the antibody-IFN α conjugate relative to free IFN α . These authors used a chemical method to attach the IFN α to the antibody.

[0008] Alkan *et al.*, (Journal of Interferon Research, volume 4, number 3, p. 355-63, 1984) demonstrated that attaching human IFN α to an antibody that binds to the Epstein-Barr virus (EBV) membrane antigen (MA) increased its antiproliferative activities towards cells that express the EBV-MA antigen. This increased potency was dependent on both antigen expression by the target cells and the binding specificity of the antibody. The cell line tested was the cancer cell line QIMR-WIL, a myeloblastic leukemia. The authors suggested that the attachment of IFN α to an antibody could be used as a treatment for cancer since it would reduce tumour growth. Alkan *et al* did not address the potential toxicity of these antibody-IFN α conjugates arising from their interactions with normal, antigen-negative cells.

[0009] It is also known that the linkage between an antibody and IFN α may be accomplished by making a fusion protein construct. For example, IDEC (WO01/97844) disclose a direct fusion of human IFN α to the C terminus of the heavy chain of an IgG targeting the tumour antigen CD20. Other groups have disclosed the use of various linkers between the C-terminus of an IgG heavy chain and the IFN α . For example, US 7,456,257 discloses that the C-terminus of an antibody heavy chain constant region may be connected to IFN α via an intervening serine-glycine rich (S/G) linker of the sequence (GGGGS)_n, where n may be 1, 2 or 3, and that there are no significant differences in the IFN α activity of the fusion protein construct regardless of linker length.

[0010] Morrison *et al.* (US2011/0104112 A1; and Xuan C, Steward KK, Timmerman JM, Morrison SL. Targeted delivery of interferon- α via fusion to anti-CD20 results in potent antitumor activity against B-cell lymphoma. Blood 2010;115:2864–71) also disclose IFN α linked to the C-terminus of the heavy chain of a cancer-targeting IgG

antibody, with an intervening S/G linker, and observed that the fusion of the IgG and linker to the IFN α reduced the activity of IFN α on cells that did not express the corresponding antigen on the cell surface. The decreased IFN activity of these fusion protein constructs was modest when compared to human non-fusion protein IFN α (free IFN α) acting on human cells, but appeared to be more significant for murine IFN α on murine cells. The decrease in the activity of human IFN α that results from fusing it to the C-terminus of an antibody, as observed by Morrison *et al*, and in US 7,456,257 is modest and is generally considered to be a disadvantage since it reduces potency of the IFN. This disadvantage was pointed out, for example, by Rossi *et al* (Blood vol. 114, No. 18, pp3864-71), who used an alternative strategy of attaching the IFN α to a tumor targeting antibody in such a way that no loss in IFN α activity was observed.

[0011] In general the prior art teaches to use a potent IFN and to target this IFN to cancer cells. While this approach results in an increase in activity of the IFN against cancer cells, it does not address the issue of activity of the IFN on normal “off-target” cells. In prior art examples referred to above, the human IFN α portion of the antibody-IFN α fusion protein maintained a high proportion of native IFN α activity when exposed to human cells that do not express the corresponding antigen on their cell surfaces. This activity may lead to toxicity arising from the activation of non-cancerous, normal (“off target”) cells by the IFN α portion of the fusion protein. Accordingly, there exists a need to decrease the “off-target” activity of IFN-based drugs, while retaining the “on-target”, therapeutic effect of such drugs. The maintenance of target-specific activity and at the same time a reduction in non-target toxicity of these types of therapeutic agents would create a greater therapeutic concentration window for therapeutically useful peptides. It would for example be desirable to use human IFN α in a form such that its activity can be directed to the cancer cells while minimizing its effects on normal human cells. Ideally the type I interferon receptor on the cancer cells would be maximally stimulated, while the same receptor on non-cancerous cells would experience minimal stimulation. There is a need to target human IFN α to the cancer cells in such a way that it has dramatically more activity on the cancer cells, which display the antigen, than on the normal cells, which do not display the antigen. The same logic applies to other potentially therapeutic molecules,

e.g. other cytokines, peptide and polypeptide hormones, chemokines, growth factors, apoptosis-inducing factors and the like.

[0012] The logic of this approach has been demonstrated in WO 2013/059885, and WO 2014/178820, the disclosure of each of which is incorporated herein by cross reference.

SUMMARY OF INVENTION

[0013] In a first aspect the present invention provides a fusion polypeptide comprising a first domain and a second domain, wherein the first domain comprises a polypeptide ligand which binds to a cell surface-associated antigen and the second domain comprises human aglycosylated interferon α 2b (IFN α 2b) having a sequence of SEQ ID NO: 1 or SEQ ID NO: 2 and wherein the aglycosylated IFN α 2b further comprises one or more amino acid substitutions or deletions which attenuate the activity of the aglycosylated IFN α 2b.

[0014] In another aspect the present invention provides a fusion polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs: 31, 61 to 77, 83 and 87, and a sequence selected from the group consisting of SEQ ID NOs: 81, 82 and 84.

[0015] In another aspect the present invention provides a fusion polypeptide comprising SEQ ID NO: 87 and SEQ ID NO: 81.

[0016] In another aspect the present invention provides a fusion polypeptide comprising SEQ ID NO: 79 and SEQ ID NO: 85.

[0017] In another aspect the present invention provides a fusion polypeptide comprising SEQ ID NO: 80 and SEQ ID NO: 86.

[0018] In another aspect the present invention provides a fusion polypeptide comprising SEQ ID NO: 78.

[0019] In another aspect the present invention provides a composition comprising the fusion polypeptide of the present invention and a pharmaceutically acceptable carrier or diluent.

[0020] In another aspect the present invention provides a method of treating a tumour in a subject comprising administering to the subject the fusion polypeptide of the present invention or the composition of the present invention wherein the first domain of the fusion polypeptide binds to cells of the tumour.

[0021] In another aspect the present invention provides the use of the fusion polypeptide of the present invention in the treatment of a tumour wherein first domain of the fusion polypeptide binds to the tumour.

[0022] In another aspect the present invention provides an isolated polynucleotide(s) encoding the fusion polypeptide(s) of the present invention.

[0023] In another aspect the present invention provides a vector comprising the one or more polynucleotides of the present invention.

[0024] In another aspect the present invention provides a transformed cell comprising the vector of the present invention.

[0025] In another aspect the present invention provides a method of generating a polypeptide ligand-attenuated IFN α 2b fusion polypeptide in mammalian cells, wherein the polypeptide ligand-attenuated IFN α 2b fusion polypeptide has reduced heterogeneity and/or enhanced FcRn binding and/or improved target selectivity, the method comprising culturing a recombinant mammalian cell comprising a polynucleotide encoding the polypeptide ligand-attenuated IFN α 2b fusion polypeptide wherein T106 of the IFN α 2b sequence is replaced with another amino acid or is deleted such that on expression in mammalian cells the IFN α 2b component of the fusion protein is aglycosylated.

BRIEF DESCRIPTION OF THE DRAWINGS

[0026] Figure 1: Anti-proliferative activity upon treatment of (A) ARP1 and (B) NCI-H929 cells with anti-CD38-attenuated IFN α 2b fusion proteins in IgG1 or IgG4 format with and without O-linked glycosylation of the IFN α 2b.

[0027] Figure 2 A, B, C, D and E. Anti-proliferative activity of anti-CD38-attenuated IFN α 2b fusion proteins with different amino acid substitutions removing the O-linked glycosylation site from the attenuated IFN α 2b.

[0028] Figure 3: On-target activities of (A) A10.21 and (B) A10.43 anti-CD38-attenuated IFN α 2b fusion proteins with (T106T) and without (T106A) O-linked glycosylation of the IFN α 2b.

[0029] Figure 4: Off-target activities of (A) A10.21 and (B) A10.43 anti-CD38-attenuated IFN α 2b fusion proteins with (T106T) and without (T106A) O-linked glycosylation of the IFN α 2b.

[0030] Figure 5: Off-target activity by anti-CD38-attenuated IFN α 2b fusion proteins with (T106T) and without (T106A or Δ T106) O-linked glycosylation of the IFN α 2b.

[0031] Figure 6: A, B, C, D, E and F: Off-target activity of anti-CD38-attenuated IFN α 2b fusion proteins with different amino acid substitutions removing the O-linked glycosylation site from the attenuated IFN α 2b.

[0032] Figure 7: Off-target activity of A10.43 anti-CD38 –attenuated IFN α 2b fusion proteins with (T106T) or without (T106A) O-linked glycosylation of the IFN α 2b.

[0033] Figure 8: Potency of sub-optimal dosages of anti-CD38-attenuated IFN α 2b fusion proteins with (T106T) or without (T106A) O-linked glycosylation in treating tumours in a murine model of multiple myeloma.

[0034] Figure 9: Number of charged species of A10.21 anti-CD38-attenuated IFN α 2b fusion proteins with (T106T) or without (T106A, Δ T106, T106S, T106V, T106G, T106E) O-linked glycosylation of the IFN α 2b, as assessed by the number of bands on IEF gel.

[0035] Figure 10: Number of charged species of A10.21 anti-CD38-attenuated IFN α 2b fusion proteins with (T106T) or without (T106A) O-linked glycosylation of the IFN α 2b and with varying Fc isotypes, as assessed by the number of bands on IEF gel.

[0036] Figure 11: Number of charged species of A10.21 (IgG4 with S228P) anti-CD38-attenuated IFN α 2b fusion proteins with (T106T) or without (T106A) O-linked glycosylation of the IFN α 2b in the presence of YTE substitutions in the antibody constant region, as assessed by the number of bands on IEF gel.

[0037] Figure 12: Number of charged species of A10.21 (IgG4 with S228P) anti-CD38-attenuated IFN α 2b fusion proteins with (T106T) or without (T106A) O-linked glycosylation of the IFN α 2b in the presence of a variety of IFN attenuating substitutions, as assessed by the number of bands on IEF gel.

[0038] Figure 13: Number of charged species of antibodies with differing target specificities; anti-CD138 antibody, anti-HLA antibody and anti-CD38 antibody (A02.12) (all IgG4 with S228P) fused to attenuated IFN α 2b with (T106T) or without (T106A) O-linked glycosylation of the IFN α 2b, as assessed by the number of bands on IEF gel.

[0039] Figure 14: “On-target” activities of anti-CD38-attenuated IFN α 2b fusion proteins (A10.21 IgG4 (S228P) IFN (A145D)) with (T106T) and without (T106A, Δ T106, T106S, T106V, T106G, T106E) O-linked glycosylation of the IFN α 2b.

[0040] Figure 15: “On-target” activities of two different anti-CD38 antibody-attenuated IFN α 2b fusion proteins (A02.12 and A10.21, both IgG4 with S228P) which bind different epitopes on CD38 with (T106T) or without (T106A) O-linked glycosylation of the IFN α 2b.

[0041] Figure 16: “On-target” activities of A10.21 anti-CD38-attenuated IFN α 2b fusion proteins (A10.21 IgG4 (S228P) IFN) with (T106T) and without (T106A) O-linked glycosylation of the IFN α 2b, with a variety of IFN attenuating substitutions (R33A, R144I, R145Q, A145K or A145G).

[0042] Figure 17: "On-target" activities of antibodies with differing target specificities; anti-CD138 antibody and anti-HLA antibody (both IgG4 with S228P) fused to attenuated IFN α 2b with (T106T) or without (T106A) O-linked glycosylation of the IFN α 2b.

[0043] Figure 18: "On-target" activities of A10.21 anti-CD38-attenuated IFN α 2b fusion proteins (A10.21 IgG4 (S228P) IFN (A145D)) with (T106T) and without (T106A) O-linked glycosylation of the IFN α 2b, in the presence of YTE substitution in the antibody heavy chain.

[0044] Figure 19: "On-target" activities of A10.21 anti-CD38-attenuated IFN α 2b (A145D) fusion proteins with (T106T) and without (T106A) O-linked glycosylation of the IFN α 2b, with a variety of immunoglobulin Fc isotypes.

[0045] Figure 20: Selectivity index of A10.21 anti-CD38-attenuated IFN α 2b fusion proteins with and without O-linked glycosylation of the IFN α 2b in the presence of a variety of amino acid substitutions to remove glycosylation of the IFN, YTE substitutions in the immunoglobulin constant region for extended half-life, IFN attenuation and Fc isotypes.

DETAILED DESCRIPTION OF THE INVENTION

[0046] Throughout this specification, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element or integer or group of elements or integers but not the exclusion of any other element or integer or group of elements or integers.

[0047] The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

[0048] All publications mentioned in this specification are herein incorporated by reference in their entirety.

[0049] It must be noted that, as used in the subject specification, the singular forms "a", "an" and "the" include plural aspects unless the context clearly dictates otherwise. Thus, for example, reference to "an agent" includes a single agent, as well as two or more agents; reference to "a molecule" includes a single molecule, as well as two or more molecules; and so forth.

[0050] The constructs of the present invention are polypeptide ligand-attenuated aglycosylated IFN α 2b fusion constructs, which show an elevated antigen-selectivity index with respect to activating signaling pathways due to the action of both the ligand targeting to a cell surface receptor on a cell of interest and the attenuated IFN α 2b having reduced affinity to a cell surface IFN receptor. These constructs are based on the discovery outlined in WO 2013/059885 that, in the context of an antibody-IFN fusion construct, the IFN portion can be mutated in such a way that the IFN activity on antigen-negative cells is dramatically attenuated, while the IFN activity on antigen-positive cells is only modestly, if at all, attenuated. Such constructs display one, two, three, four or five orders of magnitude greater potency on antigen-positive cells compared to antigen negative cells than does the free IFN. In one embodiment, the antibody-attenuated IFN construct retains at least 1%, at least 10%, at least 20%, at least 30%, at least 40% or at least 50% of the potency on antigen-positive cells as the non-attenuated free (*i.e.* not attached to an antibody) IFN. In addition, in one embodiment the antibody-attenuated IFN construct retains at least 30%, at least 50%, at least 75% or at least 90% of the maximal activity of the non-attenuated free (*i.e.* not attached to an antibody) IFN; in this context, "maximal activity" should be understood as meaning the amount of signaling activity (or downstream effect thereof) at the high, plateau portion of a dose-response curve, where further increases in the agent does not further increase the amount of response).

[0051] The present inventors have now found that an unexpected advantage is obtained by using constructs comprising aglycosylated IFN α 2b as compared to the constructs comprising O-glycosylated IFN α 2b. In some embodiments these advantages include one or more of an increase in ON-target activity, increased target selectivity and

enhanced affinity to FcRn, whilst providing a less heterogeneous product than the O-glycosylated IFN α 2b when produced in a mammalian cell expression system. Enhanced FcRn binding is desirable to improve the pK of a biological therapeutic agent which comprises an Fc region. Increased target selectivity is desirable as it potentially reduces OFF-target toxicity whilst substantially maintaining ON-target activity. A reduction in heterogeneity allows increases in yields of purified product from a mammalian cell culture system.

[0052] Accordingly, in a first aspect, the present invention provides a fusion polypeptide comprising a first and a second domain, wherein the first domain comprises a polypeptide ligand which binds to a cell surface-associated antigen and the second domain comprises aglycosylated interferon α 2b (IFN α 2b) having a sequence of SEQ ID NO: 1 or SEQ ID NO: 2, and wherein the aglycosylated IFN α 2b further comprises one or more amino acid substitutions or deletions which attenuate the activity of the aglycosylated IFN α 2b.

[0053] In an embodiment of the present invention the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 in which the residue at position 106 is A, C, D, E, F, G, H, I, K, L, M, N, P, Q, R, S, V, W or Y. This represents a substitution of the T106 normally present in human IFN α 2b with a naturally occurring amino acid which does not permit O-linked glycosylation at this position when produced in mammalian cell culture. In another embodiment of the present invention the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 2. This represents a deletion of residue T106 found in normal human IFN α 2b, which also removes the O-linked glycosylation site found in this molecule. As demonstrated herein, each of the substitutions or deletion removes the O-glycosylation site from human attenuated IFN α 2b and reduces the heterogeneity of the molecule as measured in IEF gels, when expressed by CHO cells, and whilst at least substantially maintaining the activity of the attenuated IFN α 2b to bind cell surface IFN receptors and to initiate downstream signaling.

[0054] In additional embodiments the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 modified by an attenuating mutation selected from the group consisting of L15A,

R22A, R23A, S25A, L26A, F27A, L30A, L30V, K31A, D32A, R33A, R33K, R33Q, H34A, Q40A, D114R, L117A, R120A, R120E, R125A, R125E, K131A, E132A, K133A, K134A, M148A, R149A, S152A, L153A, N156A, (L30A, H57Y, E58N and Q61S), (M148A, H57Y, E58N and Q61S), (L153A, H57Y, E58N and Q61S), (R144A, H57Y, E58N and Q61S), (N65A, L80A, Y85A and Y89A,) (N65A, L80A, Y85A, Y89A and D114A), (N65A, L80A, Y85A, Y89A and L117A), (N65A, L80A, Y85A, Y89A and R120A), (Y85A, Y89A and D114A), (D114A and R120A), (L117A and R120A), (L117A, R120A and K121A), (R120A and K121A), (R120E and K121E), replacement of R at position 144 with A, D, E, G, H, I, K, L, N, Q, S, T, V or Y, replacement of A at position 145 with D, E, G, H, I, K, L, M, N, Q, S, T, V or Y, and deletion of residues L161 to E165.

[0055] In additional embodiments the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 2 modified by an attenuating mutation selected from the group consisting of L15A, R22A, R23A, S25A, L26A, F27A, L30A, L30V, K31A, D32A, R33A, R33K, R33Q, H34A, Q40A, D113R, L116A, R119A, R119E, R124A, R124E, K130A, E131A, K132A, K133A, M147A, R148A, S149A, L152A, N155A, (L30A, H57Y, E58N and Q61S), (M147A, H57Y, E58N and Q61S), (L152A, H57Y, E58N and Q61S), (R143A, H57Y, E58N and Q61S), (N65A, L80A, Y85A and Y89A,) (N65A, L80A, Y85A, Y89A and D113A), (N65A, L80A, Y85A, Y89A and L116A), (N65A, L80A, Y85A, Y89A and R1190A), (Y85A, Y89A and D113A), (D113A and R119A), (L116A and R119A), (L116A, R119A and K120A), (R119A and K120A), (R119E and K120E), replacement of R at position 143 with A, D, E, G, H, I, K, L, N, Q, S, T, V or Y, replacement of A at position 144 with D, E, G, H, I, K, L, M, N, Q, S, T, V or Y, and deletion of residues L160 to E164.

[0056] In another embodiment the sequence of the aglycosylated IFN α 2b modified by an attenuating mutation is selected from the group consisting of SEQ ID NOs: 3 to 30 and SEQ ID NOs: 32 to 47.

[0057] In another embodiment the cell surface-associated antigen is selected from the group consisting of CD38, CD138, RANK-Ligand, HM1.24, CD56, CS1, CD20, CD74, IL-6R, Blys (BAFF), BCMA, HLA-SR, HLA-DR, Kininogen, beta2 microglobulin, FGFR3, ICAM-1, matriptase, CD52, EGFR, GM2, alpha4-integrin, IFG-1R, KIR, CD3,

CD4, CD8, CD24, CD44, CD69, CD71, CD79, CD83, CD86, CD96, HLA, PD-1, ICOS, CD33, CD115, CD11c, CD19, CD52, CD14, FSP1, FAP, PDGFR alpha, PDGFR beta, ASGR1, ASGR2, FSP1, RTI140/Ti-alpha, HTI56, VEGF receptor, CD241 the product of the RCHE gene, CD117 (c-kit), CD71 (transferrin receptor), CD36 (thrombospondin receptor), CD34, CD45RO, CD45RA, CD115, CD168, CD235, CD236, CD237, CD238, CD239 and CD240.

[0058] In certain embodiments the polypeptide ligand is an antibody or antigen binding portion thereof.

[0059] In another embodiment the polypeptide ligand is an antibody which binds CD38. It is preferred that the V_H sequence of the antibody is selected from the group consisting of SEQ ID Nos: 48 to 56 and 58 and that the V_L sequence of the antibody is selected from the group consisting of SEQ ID Nos: 81, 82 and 84.

[0060] In another embodiment the polypeptide ligand is an antibody which binds CD138. It is preferred that the V_H sequence of the antibody is SEQ ID NO: 59 and that the V_L sequence of the antibody is SEQ ID NO: 85.

[0061] In another embodiment the polypeptide ligand binds RANK-Ligand. It is preferred that the sequence of the polypeptide ligand is SEQ ID NO: 57.

[0062] In another embodiment the first domain is linked to the second domain via a peptide bond. The first domain may be linked to the second domain directly by a peptide bond (a "zero-length linker") or via a peptide linker of from 1 to 20 amino acids in length. The linker may be $(SGGGGS)_n$ where n is 1 to 3. Examples of linkers include SGGGGS and SGGGSGGGGSGGGGS.

[0063] In another embodiment the C-terminus of the first domain is linked to N-terminus of the second domain.

[0064] In another embodiment the amino acid sequence of the first domain is glycosylated.

[0065] In another aspect the present invention provides a fusion polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs: 31, 61 to 77, 83 and 87, and a sequence selected from the group consisting of SEQ ID NOs: 81, 82 and 84.

[0066] In another aspect the present invention provides a fusion polypeptide comprising SEQ ID NO: 87 and SEQ ID NO: 81.

[0067] In another aspect the present invention provides a fusion polypeptide comprising SEQ ID NO: 79 and SEQ ID NO: 85.

[0068] In another aspect the present invention provides a fusion polypeptide comprising SEQ ID NO: 80 and SEQ ID NO: 86.

[0069] In another aspect the present invention provides a fusion polypeptide comprising SEQ ID NO: 78.

[0070] As will be understood from the discussion above particular forms of the fusion polypeptide of the current invention are as follows:

- a. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 in which the residue at position 106 is A.
- b. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 in which the residue at position 106 is C.
- c. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 in which the residue at position 106 is D.
- d. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 in which the residue at position 106 is E.
- e. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 in which the residue at position 106 is F.
- f. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 in which the residue at position 106 is G.

- g. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 in which the residue at position 106 is H.
- h. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 in which the residue at position 106 is I.
- i. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 in which the residue at position 106 is K.
- j. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 in which the residue at position 106 is L.
- k. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 in which the residue at position 106 is M.
- l. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 in which the residue at position 106 is N.
- m. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 in which the residue at position 106 is P.
- n. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 in which the residue at position 106 is Q.
- o. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 in which the residue at position 106 is R.
- p. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 in which the residue at position 106 is V.
- q. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 in which the residue at position 106 is W.
- r. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 in which the residue at position 106 is Y.

- s. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 or SEQ ID NO: 2 modified by the attenuating mutation L15A.
- t. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 or SEQ ID NO: 2 modified by the attenuating mutation A19W.
- u. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 or SEQ ID NO: 2 modified by the attenuating mutation R22A.
- v. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 or SEQ ID NO: 2 modified by the attenuating mutation R23A.
- w. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 or SEQ ID NO: 2 modified by the attenuating mutation S25A.
- x. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 or SEQ ID NO: 2 modified by the attenuating mutation L26A.
- y. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 or SEQ ID NO: 2 modified by the attenuating mutation F27A.
- z. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 or SEQ ID NO: 2 modified by the attenuating mutation L30A or L30V.

- aa. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 or SEQ ID NO: 2 modified by the attenuating mutation K31A.
- bb. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 or SEQ ID NO: 2 modified by the attenuating mutation D32A.
- cc. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 or SEQ ID NO: 2 modified by the attenuating mutation R33A, R33K or R33Q.
- dd. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 or SEQ ID NO: 2 modified by the attenuating mutation H34A.
- ee. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 or SEQ ID NO: 2 modified by the attenuating mutation Q40A.
- ff. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 modified by the attenuating mutation D114R or SEQ ID NO: 2 modified by the attenuating mutation D113R.
- gg. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 modified by the attenuating mutation L117A or SEQ ID NO: 2 modified by the attenuating mutation L116A.
- hh. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 modified by the attenuating mutation R120A or R120E or SEQ ID NO: 2 modified by the attenuating mutation R119A or R119E.

- ii. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 modified by the attenuating mutation R125A or R125E or SEQ ID NO: 2 modified by the attenuating mutation R124A or R124E.
- jj. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 modified by the attenuating mutation K131A or SEQ ID NO: 2 modified by the attenuating mutation K130A.
- kk. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 modified by the attenuating mutation E132A or SEQ ID NO: 2 modified by the attenuating mutation E131A.
- ll. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 modified by the attenuating mutation K133A or SEQ ID NO: 2 modified by the attenuating mutation K132A.
- mm. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 modified by the attenuating mutation K134A or SEQ ID NO: 2 modified by the attenuating mutation K133A.
- nn. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 modified by the attenuating mutation M148A or SEQ ID NO: 2 modified by the attenuating mutation M147A.
- oo. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 modified by the attenuating mutation R149A or SEQ ID NO: 2 modified by the attenuating mutation R148A.

- pp. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 modified by the attenuating mutation S152A or SEQ ID NO: 2 modified by the attenuating mutation S151A.
- qq. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 modified by the attenuating mutation L153A or SEQ ID NO: 2 modified by the attenuating mutation L152A.
- rr. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 modified by the attenuating mutation N156A or SEQ ID NO: 2 modified by the attenuating mutation N155A.
- ss. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 or SEQ ID NO: 2 modified by the attenuating mutations L30A, H57Y, E58N and Q61S.
- tt. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 modified by the attenuating mutations M148A, H57Y, E58N and Q61S or SEQ ID NO: 2 modified by the attenuating mutations M147A, H57Y, E58N and Q61S.
- uu. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 modified by the attenuating mutations L153A, H57Y, E58N and Q61S or SEQ ID NO: 2 modified by the attenuating mutations L152A, H57Y, E58N and Q61S.
- vv. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 modified by the attenuating mutations R144A, H57Y, E58N and Q61S or SEQ ID NO: 2 modified by the attenuating mutations R143A, H57Y, E58N and Q61S.

- ww. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 or SEQ ID NO: 2 modified by the attenuating mutations N65A, L80A, Y85A and Y89A.
- xx. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 modified by the attenuating mutations N65A, L80A, Y85A, Y89A and D114A or SEQ ID NO: 2 modified by the attenuating mutations N65A, L80A, Y85A, Y89A and D113A.
- yy. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 modified by the attenuating mutations N65A, L80A, Y85A, Y89A and L117A or SEQ ID NO: 2 modified by the attenuating mutations N65A, L80A, Y85A, Y89A and L116A.
- zz. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 modified by the attenuating mutations N65A, L80A, Y85A, Y89A and R120A or SEQ ID NO: 2 modified by the attenuating mutations N65A, L80A, Y85A, Y89A and R119A.
- aaa. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 modified by the attenuating mutations Y85A, Y89A and D114A or SEQ ID NO: 2 modified by the attenuating mutations Y85A, Y89A and D113A.
- bbb. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 modified by the attenuating mutations D114A and R120A or SEQ ID NO: 2 modified by the attenuating mutations D113A and R119A.
- ccc. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 modified by the attenuating mutations L117A and R120A or SEQ ID NO: 2 modified by the attenuating mutations L116A and R119A.

- ddd. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 modified by the mutations L117A, R120A and K121A or SEQ ID NO: 2 modified by the mutations L116A, R119A and K120A.
- eee. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 modified by the mutations R120A and K121A or SEQ ID NO: 2 modified by the mutations R119A and K120A.
- fff. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 modified by the mutations R120E and K121E or SEQ ID NO: 2 modified by the mutations R119E and K120E.
- ggg. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b SEQ ID NO: 1 is modified by replacement of R at position 144 with A, D, E, G, H, I, K, L, N, Q, S, T, V or Y or SEQ ID NO: 2 is modified by replacement of R at position 143 with A, D, E, G, H, I, K, L, N, Q, S, T, V or Y.
- hhh. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 modified by replacement of A at position 145 with D, E, G, H, I, K, L, M, N, Q, S, T, V or Y or SEQ ID NO: 2 modified by replacement of A at position 144 with D, E, G, H, I, K, L, M, N, Q, S, T, V or Y.
- iii. The fusion polypeptide in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 modified by deletion of residues L161 to E165 or SEQ ID NO: 2 modified by deletion of residues L161 to E165.

- jjj. The fusion polypeptide as claimed in claim 1 in which the sequence of the aglycosylated IFN α 2b is selected from the group consisting of SEQ ID NOs: 3 to 30 and SEQ ID NOs: 32 to 47.

[0071] The term "antibody", as used herein, broadly refers to any immunoglobulin (Ig) molecule comprised of four polypeptide chains, two heavy (H) chains and two light (L) chains, or any functional fragment, mutant, variant, or derivation thereof, which retains the essential epitope binding features of an Ig molecule. Such mutant, variant, or derivative antibody formats are known in the art, non-limiting embodiments of which are discussed below.

[0072] In a full-length antibody, each heavy chain is comprised of a heavy chain variable region (abbreviated herein as HCVR or V_H) and a heavy chain constant region. The heavy chain constant region is comprised of three domains, CH1, CH2 and CH3. Each light chain is comprised of a light chain variable region (abbreviated herein as LCVR or V_L) and a light chain constant region. The light chain constant region is comprised of one domain, CL, which in humans may be of either the κ or λ class. The V_H and V_L regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each V_H and V_L is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. Immunoglobulin molecules can be of any type (e.g., IgG, IgE, IgM, IgD, IgA and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass.

[0073] The term "antigen binding domain" or "antigen binding portion" of an antibody, as used herein, refers to one or more fragments of an antibody or protein that retain the ability to specifically bind to an antigen (e.g., CD38). It has been shown that the antigen-binding function of an antibody can be performed by fragments of a full-length antibody. Such antibody embodiments may also be bispecific, dual specific, or multi-specific formats, specifically binding to two or more different antigens. Examples of binding fragments encompassed within the term "antigen-binding portion" of an antibody include (i) a Fab fragment, a monovalent fragment consisting of the V_L, V_H, C_L and CH1

domains; (ii) a F(ab')₂ fragment, a bivalent fragment comprising two Fab fragments in addition to a portion of the hinge region, linked by a disulfide bridge at the hinge region; (iii) an Fd fragment consisting of the V_H and CH1 domains; (iv) an Fv fragment consisting of the V_L and V_H domains of a single arm of an antibody, (v) a domain antibody (dAb) (Ward *et al.* 1989 Nature 341 544-6, Winter *et al.*, PCT publication WO 90/05144 A1 herein incorporated by reference), which comprises a single variable domain; and (vi) an isolated complementarity determining region (CDR). Furthermore, although the two domains of the Fv fragment, V_L and V_H, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the V_L and V_H regions pair to form monovalent molecules (known as single chain Fv (scFv); see e.g., Bird *et al.* 1988 Science 242 423-6; Huston *et al.* 1988 Proc Natl Acad Sci U S A 85 5879-83). Such single chain antibodies are also intended to be encompassed within the term "antigen-binding portion" of an antibody. Other forms of single chain antibodies, such as diabodies, are also encompassed. Diabodies are bivalent, bispecific antibodies in which V_H and V_L domains are expressed on a single polypeptide chain, but using a linker that is too short to allow for pairing between the two domains on the same chain, thereby forcing the domains to pair with complementary domains of another chain and creating two antigen binding sites (see e.g., Holliger, P., *et al.*, 1993, Proc. Natl. Acad. Sci. USA 90:6444-6448; Poljak, R. J., *et al.*, 1994, Structure 2:1121-1123). Such antibody binding portions are known in the art (Kontermann and Dubel eds., Antibody Engineering 2001 Springer-Verlag. New York. 790 pp., ISBN 3-540-41354-5). In an embodiment the antibody binding portion is a Fab fragment.

[0074] The antibody described herein may be a humanized antibody. The term "humanized antibody" shall be understood to refer to a protein comprising a human-like variable region, which includes CDRs from an antibody from a non-human species (e.g., mouse or rat or non-human primate) grafted onto or inserted into FRs from a human antibody (this type of antibody is also referred to a "CDR-grafted antibody"). Humanized antibodies also include proteins in which one or more residues of the human protein are modified by one or more amino acid substitutions and/or one or more FR residues of the human protein are replaced by corresponding non-human residues. Humanized antibodies may also comprise residues which are found in neither the human antibody or in the non-

human antibody. Any additional regions of the protein (e.g., Fc region) are generally human. Humanization can be performed using a method known in the art, e.g., US5,225,539, US6,054,297, US7,566,771 or US5,585,089. The term “humanized antibody” also encompasses a super-humanized antibody, e.g., as described in US7,732,578.

[0075] The antibody described herein may be human. The term “human antibody” as used herein refers to proteins having variable and, optionally, constant antibody regions found in humans, e.g. in the human germline or somatic cells or from libraries produced using such regions. The “human” antibodies can include amino acid residues not encoded by human sequences, e.g. mutations introduced by random or site directed mutations in vitro (in particular mutations which involve conservative substitutions or mutations in a small number of residues of the protein, e.g. in 1, 2, 3, 4 or 5 of the residues of the protein). These “human antibodies” do not necessarily need to be generated as a result of an immune response of a human, rather, they can be generated using recombinant means (e.g., screening a phage display library) and/or by a transgenic animal (e.g., a mouse) comprising nucleic acid encoding human antibody constant and/or variable regions and/or using guided selection (e.g., as described in or US5,565,332). This term also encompasses affinity matured forms of such antibodies. For the purposes of the present disclosure, a human protein will also be considered to include a protein comprising FRs from a human antibody or FRs comprising sequences from a consensus sequence of human FRs and in which one or more of the CDRs are random or semi-random, e.g., as described in US6,300,064 and/or US6,248,516.

[0076] The antibody portions of polypeptides of the present invention may be full length antibodies of any class, preferably IgG1, IgG2 or IgG4. The constant domains of such antibodies are preferably human. The variable regions of such antibodies may be of non-human origin or, preferably, be of human origin or be humanized. Antibody fragments may also be used in place of the full length antibodies.

[0077] The term “antibody” also includes engineered antibodies. As will be appreciated there are many variations of engineered antibodies (e.g. mouse monoclonal, chimeric, humanized and human monoclonal antibodies, single chain variable antibody

fragments (scFv's), minibodies, aptamers, as well as bispecific antibodies and diabodies as described above).

[0078] Single variable region domains (termed dAbs) are, for example, disclosed in (Ward et al., 1989, Nature 341: 544-546; Hamers-Casterman et al., 1993, Nature 363: 446-448; Davies & Riechmann, 1994, FEBS Lett. 339: 285-290).

[0079] Minibodies are small versions of whole antibodies, which encode in a single chain the essential elements of a whole antibody. Suitably, the minibody is comprised of the VH and VL domains of a native antibody fused to the hinge region and CH3 domain of the immunoglobulin molecule as, for example, disclosed in U.S. Patent No 5,837,821.

[0080] In an alternate embodiment, the engineered antibody may comprise non-immunoglobulin derived, protein frameworks. For example, reference may be made to (Ku & Schutz, 1995, Proc. Natl. Acad. Sci. USA 92: 6552-6556) which discloses a four-helix bundle protein cytochrome b562 having two loops randomized to create CDRs, which have been selected for antigen binding.

[0081] There is a plethora of non-antibody recognition protein or protein domain scaffolds that may be utilised as the antigen binding domains in the constructs of this invention. These include scaffolds based on cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) (Evibody; US7,166,697); human transferrin (Trans-body); a three-helix bundle from the Z-domain of Protein A (Affibody); a monomeric or trimeric human C-type lectin domain (Tetranectin); the tenth human fibronectin type III domain (AdNectin); the Kunitz-type domain of human or bovine trypsin inhibitor; insect Defensin A (IICA29), APPI (Kuntiz domains); lipocalins, FABP, Bilin-binding protein, Apoloprotein D (Anticalins); human α -crystallin or ubiquitin molecule (Affilin); trypsin inhibitor II (Microbody); α 2p8 or Ankyrin repeat (repeat-motif proteins), Charybdotoxin (Scorpion toxins), Min-23, Cellulose binding domain (Knottins); Neocarzinostatin, CBM4-2 and Tendamistat.

[0082] Further, in addition to scaffolds provided for by antibody-derived domains or non-antibody folds as described above, there are naturally occurring ligand binding proteins or protein domains that may be utilised as the ligand binding domains in this invention. For example, protein domains that possess ligand binding properties include

extracellular domains of receptors, PDZ modules of signaling proteins, such as Ras-binding protein AF-6, adhesion molecules, and enzymes.

[0083] Using methods well known in the art to increase binding, by for example, affinity maturation, or to decrease immunogenicity by removing predicted MHC class II-binding motifs. The therapeutic utility of the antibodies described herein can be further enhanced by modulating their functional characteristics, such as antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), serum half-life, biodistribution and binding to Fc receptors or the combination of any of these. This modulation can be achieved by protein-engineering, glyco-engineering or chemical methods. Depending on the therapeutic application required, it could be advantageous to either increase or decrease any of these activities.

[0084] An example of glyco-engineering used the Potelligent® method as described in Shinkawa T. et al., 2003 (J Biol Chem 278: 3466-73).

[0085] Numerous methods for affinity maturation of antibodies are known in the art. Many of these are based on the general strategy of generating panels or libraries of variant proteins by mutagenesis followed by selection and/or screening for improved affinity. Mutagenesis is often performed at the DNA level, for example by error prone PCR (Thie, Voedisch et al. 2009, Methods Mol Biol 525: 309-322), by gene shuffling (Kolkman and Stemmer 2001, Nat Biotechnol. May; 19(5):423-8), by use of mutagenic chemicals or irradiation, by use of 'mutator' strains with error prone replication machinery (Greener 1996, In Vitro Mutagenesis Protocols. Humana press, NJ) or by somatic hypermutation approaches that harness natural affinity maturation machinery (Peled, Kuang et al. 2008, Annu Rev Immunol. 26:481-511). Mutagenesis can also be performed at the RNA level, for example by use of Q β replicase (Kopsidas, Roberts et al. 2006, Immunol Lett. 2006 Nov 15; 107(2):163-8). Library-based methods allowing screening for improved variant proteins can be based on various display technologies such as phage, yeast, ribosome, bacterial or mammalian cells, and are well known in the art (Benhar 2007, Expert Opin Biol Ther. May; 7(5): 763-79). Affinity maturation can be achieved by more directed/predictive methods for example by site-directed mutagenesis or gene synthesis

guided by findings from 3D protein modeling (see for example Queen, Schneider et al. 1989, PNAS, 86(24): 10029-33 or US patent 6,180,370 or US patent 5,225,539).

[0086] Methods of increasing ADCC have been described by Ferrara, Brunker et al. 2006, Biotechnol Bioeng; 93:851-61; Li, Sethuraman et al. 2006, Nat Biotechnol; 24:210-5; Stavenhagen, Gorlatov et al. 2007, Cancer Res; 67:8882-90; Shields, Namenuk et al. 2001, J Biol Chem; 276:6591-604; Shinkawa, Nakamura et al. 2003, J Biol Chem; 278:3466-73; and WO 2008/006554.

[0087] Methods of increasing CDC have been described by Idusogie, Wong et al. 2001, J Immunol; 176:346-56; Dall'Acqua, Cook et al. 2006, J Biol Chem; 281:23514-24; Michaelsen, Aase et al. 1990, Scand J Immunol; 32:517-28; Brekke, Bremnes et al. 1993, Mol Immunol; 30:1419-25; Tan, Shopes et al. 1990, PNAS; 87:162-6; and Norderhaug, Brekke et al. 1991, Eur J Immunol; 21:2379-84.

[0088] References describing methods of increasing ADCC and CDC include Natsume, In et al. 2008, Cancer Res; 68:3863-72. The disclosure of each of these references is included herein by cross reference. In certain embodiments it may be advantageous to reduce or eliminate ADCC and CDC activities of the antibody component of the polypeptide of the invention, so that the IFN α 2b activity is the principal activity of the polypeptide which modulates target cell survival.

[0089] A number of methods for modulating antibody serum half-life and biodistribution are based on modifying the interaction between antibody and the neonatal Fc receptor (FcRn), a receptor with a key role in protecting IgG from catabolism, and maintaining high serum antibody concentration. Dall'Acqua et al describe substitutions in the Fc region of IgG1 that enhance binding affinity to FcRn, thereby increasing serum half-life (Dall'Acqua, Woods et al. 2002, J Immunol; 169:5171-80) and further demonstrate enhanced bioavailability and modulation of ADCC activity with triple substitution of M252Y/S254T/T256E (with residue numbering according to the EU Index) or M265Y/S267T/T269 (with residue numbering according to the Kabat numbering system) (Dall'Acqua, Kiener et al. 2006, J Biol Chem; 279:6213-6). See also U.S Pat. Nos 6,277,375; 6,821,505; and 7,083,784. Hinton et al have described constant domain amino

acid substitutions at positions 250 and 428 that confer increased *in vivo* half-life (Hinton, Johlfs et al. 2004, J Biol Chem; 279:6213-6; Hinton, Xiong et al. 2006, J Immunol; 176:346-56). See also U.S Pat. No 7,217,797. Petkova et al have described constant domain amino acid substitutions at positions 307, 380 and 434 that confer increased *in vivo* half-life (Petkova, Akilesh et al. 2006, Int Immunol; 18:1759-69). See also Shields et al 2001, J Biol Chem; 276:6591-604 and WO 2000/42072. Other examples of constant domain amino acid substitutions which modulate binding to Fc receptors and subsequent function mediated by these receptors, including FcRn binding and serum half-life, are described in U.S Pat. Application Nos 20090142340; 20090068175 and 20090092599. The substitution referred to herein as "S228P" which is numbered according to the EU index as in Kabat has also been referred to as "S241P" according to Kabat et al. (1987 Sequences of proteins of immunological interest. United States Department of Health and Human Services, Washington DC.). This substitution stabilizes the hinge region of IgG4 molecules, having the effect of making the sequence of the core of the hinge region the same as that of an IgG1 or IgG2 isotype antibody. This results in a reduction in the spontaneous dissociation and reassociation of the heavy chains which often leads to the production of heterodimeric IgG4 antibodies.

[0090] The glycans linked to antibody molecules are known to influence interactions of antibody with Fc receptors and glycan receptors and thereby influence antibody activity, including serum half-life (Kaneko, Nimmerjahn et al. 2006, Science; 313:670-3; Jones, Papac et al. 2007, Glycobiology; 17:529-40; and Kanda, Yamada et al. 2007, Glycobiology; 17:104-18). Hence, certain glycoforms that modulate desired antibody activities can confer therapeutic advantage. Methods for generating engineered glycoforms are known in the art and include but are not limited to those described in U.S. Pat. Nos US6,602,684; US7,326,681; US7,388,081 and in WO 2008/006554.

[0091] Extension of half-life by addition of polyethylene glycol (PEG) has been widely used to extend the serum half-life of proteins, as reviewed, for example, by Fishburn 2008, J Pharm Sci; 97:4167-83.

[0092] As will be recognised it is possible to make conservative amino acid substitutions within the sequences of the current invention. By "conservative substitution"

is meant amino acids having similar properties. As used in this specification the following groups of amino acids are to be seen as conservative substitutions: H, R and K; D, E, N and Q; V, I and L; C and M; S, T, P, A and G; and F, Y and W. It is not intended, however, that substitutions other than those specifically recited are made at the sites of attenuation and/or glycosylation.

[0093] The term "cell surface-associated antigen", as used herein, broadly refers to any antigen expressed on surfaces of cells, including without limitation malignant cells or infectious or foreign cells.

[0094] In certain aspects of the present invention, the fusion polypeptide constructs or compositions of the present invention may be used to treat patients with cancer. Cancers contemplated herein include: a group of diseases and disorders that are characterized by uncontrolled cellular growth (e.g. formation of tumor) without any differentiation of those cells into specialized and different cells. Such diseases and disorders include ABL1 protooncogene, AIDS related cancers, acoustic neuroma, acute lymphocytic leukaemia, acute myeloid leukaemia, adenocystic carcinoma, adrenocortical cancer, agnogenic myeloid metaplasia, alopecia, alveolar soft-part sarcoma, anal cancer, angiosarcoma, aplastic anaemia, astrocytoma, ataxia-telangiectasia, basal cell carcinoma (skin), bladder cancer, bone cancers, bowel cancer, brain stem glioma, brain and CNS tumors, breast cancer, carcinoid tumors, cervical cancer, childhood brain tumors, childhood cancer, childhood leukaemia, childhood soft tissue sarcoma, chondrosarcoma, choriocarcinoma, chronic lymphocytic leukaemia, chronic myeloid leukaemia, colorectal cancers, cutaneous T-Cell lymphoma, dermatofibrosarcoma-protuberans, desmoplastic-small-round-cell-tumor, ductal carcinoma, endocrine cancers, endometrial cancer, ependymoma, esophageal cancer, Ewing's sarcoma, extra-hepatic bile duct cancer, eye cancer, eye: melanoma, retinoblastoma, fallopian tube cancer, fanconi anemia, fibrosarcoma, gall bladder cancer, gastric cancer, gastrointestinal cancers, gastrointestinal-carcinoid-tumor, genitourinary cancers, germ cell tumors, gestational-trophoblastic-disease, glioma, gynaecological cancers, hematological malignancies, hairy cell leukaemia, head and neck cancer, hepatocellular cancer, hereditary breast cancer, histiocytosis, Hodgkin's disease, human papillomavirus, hydatidiform mole, hypercalcemia, hypopharynx cancer, intraocular melanoma, islet cell cancer, Kaposi's sarcoma, kidney cancer, Langerhan's-cell-

histiocytosis, laryngeal cancer, leiomyosarcoma, leukemia, Li-Fraumeni syndrome, lip cancer, liposarcoma, liver cancer, lung cancer, lymphedema, lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, male breast cancer, malignant-rhabdoid-tumor-of-kidney, medulloblastoma, melanoma, merkel cell cancer, mesothelioma, metastatic cancer, mouth cancer, multiple endocrine neoplasia, mycosis fungoides, myelodysplastic syndromes, multiple myeloma, myeloproliferative disorders, nasal cancer, nasopharyngeal cancer, nephroblastoma, neuroblastoma, neurofibromatosis, nijmegen breakage syndrome, non-melanoma skin cancer, non-small-cell-lung-cancer-(NSCLC), ocular cancers, oesophageal cancer, oral cavity cancer, oropharynx cancer, osteosarcoma, ostomy ovarian cancer, pancreas cancer, paranasal cancer, parathyroid cancer, parotid gland cancer, penile cancer, peripheral-neuroectodermal-tumors, pituitary cancer, polycythemia vera, prostate cancer, rare-cancers-and-associated-disorders, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, Rothmund-Thomson syndrome, salivary gland cancer, sarcoma, schwannoma, Sezary syndrome, skin cancer, small cell lung cancer (SCLC), small intestine cancer, soft tissue sarcoma, spinal cord tumors, squamous-cell-carcinoma-(skin), stomach cancer, synovial sarcoma, testicular cancer, thymus cancer, thyroid cancer, transitional-cell-cancer-(bladder), transitional-cell-cancer-(renal-pelvis-/ureter), trophoblastic cancer, urethral cancer, urinary system cancer, uroplakins, uterine sarcoma, uterus cancer, vaginal cancer, vulva cancer, Waldenstrom's-macroglobulinemia and Wilms' tumor. In an embodiment the tumor is selected from a group of multiple myeloma or non-hodgkin's lymphoma.

[0095] As contemplated for the treatment of cancer, the antibody portions of the fusion constructs of the present invention may bind to tumour-associated antigens, *i.e.*, cell surface antigens that are selectively expressed by cancer cells or over-expressed in cancer cells relative to most normal cells. There are many tumour-associated antigens (TAAs) known in the art. Non-limiting examples of TAAs include enzyme tyrosinase; melanoma antigen GM2; alphafetoprotein (AFP); carcinoembryonic antigen (CEA); Mucin 1 (MUC1); Human epidermal growth factor receptor (Her2/Neu); T-cell leukemia/lymphoma 1 (TCL1) oncoprotein. Exemplary TAAs associated with a number of different cancers are telomerase (hTERT); prostate-specific membrane antigen (PSMA); urokinase plasminogen activator and its receptor (uPA/uPAR); vascular

endothelial growth factor and its receptor (VEGF/VEGFR); extracellular matrix metalloproteinase inducer (EMMPRIN/CD147); epidermal growth factor (EGFR); platelet-derived growth factor and its receptor (PDGF/PDGFR) and c-kit (CD117).

[0096] A list of other TAAs is provided in US 2010/0297076, the disclosure of which is included herein by reference. Of particular interest are cell surface antigens associated with multiple myeloma leukemia or lymphoma cells, including but not limited to CD38, CD138, CD79, CS1, and HM1.24. In one embodiment an antigen for ligand-attenuated IFN constructs, for example, an antibody-attenuated interferon construct, is CD38.

[0097] CD38 is a 46kDa type II transmembrane glycoprotein. It has a short N-terminal cytoplasmic tail of 20 amino acids, a single transmembrane helix and a long extracellular domain of 256 amino acids (Bergsagel, P., *Blood*; 85:436, 1995 and Liu, Q., *Structure*, 13:1331, 2005). It is expressed on the surface of many immune cells including CD4 and CD8 positive T cells, B cells, NK cells, monocytes, plasma cells and on a significant proportion of normal bone marrow precursor cells (Malavasi, F., *Hum. Immunol.* 9:9, 1984). In lymphocytes, however, the expression appears to be dependent on the differentiation and activation state of the cell. Resting T and B cells are negative while immature and activated lymphocytes are predominantly positive for CD38 expression (Funaro, A., *J. Immunol.* 145:2390, 1990). Additional studies indicate mRNA expression in non-hemopoietic organs such as pancreas, brain, spleen and liver (Koguma, T., *Biochim. Biophys. Acta* 1223:160, 1994.)

[0098] CD38 is a multifunctional ectoenzyme that is involved in transmembrane signaling and cell adhesion. It is also known as cyclic ADP ribose hydrolase because it can transform NAD^+ and NADP^+ into cADPR, ADPR and NAADP, depending on extracellular pH. These products induce Ca^{2+} -mobilization inside the cell which can lead to tyrosine phosphorylation and activation of the cell. CD38 is also a receptor that can interact with a ligand, CD31. Activation of receptor via CD31 leads to intracellular events including Ca^{2+} mobilization, cell activation, proliferation, differentiation and migration (reviewed in Deaglio, S., *Trends in Mol. Med.* 14:210, 2008.)

[0099] CD38 is expressed at high levels on multiple myeloma cells, in most cases of T- and B-lineage acute lymphoblastic leukemias, some acute myelocytic leukemias, follicular center cell lymphomas and T lymphoblastic lymphomas. (Malavasi, F., J. Clin Lab Res. 22:73, 1992). More recently, CD38 expression has become a reliable prognostic marker in B-lineage chronic lymphoblastic leukemia (B-CLL) (Ibrahim, S., Blood. 98:181, 2001 and Durig, J., Leuk. Res. 25:927, 2002). Independent groups have demonstrated that B-CLL patients presenting with a CD38⁺ clone are characterized by an unfavorable clinical course with a more advance stage of disease, poor responsiveness to chemotherapy and shorter survival time (Morabito, F., Haematologica. 87:217,2002). The consistent and enhanced expression of CD38 on lymphoid tumors makes this an attractive target for therapeutic antibody technologies.

[0100] Preferred antigens for the development of antibody-attenuated aglycosylated IFN α 2b fusion protein constructs which target cancer are antigens which show selective or greater expression on the cancer cells than on most other, non-transformed cells within the body. Non-protein examples of such antigens include, sphingolipids, ganglioside GD2 (Saleh *et al.*, 1993, J. Immunol., 151, 3390-3398), ganglioside GD3 (Shitara *et al.*, 1993, Cancer Immunol. Immunother. 36:373-380), ganglioside GM2 (Livingston *et al.*, 1994, J. Clin. Oncol. 12:1036-1044), ganglioside GM3 (Hoon *et al.*, 1993, Cancer Res. 53:5244-5250) and Lewis^x, lewis^y and lewis^{xy} carbohydrate antigens that can be displayed on proteins or glycolipids. Examples of protein antigens are HER-2/neu, human papillomavirus-E6 or -E7, MUC-1; KS 1/4 pan-carcinoma antigen (Perez and Walker, 1990, J. Immunol. 142:3662-3667; Bumal, 1988, Hybridoma 7(4):407-415); ovarian carcinoma antigen CA125 (Yu *et al.*, 1991, Cancer Res. 51(2):468-475); prostatic acid phosphate (Tailor *et al.*, 1990, Nucl. Acids Res. 18(16):4928); prostate specific antigen (Henttu and Vihko, 1989, Biochem. Biophys. Res. Comm. 160(2):903-910; Israeli *et al.*, 1993, Cancer Res. 53:227-230); melanoma-associated antigen p97 (Estin *et al.*, 1989, J. Natl. Cancer Instit. 81(6):445-446); melanoma antigen gp75 (Vijayasardahl *et al.*, 1990, J. Exp. Med. 171(4):1375-1380); prostate specific membrane antigen; carcinoembryonic antigen (CEA) (Foon *et al.*, 1994, Proc. Am. Soc. Clin. Oncol. 13:294), MUC16 (antibodies include MJ-170, MJ-171, MJ-172 and MJ-173 [US 7,202,346], 3A5 [US 7,723,485]).NMB (US 8,039,593), malignant human lymphocyte antigen-APO-1

(Bernhard *et al.*, 1989, Science 245:301-304); high molecular weight melanoma antigen (HMW-MAA) (Natali *et al.*, 1987, Cancer 59:55-63; Mittelman *et al.*, 1990, J. Clin. Invest. 86:2136-2144); Burkitt's lymphoma antigen-38.13; CD19 (Ghetie *et al.*, 1994, Blood 83:1329-1336); human B-lymphoma antigen-CD20 (Reff *et al.*, 1994, Blood 83:435-445); GICA 19-9 (Herlyn *et al.*, 1982, J. Clin. Immunol. 2:135), CTA-1 and LEA; CD33 (Sgouros *et al.*, 1993, J. Nucl. Med. 34:422-430); oncofetal antigens such as alpha-fetoprotein for liver cancer or bladder tumor oncofetal antigen (Hellstrom *et al.*, 1985, Cancer Res. 45:2210-2188); differentiation antigens such as human lung carcinoma antigen L6 or L20 (Hellstrom *et al.*, 1986, Cancer Res. 46:3917-3923); antigens of fibrosarcoma; human leukemia T cell antigen-Gp37 (Bhattacharya-Chatterjee *et al.*, 1988, J. Immunol. 141:1398-1403); tumor-specific transplantation type of cell-surface antigen (TSTA) such as virally-induced tumor antigens including T-antigen, DNA tumor virus and envelope antigens of RNA tumor viruses; neoglycoproteins, breast cancer antigens such as EGFR (Epidermal growth factor receptor), polymorphic epithelial mucin (PEM) (Hilkens *et al.*, 1992, Trends in Bio. Chem. Sci. 17:359); polymorphic epithelial mucin antigen; human milk fat globule antigen; colorectal tumor-associated antigens such as TAG-72 (Yokata *et al.*, 1992, Cancer Res. 52:3402-3408), CO 17-1A (Ragnhammar *et al.*, 1993, Int. J. Cancer 53:751-758); differentiation antigens (Feizi, 1985, Nature 314:53-57) such as I(Ma) found in gastric adenocarcinomas, SSEA-1 found in myeloid cells, VEP8, VEP9, Myl, VIM-D5, M18 and M39 found in breast epithelial cancers, D₁₅₆₋₂₂ found in colorectal cancer, TRA-1-85 (blood group H), C14 found in colonic adenocarcinoma, F3 found in lung adenocarcinoma, AH6 found in gastric cancer, Y hapten found in embryonal carcinoma cells, TL5 (blood group A), E1 series (blood group B) antigens found in pancreatic cancer, FC10.2 found in embryonal carcinoma cells, gastric adenocarcinoma antigen, CO-514 (blood group Le^a) found in adenocarcinoma, NS-10 found in adenocarcinomas, CO-43 (blood group Le^b), G49 found in A431 cells, 19.9 found in colon cancer; gastric cancer mucins; R₂₄ found in melanoma, MH2 (blood group ALe^b/Le^y) found in colonic adenocarcinoma, 4.2, D1.1, OFA-1, G_{M2}, OFA-2 and M1:22:25:8 found in embryonal carcinoma cells and SSEA-3 and SSEA-4. HMW-MAA (SEQ ID NO:433), also known as melanoma chondroitin sulfate proteoglycan, is a membrane-bound protein of 2322 residues which is overexpressed on over 90% of the surgically removed benign

nevi and melanoma lesions (Camploi, et. al, Crit Rev Immunol.;24:267,2004). Accordingly it may be a potential target cell surface associated antigen.

[0101] Other example cancer antigens for targeting with fusion protein constructs of the present invention include (exemplary cancers are shown in parentheses): CD5 (T-cell leukemia/lymphoma), CA15-3 (carcinomas), CA19-9 (carcinomas), L6 (carcinomas), CA 242 (colorectal), placental alkaline phosphatase (carcinomas), prostatic acid phosphatase (prostate), MAGE-1 (carcinomas), MAGE-2 (carcinomas), MAGE-3 (carcinomas), MAGE-4 (carcinomas), transferrin receptor (carcinomas), p97 (melanoma), MUC1 (breast cancer), MART1 (melanoma), CD20 (non Hodgkin's lymphoma), CD52 (leukemia), CD33 (leukemia), human chorionic gonadotropin (carcinoma), CD38 (multiple myeloma), CD21 (B-cell lymphoma), CD22 (lymphoma), CD25 (B-cell Lymphoma), CD37 (B-cell lymphoma), CD45 (acute myeloblastic leukemia), HLA-DR (B-cell lymphoma), IL-2 receptor (T-cell leukemia and lymphomas), CD40 (lymphoma), CD79 (B cell leukemia or lymphoma, Hodgkin lymphoma), various mucins (carcinomas), P21 (carcinomas), MPG (melanoma), Ep-CAM (Epithelial Tumors), Folate-receptor alpha (Ovarian), A33 (Colorectal), G250 (renal), Ferritin (Hodgkin lymphoma), de2-7 EGFR (glioblastoma, breast, and lung), Fibroblast activation protein (epithelial) and tenascin metalloproteinases (glioblastoma). Some specific, useful antibodies include, but are not limited to, BR64 (Trail *et al.*, 1997, Cancer Research 57:100 105), BR96 mAb (Trail *et al.*, 1993, Science 261:212-215), mAbs against the CD40 antigen, such as S2C6 mAb (Francisco *et al.*, 2000, Cancer Res. 60:3225-3231) or other anti-CD40 antibodies, such as those disclosed in U.S Patent Publication Nos. 2003-0211100 and 2002-0142358; mAbs against the CD30 antigen, such as AC10 (Bowen *et al.*, 1993, J. Immunol. 151:5896-5906; Wahl *et al.*, 2002 Cancer Res. 62(13):3736-42) or MDX-0060 (U.S. Patent Publication No. 2004-0006215) and mAbs against the CD70 antigen, such as 1F6 mAb and 2F2 mAb (see, e.g., U.S. Patent Publication No. 2006-0083736) or antibodies 2H5, 10B4, 8B5, 18E7, 69A7 (US 8,124,738). Other antibodies have been reviewed elsewhere (Franke *et al.*, 2000, Cancer Biother. Radiopharm. 15:459 76; Murray, 2000, Semin. Oncol. 27:64 70; Breitling, F., and Dubel, S., Recombinant Antibodies, John Wiley, and Sons, New York, 1998).

[0102] In certain embodiments, useful antibodies can bind to a receptor or a complex of receptors expressed on a target cell. The receptor or receptor complex can comprise an

immunoglobulin gene superfamily member, a major histocompatibility protein, a cytokine receptor, a TNF receptor superfamily member, a chemokine receptor, an integrin, a lectin, a complement control protein, a growth factor receptor, a hormone receptor or a neurotransmitter receptor. Non-limiting examples of appropriate immunoglobulin superfamily members are CD2, CD3, CD4, CD8, CD19, CD22, CD79, CD90, CD152/CTLA-4, PD-1, B7-H4, B7-H3, and ICOS. Non-limiting examples of suitable TNF receptor superfamily members are TACI, BCMA, CD27, CD40, CD95/Fas, CD134/OX40, CD137/4-1BB, TNFR1, TNFR2, RANK, osteoprotegerin, APO 3, Apo2/TRAIL R1, TRAIL R2, TRAIL R3, and TRAIL R4. Non-limiting examples of suitable integrins are CD11a, CD11b, CD11c, CD18, CD29, CD41, CD49a, CD49b, CD49c, CD49d, CD49e, CD49f, CD103 and CD104. Non-limiting examples of suitable lectins are S type, C type, and I type lectin. Examples of antibodies to CEA are shown in Table 1.

Table 1

CEA Antibodies			
Ab Clones	Patent	Assignee	Comments
COL-1	US 6,417,337	The Dow Chemical Company	Humanized
806.077	US 6,903,203	AstraZeneca UK Ltd.	Humanized
T84.66	US 7,776,330	City of Hope	Humanized

[0103] Antibodies that bind the CD22 antigen expressed on human B cells include, for example, HD6, RFB4, UV22-2, To15, 4KB128 and a humanized anti-CD22 antibody (hLL2) (see, e.g., Li *et al.* (1989) Cell. Immunol. 111: 85-99; Mason *et al.* (1987) Blood

69: 836-40; Behr *et al.* (1999) Clin. Cancer Res. 5: 3304s-3314s; Bonardi *et al.* (1993) Cancer Res. 53: 3015-3021).

[0104] Antibodies to CD33 include, for example, HuM195 (see, e.g., Kossman *et al.* (1999) Clin. Cancer Res. 5: 2748-2755; US5693761) and CMA-676 (see, e.g., Sievers *et al.*, (1999) Blood 93: 3678-3684).

[0105] Illustrative anti-MUC-1 antibodies include, but are not limited to Mc5 (see, e.g., Peterson *et al.* (1997) Cancer Res. 57: 1103-1108; Ozzello *et al.* (1993) Breast Cancer Res. Treat. 25: 265-276), and hCTMO1 (see, e.g., Van Hof *et al.* (1996) Cancer Res. 56: 5179-5185).

[0106] Illustrative anti-TAG-72 antibodies include, but are not limited to CC49 (see, e.g., Pavlinkova *et al.* (1999) Clin. Cancer Res. 5: 2613-2619), B72.3 (see, e.g., Divgi *et al.* (1994) Nucl. Med. Biol. 21: 9-15), and those disclosed in U.S. Pat. No. 5,976,531.

[0107] Illustrative anti-HM1.24 antibodies include, but are not limited to a mouse monoclonal anti-HM1.24 and a humanized anti-HM1.24 IgG1kappa antibody (see, e.g., Ono *et al.* (1999) Mol. Immuno. 36: 387-395).

[0108] In certain embodiments the targeting moiety comprises an anti-Her2 antibody. The erBB 2 gene, more commonly known as (Her-2/neu), is an oncogene encoding a transmembrane receptor. Several antibodies have been developed against Her-2/neu, and some of these are in clinical use. These include trastuzumab (e.g., HERCEPTIN™; Fornir *et al.* (1999) Oncology (Huntingt) 13: 647-58), TAB-250 (Rosenblum *et al.* (1999) Clin. Cancer Res. 5: 865-874), BACH-250 (Id.), TA1 (Maier *et al.* (1991) Cancer Res. 51: 5361-5369), and the mAbs described in U.S. Pat. Nos. 5,772,997; 5,770,195 (mAb 4D5; ATCC CRL 10463); and U.S. Pat. No. 5,677,171.

[0109] Other fully human anti-Her2/neu antibodies are well known to those of skill in the art. Such antibodies include, but are not limited to the C6 antibodies such as C6.5, DPL5, G98A, C6MH3-B1, B1D2, C6VLB, C6VLD, C6VLE, C6VLF, C6MH3-D7, C6MH3-D6, C6MH3-D5, C6MH3-D3, C6MH3-D2, C6MH3-D1, C6MH3-C4, C6MH3-C3, C6MH3-B9, C6MH3-B5, C6MH3-B48, C6MH3-B47, C6MH3-B46, C6MH3-B43,

C6MH3-B41, C6MH3-B39, C6MH3-B34, C6MH3-B33, C6MH3-B31, C6MH3-B27, C6MH3-B25, C6MH3-B21, C6MH3-B20, C6MH3-B2, C6MH3-B16, C6MH3-B15, C6MH3-B11, C6MH3-B1, C6MH3-A3, C6MH3-A2, and C6ML3-9. These and other anti-HER2/neu antibodies are described in U.S. Pat. Nos. 6,512,097 and 5,977,322, in PCT Publication WO 97/00271, in Schier *et al.* (1996) J Mol Biol 255: 28-43, Schier *et al.* (1996) J Mol Biol 263: 551-567, and the like.

[0110] More generally, antibodies directed to various members of the epidermal growth factor receptor family are well suited for use as targeting antibodies or antigen binding portions thereof in the constructs of the present invention. Such antibodies include, but are not limited to anti-EGFR antibodies as described in U.S. Pat. Nos. 5,844,093 and 5,558,864, and in European Patent No. 706,799A. Other illustrative anti-EGFR family antibodies include, but are not limited to antibodies such as C6.5, C6ML3-9, C6MH3-B1, C6-B1D2, F5, HER3.A5, HER3.F4, HER3.H1, HER3.H3, HER3.E12, HER3.B12, EGFR.E12, EGFR.C10, EGFR.B11, EGFR.E8, HER4.B4, HER4.G4, HER4.F4, HER4.A8, HER4.B6, HER4.D4, HER4.D7, HER4.D11, HER4.D12, HER4.E3, HER4.E7, HER4.F8 and HER4.C7 and the like (see, e.g., U.S. Patent publications US 2006/0099205 A1 and US 2004/0071696 A1 which are incorporated herein by reference).

[0111] CD38 is of particular interest as an antibody target for fusion protein constructs of the present invention. Antibodies to CD38 include for example, AT13/5 (see, e.g., Ellis *et al.* (1995) J. Immunol. 155: 925-937), HB7, and the like.

[0112] The present invention also provides compositions comprising the fusion polypeptides of the present invention. These compositions can further comprise at least one of any suitable auxiliary, such as, but not limited to, diluent, binder, stabiliser, buffers, salts, lipophilic solvents, preservative, adjuvant or the like. Pharmaceutically acceptable auxiliaries are preferred. Non-limiting examples of, and methods of preparing such sterile solutions are well known in the art, such as, but not limited to, Gennaro, Ed., Remington's Pharmaceutical Sciences, 18th Edition, Mack Publishing Co. (Easton, Pa.) 1990. Pharmaceutically acceptable carriers can be routinely selected that are suitable for the mode of administration, solubility and/or stability of the antibody composition as well known in the art or as described herein.

[0113] Pharmaceutical excipients and additives useful in the present composition include but are not limited to proteins, peptides, amino acids, lipids, and carbohydrates (e.g., sugars, including monosaccharides, di-, tri-, tetra-, and oligosaccharides; derivatised sugars such as alditols, aldonic acids, esterified sugars and the like; and polysaccharides or sugar polymers), which can be present singly or in combination, comprising alone or in combination 1-99.99% by weight or volume. Exemplary protein excipients include serum albumin, such as human serum albumin (HSA), recombinant human albumin (rHA), gelatin, casein, and the like. Representative amino acids which can also function in a buffering capacity include alanine, glycine, arginine, betaine, histidine, glutamic acid, aspartic acid, cysteine, lysine, leucine, isoleucine, valine, methionine, phenylalanine, aspartame, and the like. One preferred amino acid is histidine. A second preferred amino acid is arginine.

[0114] Carbohydrate excipients suitable for use in the invention include, for example, monosaccharides, such as fructose, maltose, galactose, glucose, D-mannose, sorbose, and the like; disaccharides, such as lactose, sucrose, trehalose, cellobiose, and the like; polysaccharides, such as raffinose, melezitose, maltodextrins, dextrans, starches, and the like; and alditols, such as mannitol, xylitol, maltitol, lactitol, xylitol sorbitol (glucitol), myoinositol and the like. Preferred carbohydrate excipients for use in the present invention are mannitol, trehalose, and raffinose.

[0115] Antibody compositions can also include a buffer or a pH adjusting agent; typically, the buffer is a salt prepared from an organic acid or base. Representative buffers include organic acid salts, such as salts of citric acid, ascorbic acid, gluconic acid, carbonic acid, tartaric acid, succinic acid, acetic acid, or phthalic acid; Tris, tromethamine hydrochloride, phosphate buffers or amino acid buffers. Preferred buffers for use in the present compositions are organic acid salts, such as citrate or amino acids.

[0116] Additionally, the compositions of the invention can include polymeric excipients/additives, such as polyvinylpyrrolidones, ficolls (a polymeric sugar), dextrates (e.g., cyclodextrins, such as 2-hydroxypropyl- β -cyclodextrin), polyethylene glycols, flavoring agents, antimicrobial agents, sweeteners, antioxidants, antistatic agents,

surfactants (e.g., polysorbates such as “TWEEN® 20” and “TWEEN® 80”), lipids (e.g., phospholipids, fatty acids), steroids (e.g., cholesterol), and chelating agents (e.g., EDTA).

[0117] These and additional known pharmaceutical excipients and/or additives suitable for use in the antibody compositions according to the invention are known in the art, e.g., as listed in “Remington: The Science & Practice of Pharmacy”, 19th ed., Williams & Williams, (1995), and in the “Physician's Desk Reference”, 52nd ed., Medical Economics, Montvale, N.J. (1998), the disclosures of which are entirely incorporated herein by reference. Preferred carrier or excipient materials are carbohydrates (e.g., saccharides and alditols) and buffers (e.g., citrate) or polymeric agents.

[0118] Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications which fall within the spirit and scope. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations of any two or more of said steps or features.

[0119] Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any materials and methods similar or equivalent to those described herein can be used to practice or test the present invention, the preferred materials and methods are now described.

EXAMPLES

General Methods

Production of antibody-fusion constructs in HEK-293E cells.

[0120] The DNA sequences of a number of the domains in the fusion polypeptides of the present are provided in the attached Sequence listing incorporated herein. DNA plasmids encoding protein constructs (antibody-attenuated IFN α 2b fusion constructs) were prepared using HiSpeed Plasmid Maxi Kit (Qiagen, Valencia, CA) and then transfected into HEK293E cells (CNRC, Montreal, Canada), grown in F17 synthetic medium

supplemented with 0.45% (w/v) D-(+)-Glucose (Sigma, Castle Hill, NSW), 25 µg/mL Geneticin (Invitrogen, Carlsbad, CA), and 1 x GlutaMAX (Invitrogen, Carlsbad, CA) using a commercially available transfection reagent and OptiMEM medium (Invitrogen, Carlsbad, CA). After allowing for expression for 6 days in an incubator supplied with 5% CO₂ and 120 rpm shaking, the culture media was isolated and subjected to affinity purification using Protein A Mab Select SuReTM agarose beads (GE Healthcare, Piscataway, NJ). Purified protein constructs were buffer-exchanged into 0.2M arginine HCl, 25mM citric acid, 71.5mM sodium hydroxide at pH 6.0 using a PD Midi-Trap G-25 column (GE Healthcare, Piscataway, NJ) or a HiPrep 26/10 Desalting column (HiTrap Desalting HiPrep 26/10 Desalting). Purified protein constructs were then concentrated using 50 kDa Amicon Ultra centrifugal filter devices (Millipore, Billerica, MA), followed by protein concentration determination by reading absorbance at 280 nm.

Production of antibody-fusion constructs in EXP1293 cells.

[0121] DNA plasmids encoding protein constructs (antibody- IFNα2b related constructs) were prepared using HiSpeed Plasmid Maxi Kit (Qiagen, Valencia, CA) and then transfected into EXP1293 cells (Life Technologies, Carlsbad, CA), grown in EXP1 Expression medium (Life Technologies, Carlsbad, CA) using transfection reagent provided in the EXP1293 transfection kit and OptiMEM medium (Invitrogen, Carlsbad, CA). After allowing for expression for 3 days in an incubator supplied with 5% CO₂ and 125 rpm shaking, the culture media was isolated and subjected to affinity purification using Protein A Mab Select SuReTM agarose beads (GE Healthcare, Piscataway, NJ). Purified protein constructs were buffer-exchanged into 0.2M arginine HCl, at pH 6.0 using a PD Midi-Trap G-25 column (GE Healthcare, Piscataway, NJ) or a HiPrep 26/10 Desalting column (HiTrap Desalting HiPrep 26/10 Desalting). Purified protein constructs were then concentrated using 50 kDa Amicon Ultra centrifugal filter devices (Millipore, Billerica, MA), followed by protein concentration determination by reading absorbance at 280 nm.

Production of antibody-fusion constructs in CHO cells.

[0122] DNA plasmids encoding protein constructs (antibody- IFNα2b related constructs) were prepared using HiSpeed Plasmid Maxi Kit (Qiagen, Valencia, CA) and

then transfected into CHO cells (Lonza) grown in Freestyle™ CHO Expression Medium (Invitrogen, Carlsbad, CA) using a commercially available transfection reagent and OptiPro SFM™ medium (Invitrogen, Carlsbad, CA). After allowing for expression for 6 days in an incubator supplied with 10% CO₂ and 120 rpm shaking, the culture media was isolated and subjected to affinity purification using Protein A Mab Select SuRe™ agarose beads (GE Healthcare, Piscataway, NJ). Purified protein constructs were buffer-exchanged into 0.2M arginine.HCl, 25mM citric acid, 71.5mM sodium hydroxide at pH 6.0 using a PD Midi-Trap G-25 column (GE Healthcare, Piscataway, NJ) or a HiPrep 26/10 Desalting column (HiTrap Desalting HiPrep 26/10 Desalting). Purified protein constructs were then concentrated using 50 kDa Amicon Ultra centrifugal filter devices (Millipore, Billerica, MA), followed by protein concentration determination by reading absorbance at 280 nm.

Method for measuring antigen-targeted activity of antibody-IFN α 2b fusion protein constructs

[0123] “On target (Daudi) assay”: This assay was used to quantify the anti-proliferative activity of IFN α 2b and antibody-IFN α 2b fusion protein constructs on cells that display both IFN receptor and the antigen targeted by the antibody to which the IFN α 2b is fused. Daudi cells express both CD20 and CD38 as cell surface associated antigens, as well as cell surface IFN receptors. The viability of the Daudi cells was measured using the reagent CellTiter-Glo®, Cat #G7570, from Promega (Madison, Wisconsin). This is a luminescence-based assay that determines the viability of cells in culture based on quantitation of ATP. The signal strength is proportional to the number of viable cells in a microtiter plate well. The details of the assay are as follows:

[0124] Daudi cells (obtained from ATCC, Manassas, VA) were cultured in a T75 flask (TPP, Trasadingen, Switzerland, cat# 90076) to a preferred density of between 0.5×10^5 and 0.8×10^5 viable cells/ml in RPMI 1640 (Mediatech, Inc., Manassas, VA, cat # 10-040-CV) with 10% Fetal Bovine Serum (FBS; Hyclone, Logan, UT cat# SH30070.03). Cells were harvested by centrifuging at 400g for five minutes, decanting the supernatant, and resuspending the cell pellet in RPMI 1640 + 10% FBS. Cells were then counted and the density was adjusted to 3.0×10^5 cells/ml in RPMI 1640 + 10% FBS. Then, 50 μ l of the cell suspension was aliquoted into each well of a 96 well round bottom tissue culture plate

(hereafter, “experimental plate”) (TPP, cat# 92067). On a separate, sterile 96 well plate (hereafter, “dilution plate”; Costar, Corning, NY cat# 3879), test articles were serially diluted in duplicate in RPMI 1640 + 10% FBS. Then, 50 μ l/well was transferred from the dilution plate to the experimental plate. The experimental plate was then incubated for four days at 37 °C with 5% CO₂.

[0125] A mixture of the manufacturer-supplied assay buffer and assay substrate (hereafter, “CellTiterGlo reagent”, mixed according to the manufacturer’s instructions) was added to the experimental plate at 100 μ l/well. The plate was shaken for two minutes. Then, 100 μ l/well was transferred from the experimental plate to a 96 well flat bottom white opaque plate (hereafter, “assay plate”; BD Biosciences, Franklin Lakes, NJ cat# 353296). The content of the assay plate was then allowed to stabilize in the dark for 15 minutes at room temperature. The plate was read on a Victor 3V Multilabel Counter (Perkin Elmer, Waltham, MA, model# 1420-041) on the luminometry channel and the luminescence was measured. Results are presented as “relative luminescence units (RLU)”.

[0126] Data was analyzed using Prism 5 (Graphpad, San Diego, CA) using non-linear regression and three parameter curve fit to determine the midpoint of the curve (EC50). For each test article, potency relative to free IFN α 2b (or some other form of IFN with a known potency relative to IFN α 2b) was calculated as a ratio of EC50s.

[0127] One of ordinary skill in the art will appreciate that there are many other commonly used assays for measuring cell viability that could also be used.

[0128] “On target (ARP) assay” (also sometimes referred to herein as a “targeted assay”): The multiple myeloma cell line ARP-1 was a gift from Bart Barlogie MD, PhD, Director of the Myeloma Institute at the University of Arkansas Medical Center (Little Rock, AK). It is described in Hardin J. et al. (Interleukin-6 prevents dexamethasone-induced myeloma cell death. *Blood*; 84:3063, 1994). ARP-1 cells (CD38⁺) were used to test CD38 targeting antibody-IFN fusion protein constructs. Culture and assay conditions were the same as for Daudi-based assay outlined above, with the following exceptions:

ARP-1 was cultured to a density of 4.0×10^5 to 6.0×10^5 cells/ml. ARP-1 concentration was adjusted to 1.0×10^4 cells/ml prior to assay.

EXAMPLE 1

ISOELECTRIC POINTS OF ANTI-CD38 ANTIBODY ATTENUATED IFN α 2b FUSION PROTEINS

[0129] Various transiently transfected cells expressing an anti-CD38 antibody-attenuated IFN α 2b fusion constructs (Table 2) were harvested and purified using a Mab Select Sure Protein A column. Samples were desalted into 200mM Arginine, 25mM Histidine pH 6.5 using a HiLoad Superdex 200 column.

Table 2: Table of Constructs

Antibody Constructs	SEQ ID No.			
	Heavy Chain	Light Chain	IFN	VH + IFN
A10.21 IgG4 (S228P) IFN (A145D, T106T)	48	81	107	
A10.21 IgG4 (S228P) IFN (A145D, T106A)	48	81	25	87, 31
A10.21 IgG4 (S228P) IFN (A145D, Δ T106)	48	81	110	61
A10.21 IgG1 IFN (A145D, T106T)	50	81	107	
A10.21 IgG1 IFN (A145D, T106A)	50	81	25	68
A10.21 IgG1 IFN (A145D, Δ T106)	50	81		83
A10.43 IgG4 (S228P) IFN (A145D, T106T)	55	81	107	
A10.43 IgG4 (S228P) IFN (A145D, T106A)	55	81	25	74

Antibody Constructs	SEQ ID No.			
	Heavy Chain	Light Chain	IFN	VH + IFN
A10.21 IgG4 (S228P) IFN (A145D, T106S)	48	81	25	31
A10.21 IgG4 (S228P) IFN (A145D, T106V)	48	81	25	31
A10.21 IgG4 (S228P) IFN (A145D, T106G)	48	81	25	31
A10.21 IgG4 (S228P) IFN (A145D, T106E)	48	81	25	31
A10.21 IgG4 (S228P, M252Y, S254T, T256E) IFN (A145D, T106T)	49	81	107	
A10.21 IgG4 (S228P, M252Y, S254T, T256E) IFN (A145D, T106A)	49	81	25	62
A10.21 IgG4 (S228P) IFN (R144I T106T)	48	81	108	
A10.21 IgG4 (S228P) IFN (R144I, T106A)	48	81	24	63
A10.21 IgG4 (S228P) IFN (A145K, T106T)	48	81	107	
A10.21 IgG4 (S228P) IFN (A145K, T106A)	48	81	25	64
A10.21 IgG4 (S228P) IFN (A145G, T106T)	48	81	107	
A10.21 IgG4 (S228P) IFN (A145G, T106A)	48	81	25	64
A10.21 IgG4 (S228P) IFN (R33A, T106T)	48	81	109	
A10.21 IgG4 (S228P) IFN (R33A, T106A)	48	81	13	65

Antibody Constructs	SEQ ID No.			
	Heavy Chain	Light Chain	IFN	VH + IFN
A10.21 IgG4 (S228P) IFN (A145Q, T106T)	48	81	107	
A10.21 IgG4 (S228P) IFN (A145Q, T106A)	48	81	25	66
A10.21 IgG1 (L235A, G237A) IFN (A145D, T106T)	51	81	107	
A10.21 IgG1 (L235A, G237A) IFN (A145D, T106A)	51	81	25	69
A10.21 IgG2 IFN (A145D, T106T)	53	81	107	
A10.21 IgG2 IFN (A145D, T106A)	53	81	25	72
A10.21 IgG2 (A330S, P331S) IFN (A145D, T106T)		81	107	
A10.21 IgG2 (A330S, P331S) IFN (A145D, T106A)		81	25	
A02.12 IgG4 (S228P) IFN (A145D, T106T)	58	84	107	
A02.12 IgG4 (S228P) IFN (A145D, T106A)	58	84	25	77
Anti-CD138 IgG4 (S228P) IFN (A145D, T106T)	59	85	107	
Anti-CD138 IgG4 (S228P) IFN (A145D, T106A)	59	85	25	
Anti-HLA IgG4 (S228P) IFN (A145D, T106T)	60	86	107	
Anti-HLA IgG4 (S228P) IFN (A145D, T106A)	60	86	25	

[0130] Isoelectric focusing gels were used to determine the isoelectric point (pI) of the fusion polypeptide and to detect minor changes in the protein due to post-translational modifications such as phosphorylation and glycosylation.

[0131] Pre-cast IEF gel was setup in gel tanks ensuring a tight seal between gel and buffer. Then 200mL of 1x Cathode buffer was poured into inner chamber ensuring no buffer enters the outer chamber. 500mL of 1x Anode buffer was then poured into the outer chamber and filled $\frac{3}{4}$ of the tank. After the samples and ladder were loaded onto the gel, it was then run for 1 hour at 100 volt, 1 hour at 200 volt and $\frac{1}{2}$ hour at 500 volt. As soon as gel run was finished, the gel was taken out and fixed in TCA solution in a glass container for 30 min. The gel was then immediately washed with deionised water 3 times. The gel was stained in SimplyBlue SafeStain (Invitrogen Life Technologies) for a full hour, and left overnight in water to destain. The final image scanned using a scanner.

[0132] The O-linked glycosylation site of the IFN α 2b portion of the antibody-attenuated interferon fusion constructs was removed by either substituting the interferon's threonine 106 (T106) to alanine (shown as T106A), serine (T106S), valine (T106V), glycine (T106G) or glutamic acid (T106E) or by deleting T106 (shown as Δ T106). The effect of these changes on pI and the heterogeneity of the fusion constructs was investigated by comparing constructs with and without O-linked glycosylation by separation on IEF gels.

[0133] In each case, deleting T106 or substituting T106 with alanine, serine, valine, glycine or glutamic acid decreased the number of observed charged species on an IEF gel, as evidenced by a reduced number of bands when directly compared to unmodified T106, and hence the heterogeneity of the fusion construct was reduced (Figure 9). The reduced number of charged species on the IEF gel and therefore the reduced heterogeneity of the molecule incorporating T106S is consistent with removal of the O-linked glycosylation at residue 106 of IFN α 2b.

[0134] Removal of the O-linked glycosylation site in the attenuated IFN portion of the antibody fusion constructs resulted in an increased pI relative to O-link glycosylated proteins. Using the same antibody front-end of A10.21, this trend was consistent regardless

of whether the isotype of the antibody was IgG4, IgG1, IgG1 AA (IgG1 L235A, G237A, an effector function reduced form of IgG1), IgG2 or IgG2 SS (IgG2 (A330S, P331S)) in the constructs (Figure 10).

[0135] YTE substitutions (M252Y, S254T, T256E) have been shown to confer increased affinity to FcRn, presumably increasing the half-life of antibodies. Further experiments examined whether substitutions in other parts of the antibody IFN fused constructs will affect the reduced heterogeneity which resulted from a T106 deletion or substitution. The heterogeneity of glycosylated A10.21 anti-CD38-attenuated IFN α 2b fusion construct (YTE, T106T) and the non-glycosylated IFN fusion construct with the YTE substitutions (YTE, T106A) was assessed on IEF gels. Removal of glycosylation of the IFN α 2b component of fusion constructs bearing the YTE mutations decreased heterogeneity (Figure 11).

[0136] Attenuation of IFN α 2b is attained by substitutions of key amino acid residues which are responsible for binding to IFN receptors. The number of charged species of A10.21 IgG4 (S228P) IFN constructs with various attenuating amino acid substitutions in the IFN α 2b, together with (T106T) or without O-linked glycosylation (T106A) of the IFN α 2b component was evaluated. Individual amino acid residues Arginine-33, Arginine-144 and Alanine-145 of IFN α 2b were substituted one at a time with Alanine for residue 33 (R33A), Isoleucine for residue 144 (R144I) or Lysine, Glycine or Glutamine for residue 145 (A145K, A145G, A145Q). When directly compared the aglycosylated IFN fusion constructs were consistently less heterogeneous than their glycosylated counterparts (Figure 12).

[0137] The reduction in heterogeneity exhibited was independent of the antibody portion of the construct. Removal of the O-linked glycosylation site in the attenuated IFN α 2b portion of the antibody (IgG4 (S228P)) –attenuated IFN fusion constructs with specificity against HLA, CD138 and CD38 (a different epitope on CD38 to antibody A10.21 - antibody A02.12) also resulted in a decrease in heterogeneity (Figure 13) as detected by IEF.

EXAMPLE 2**ANTI-PROLIFERATIVE ACTIVITY OF ANTIBODY ATTENUATED INTERFERON α 2b FUSION PROTEINS**

[0138] The anti-proliferative effects of IFN α 2b consist of direct and indirect activities. Direct activity occurs through cancer cell growth inhibition by cell cycle arrest (Matsui et al. 2003), apoptosis by death receptor–dependent (Crowder et al. 2005) and -independent (Otsuki et al. 1998) pathways, or differentiation (Matsui et al. 2003). Target-specific direct cytotoxicity of antibody attenuated interferon fusion proteins were measured against target positive cell lines using a luminescent cell viability assay.

Anti CD38-IFN Lead Sequence Samples

[0139] The constructs (Table 3) were either stably cloned or transiently transfected and were harvested and purified using a Mab Select Sure Protein A column. Samples were desalted into 200mM Arginine, 25mM Histidine pH 6.5 using a HiLoad Superdex 200 column.

Table 3: Table of Constructs

Antibody Constructs	Seq Id No.			
	Heavy Chain	Light Chain	IFN	VH + IFN
A10.21 IgG4 (S228P) IFN (A145D, T106T)	48	81	107	
A10.21 IgG4 (S228P) IFN (A145D, T106A)	48	81	25	87, 31
A10.21 IgG4 (S228P) IFN (A145D, Δ T106)	48	81	110	61
A10.21 IgG4 (S228P) IFN (A145D, T106S)	48	81	25	31
A10.21 IgG4 (S228P) IFN (A145D, T106V)	48	81	25	31

Antibody Constructs	Seq Id No.			
	Heavy Chain	Light Chain	IFN	VH + IFN
A10.21 IgG4 (S228P) IFN (A145D, T106G)	48	81	25	31
A10.21 IgG4 (S228P) IFN (A145D, T106E)	48	81	25	31
A10.21 IgG4 (S228P, M252Y, S254T, T256E) IFN (A145D, T106T)	49	81	107	
A10.21 IgG4 (S228P, M252Y, S254T, T256E) IFN (A145D, T106A)	49	81	25	62
A10.21 IgG4 (S228P) IFN (R144I T106T)	48	81	108	
A10.21 IgG4 (S228P) IFN (R144I, T106A)	48	81	24	63
A10.21 IgG4 (S228P) IFN (A145K, T106T)	48	81	107	
A10.21 IgG4 (S228P) IFN (A145K, T106A)	48	81	25	64
A10.21 IgG4 (S228P) IFN (A145G, T106T)	48	81	107	
A10.21 IgG4 (S228P) IFN (A145G, T106A)	48	81	25	64
A10.21 IgG4 (S228P) IFN (R33A, T106T)	48	81	109	
A10.21 IgG4 (S228P) IFN (R33A, T106A)	48	81	13	65
A10.21 IgG4 (S228P) IFN (A145Q, T106T)	48	81	107	
A10.21 IgG4 (S228P) IFN (A145Q, T106A)	48	81	25	66

Antibody Constructs	Seq Id No.			
	Heavy Chain	Light Chain	IFN	VH + IFN
A10.21 IgG4 (S228P) IFN (A145N, T106T)	48	81	107	
A10.21 IgG4 (S228P) IFN (A145N, T106A)	48	81	25	66
A10.21 IgG4 (S228P) IFN (R144N, T106T)	48	81	108	
A10.21 IgG4 (S228P) IFN (R144N, T106A)	48	81	24	67
A10.21 IgG4 (S228P) IFN (R144H, T106T)	48	81	108	
A10.21 IgG4 (S228P) IFN (R144H, T106A)	48	81	24	67
A10.21 IgG1 IFN (A145D, T106T)	50	81	107	
A10.21 IgG1 IFN (A145D, T106A)	50	81	25	68
A10.21 IgG1 IFN (A145D, ΔT106)	50	81	110	83
A10.21 IgG1 (L235A, G237A) IFN (A145D, T106T)	51	81	107	
A10.21 IgG1 (L235A, G237A) IFN (A145D, T106A)	51	81	25	69
A10.21 IgG1 (L235A, G237A, M252Y, S254T, T256E) IFN (A145D, T106T)	52	81	107	
A10.21 IgG1 (L235A, G237A, M252Y, S254T, T256E) IFN (A145D, T106A)	52	81	25	
A10.21 IgG1 (M252Y, S254T, T256E) IFN (A145D, T106T)	52	81	107	
A10.21 IgG1 (M252Y, S254T, T256E) IFN (A145D, T106A)		81	25	70
A10.21 IgG2 IFN (A145D, T106T)	53	81	107	

Antibody Constructs	Seq Id No.			
	Heavy Chain	Light Chain	IFN	VH + IFN
A10.21 IgG2 IFN (A145D, T106A)	53	81	25	72
A10.21 IgG2 (A330S, P331S) IFN (A145D, T106T)		81	107	
A10.21 IgG2 (A330S, P331S) IFN (A145D, T106A)		81	25	
A10.21 IgG2 (M252Y, S254T, T256E) IFN (A145D, T106T)	54	81	107	
A10.21 IgG2 (M252Y, S254T, T256E) IFN (A145D, T106A)	54	81	25	73
A10.43 IgG4 (S228P) IFN (A145D, T106T)	55	81	107	
A10.43 IgG4 (S228P) IFN (A145D, T106A)	55	81	25	74
R10A2 IgG4 (S228P) IFN (A145D, T106T)	75	82	107	
R10A2 IgG4 (S228P) IFN (A145D, T106A)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106R)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106N)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106D)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106C)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106E)	75	82	25	

Antibody Constructs	Seq Id No.			
	Heavy Chain	Light Chain	IFN	VH + IFN
R10A2 IgG4 (S228P) IFN (A145D, T106Q)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106G)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106H)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106I)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106L)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106K)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106M)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106F)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106P)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106S)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106W)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106Y)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106V)	75	82	25	
A02.12 IgG4 (S228P) IFN (A145D, T106T)	58	84	107	

Antibody Constructs	Seq Id No.			
	Heavy Chain	Light Chain	IFN	VH + IFN
A02.12 IgG4 (S228P) IFN (A145D, T106A)	58	84	25	77
OPG-Fc (IgG2) IFN (A145D, T106T)	57		107	
OPG-Fc (IgG2) IFN (A145D, T106A)	57		25	78
Anti-CD138 IgG4 (S228P) IFN (A145D, T106T)	59	85	107	
Anti-CD138 IgG4 (S228P) IFN (A145D, T106A)	59	85	25	
Anti-HLA IgG4 (S228P) IFN (A145D, T106T)	60	86	107	
Anti-HLA IgG4 (S228P) IFN (A145D, T106A)	60	86	25	

Commercial IFN α 2b

[0140] INTRON® A, a commercial bacterially produced IFN α 2b from Schering-Plough, was used as a positive control.

Anti-Proliferative activity measurement

[0141] Anti-proliferative activity was measured using the methods described above “Daudi cell proliferation assay” and “ARP-1 Cell proliferation assay”. The ARP-1 cell proliferation assay method was used with an additional cell line NCI-H929 for the measurement of the anti-proliferative activity of antibody-attenuated IFN α 2b fusion protein. In some experiments the plates were read on a dedicated GloMax® 96 Microplate Luminometer and CellTiter-Glo® 2.0 reagents were used instead of the original CellTiter-Glo, neither of which impacted the results. The ARP-1/ NCI-H929 or Daudi cell proliferation assay was used to quantify the anti-proliferative activity of IFNs and antibody-attenuated IFN α 2b fusion protein constructs on cells that display CD38. Daudi,

ARP1 and NCI-H929 cells express CD38 as a cell surface associated antigen. The details of the assays are as follows.

[0142] In the ARP-1/ NCI-H929 cell proliferation assay viability of cells was measured using the reagent CellTiter-Glo® 2.0, Cat # G9242, from Promega (Madison, Wisconsin). This is a luminescence-based assay that determines the viability of cells in culture based on quantitation of ATP. The signal strength is proportional to the number of viable cells in a microtiter plate well. Cells (NCI-H929 from ATCC, Manassas, VA and ARP-1, a gift from Bart Barlogie MD, PhD, Director of the Myeloma Institute at the University of Arkansas Medical Center ; Little Rock, AK) were cultured in a T75 flask (TPP, Trasadingen, Switzerland, cat# 90076) to a preferred density of between 0.5×10^5 and 0.8×10^5 viable cells/mL in RPMI 1640 (Mediatech, Inc., Manassas, VA, cat # 10-040- CV) with 10% Fetal Bovine Serum (FBS; Hyclone, Logan, UT cat# SH30070.03). Cells were harvested by centrifuging at $400 \times g$ for five minutes, decanting the supernatant, and resuspending the cell pellet in RPMI 1640 + 10% FBS. Cells were then counted and the density was adjusted to 3.0×10^5 cells/mL in RPMI 1640 + 10% FBS. 50 μ L of cell suspension was seeded into each well of a 96 well round bottom tissue culture plate (hereafter, “experimental plate”) (TPP, cat# 92067). Cells were incubated at 4°C for 1 hour prior to the addition of test compounds. On a separate, sterile 96 well plate (hereafter, “dilution plate”; Costar, Corning, NY cat# 3879), test articles were serially diluted in duplicate in RPMI 1640 + 10% FBS. 50 μ L/well was transferred from the dilution plate to the experimental plate. The experimental plate was then incubated for four days at 37° C with 5% CO₂. A “CellTiter-Glo® reagent 2.0”, was added to the experimental plate at 100 μ L/well. The plate was shaken for two minutes. 100 μ L/well was transferred from the experimental plate to a 96 well flat bottom white opaque plate (hereafter, “assay plate”; BD Biosciences, Franklin 5 Lakes, NJ cat# 35 3296). The content of the assay plate was then allowed to stabilize in the dark for 15 minutes at room temperature. The plate was read on GloMax® 96 Microplate Luminometer. Results are presented as “relative luminescence units” (RLU).

[0143] Data was analyzed using Prism 5 (Graphpad, San Diego, CA) using non-linear regression and four parameter curve fit to determine the IC₅₀.

[0144] The O-linked glycosylation site of anti-CD38 antibody attenuated interferon fusion constructs were removed by either substituting threonine 106 (T106) to alanine (T106A), serine (T106S), valine (T106V), glycine (T106G) or glutamic acid (T106E) or deleting T106 (shown as Δ T106). The effect on cell proliferation was investigated by comparing A10.21 anti-CD38 antibody fused to attenuated IFN α 2b with and without O-linked glycosylation. Removal of the O-linked glycosylation site in the attenuated IFN portion of the antibody fusion constructs resulted in increased anti-proliferative activity as shown by lower IC₅₀ (nM) relative to the corresponding O-linked glycosylated fusion proteins i.e. A10.21 IgG4 (S228P) IFN (A145D, T106T) and A10.21 IgG1 IFN (A145D, T106T) in both ARP1 (Figure 1A) and NCI-H929 cells (Figure 1B). This trend was consistent regardless of whether the antibody isotype was IgG4 and IgG1.

[0145] Substitution of threonine 106 (T106) to alanine (T106A), serine (T106S), valine (T106V), glycine (T106G) or glutamic acid (T106E) resulted in increased anti-proliferative activity as shown by lower IC₅₀ (nM) relative to O-linked glycosylated fusion proteins. All non-glycosylated constructs showed higher “on-target” potency relative to their glycosylated counterpart in NCI-H929 cells (Figure 14).

[0146] The impact on anti-proliferative activity of the removal of the O-linked glycosylation site from the attenuated IFN α 2b component was examined in a range of anti-CD38 antibody-attenuated IFN α 2b fusion proteins. Variants of the anti-CD38 antibody-attenuated IFN α 2b fusion protein R10A2 IgG4 (S228P) IFN (A145D) possessing different amino acid substitutions at T106 to remove the O-linked glycosylation site on the IFN component (T106A, T106G, T106N, T106F, T106R, T106D, T106E, T106Q, T106H, T106I, T106L, T106K, T106M, T106F, T106P, T106S, T106V, T106Y and T106W, (Table 4) were examined and the results shown in Figure 2.

[0147] While the level of potency varied between different substitutions at the T106 site, all substitutions that are predicted to result in the removal of O-linked glycosylation increased potency relative to the corresponding O-linked glycosylated protein (Figure 2).

Table 4: R10A2 Anti-CD38 antibody- attenuated IFN fusion construct variants with various amino acid substitutions at T106 for removal of O-linked glycosylation.

Construct Name	Seq Id No.		
	Heavy Chain	Light Chain	IFN
R10A2 IgG4 (S228P) IFN (A145D, T106T)	75	82	107
R10A2 IgG4 (S228P) IFN (A145D, T106A)	75	82	25
R10A2 IgG4 (S228P) IFN (A145D, T106R)	75	82	25
R10A2 IgG4 (S228P) IFN (A145D, T106N)	75	82	25
R10A2 IgG4 (S228P) IFN (A145D, T106D)	75	82	25
R10A2 IgG4 (S228P) IFN (A145D, T106C)	75	82	25
R10A2 IgG4 (S228P) IFN (A145D, T106E)	75	82	25
R10A2 IgG4 (S228P) IFN (A145D, T106Q)	75	82	25
R10A2 IgG4 (S228P) IFN (A145D, T106G)	75	82	25
R10A2 IgG4 (S228P) IFN (A145D, T106H)	75	82	25
R10A2 IgG4 (S228P) IFN (A145D, T106I)	75	82	25
R10A2 IgG4 (S228P) IFN (A145D, T106L)	75	82	25
R10A2 IgG4 (S228P) IFN (A145D, T106K)	75	82	25
R10A2 IgG4 (S228P) IFN (A145D, T106M)	75	82	25
R10A2 IgG4 (S228P) IFN (A145D, T106F)	75	82	25
R10A2 IgG4 (S228P) IFN (A145D, T106P)	75	82	25
R10A2 IgG4 (S228P) IFN (A145D, T106S)	75	82	25
R10A2 IgG4 (S228P) IFN (A145D, T106W)	75	82	25
R10A2 IgG4 (S228P) IFN (A145D, T106Y)	75	82	25
R10A2 IgG4 (S228P) IFN (A145D, T106V)	75	82	25

[0148] The relative changes in the potency between two different anti-CD38 antibody interferon fusion proteins (A02.12 and A10.21) which bind different epitopes on CD38, with or without the O-linked glycosylation (A02.12 IgG4 (S228P) IFN (A145D, T106T), A02.12 IgG4 (S228P) IFN (A145D, T106A), A10.21 IgG4 (S228P) IFN (A145D, T106T) and A10.21 IgG4 (S228P) IFN (A145D, T106A) was assessed in a similar manner.

Removal of the O-linked glycosylation site in the attenuated IFN portion of the antibody (IgG4 (S228P)) fusion constructs with differing specificity against CD38 resulted in an increase in anti-proliferative activity regardless of the target of the antibody portion of the construct (Figure 15).

[0149] Attenuation of IFN α 2b is achieved by various attenuating substitutions. The anti-proliferative activity of A10.21 IgG4 (S228P) IFN constructs with various attenuating substitutions in the IFN α 2b with (T106T) and without O-linked glycosylation (T106A) (Table 5) was also evaluated. The removal of the O-linked glycosylation site in the IFN α 2b component of constructs with various attenuating substitutions all had higher potency than their glycosylated counterpart (Figure 16).

Table 5: A10.21 IgG4 (S228P) IFN constructs with various attenuating substitutions in the IFN α 2b with (T106T) and without O-linked glycosylation (T106A).

Construct Name	Seq Id No.			
	Heavy Chain	Light Chain	IFN	VH + IFN
A10.21 IgG4 (S228P) IFN (R144I T106T)	48	81	108	
A10.21 IgG4 (S228P) IFN (R144I, T106A)	48	81	24	63
A10.21 IgG4 (S228P) IFN (A145K, T106T)	48	81	107	
A10.21 IgG4 (S228P) IFN (A145K, T106A)	48	81	25	64
A10.21 IgG4 (S228P) IFN (A145G, T106T)	48	81	107	
A10.21 IgG4 (S228P) IFN (A145G, T106A)	48	81	25	64
A10.21 IgG4 (S228P) IFN (R33A, T106T)	48	81	109	
A10.21 IgG4 (S228P) IFN (R33A, T106A)	48	81	13	65
A10.21 IgG4 (S228P) IFN (A145Q, T106T)	48	81	107	
A10.21 IgG4 (S228P) IFN (A145Q, T106A)	48	81	25	66
A10.21 IgG4 (S228P) IFN (A145N, T106T)	48	81	107	
A10.21 IgG4 (S228P) IFN (A145N, T106A)	48	81	25	66
A10.21 IgG4 (S228P) IFN (R144N, T106T)	48	81	108	
A10.21 IgG4 (S228P) IFN (R144N, T106A)	48	81	24	67

Construct Name	Seq Id No.			
	Heavy Chain	Light Chain	IFN	VH + IFN
A10.21 IgG4 (S228P) IFN (R144H, T106T)	48	81	108	
A10.21 IgG4 (S228P) IFN (R144H, T106A)	48	81	24	67

[0150] To investigate whether other attenuated IFN α 2b fused antibodies/proteins which have different binding targets have modulated anti-proliferative activity as a result of removal of O-linked glycosylation, 2 constructs were created (an anti-CD138 antibody and an anti-HLA antibody and fused to IFN (A145D) with or without O-linked glycosylation (Table 6) and were tested for anti-proliferative activity.

[0151] Removal of the O-linked glycosylation site in the attenuated IFN portion of the antibody (IgG4 (S228P)) fusion constructs with specificity against HLA and CD138 resulted in an increase in anti-proliferative activity regardless of the target of the antibody portion of the construct. This was demonstrated in antibody fusion constructs against HLA and CD138 (Figure 17).

Table 6: Constructs of various IFN fusion proteins -anti-CD138 antibody and anti-HLA antibody fused to IFN (A145D) with or without O-linked glycosylation

Antibody Constructs	Seq Id No.			
	Heavy Chain	Light Chain	IFN	VH + IFN
Anti-CD138 IgG4 (S228P) IFN (A145D, T106T)	59	85	107	59
Anti-CD138 IgG4 (S228P) IFN (A145D, T106A)	59	85	25	59
Anti-HLA IgG4 (S228P) IFN (A145D, T106T)	60	86	107	
Anti-HLA IgG4 (S228P) IFN (A145D, T106A)	60	86	25	

Effect on anti-proliferative activity of the removal of O-linked glycosylation from fusion proteins comprising substitutions in the Fc regions for half-life extension or reduced effector function

[0152] YTE substitutions have been shown to confer increased affinity to FcRn, presumably increasing the half-life of antibodies. IFN fused antibodies containing the YTE substitutions were tested for anti-proliferative activity in the presence and absence of O-linked glycosylation. The following variants were made of the A10.21 anti-CD38 antibody attenuated IFN fusion protein (Table 7).

[0153] The introduction of the YTE substitution to A10.21 IgG4 (S228P) (A145D, T106A) did not impact the increase in potency caused by removal of the O-linked glycosylation from the attenuated IFN (Figure 18).

[0154] L235A and G237A substitutions in the Fc portion of IgG1 variants and A330S and P331S substitutions in the Fc portion of IgG2 variants results in reduced effector function. Attenuated IFN fused IgG1 antibodies containing L235A and G237A substitutions and attenuated IFN fused IgG2 antibodies containing A330S and P331S substitutions were tested for anti-proliferative activity in the presence and absence of O-linked glycosylation. These variants were made of the A10.21 anti-CD38 antibody attenuated IFN fusion protein (Table 7). Removal of the O-linked glycosylation site in the attenuated IFN portion of the antibody fusion constructs resulted in an increase in potency regardless of whether the isotype of the antibody in the antibody constructs was IgG1 or IgG1 AA (IgG1 (L235A, G237A)), IgG2 or IgG2 SS (IgG2 (A330S, P331S)) (Figure 19).

Table 7: A10.21 fusion proteins composed of substitutions in the Fc regions for half-life extension or reduced effector function

Antibody Constructs	Seq Id No.			
	Heavy Chain	Light Chain	IFN	VH + IFN
A10.21 IgG4 (S228P, M252Y, S254T, T256E) IFN (A145D, T106T)	49	81	107	
A10.21 IgG4 (S228P, M252Y, S254T, T256E) IFN (A145D, T106A)	49	81	25	62
A10.21 IgG1 (L235A, G237A) IFN (A145D, T106T)	51	81	107	
A10.21 IgG1 (L235A, G237A) IFN (A145D, T106A)	51	81	25	69
A10.21 IgG1 (L235A, G237A, M252Y, S254T, T256E) IFN (A145D, T106T)	52	81	107	
A10.21 IgG1 (L235A, G237A, M252Y, S254T, T256E) IFN (A145D, T106A)	52	81	25	
A10.21 IgG1 (M252Y, S254T, T256E) IFN (A145D, T106T)	52	81	107	
A10.21 IgG1 (M252Y, S254T, T256E) IFN (A145D, T106A)	111	81	25	70
A10.21 IgG2 IFN (A145D, T106T)	53	81	107	
A10.21 IgG2 IFN (A145D, T106A)	53	81	25	72
A10.21 IgG2 (A330S, P331S) IFN (A145D, T106T)	112	81	107	
A10.21 IgG2 (A330S, P331S) IFN (A145D, T106A)	112	81	25	
A10.21 IgG2 (M252Y, S254T, T256E) IFN (A145D, T106T)	54	81	107	
A10.21 IgG2 (M252Y, S254T, T256E) IFN (A145D, T106A)	54	81	25	73

[0155] Removal of the O-linked glycosylation site from the attenuated interferon portion of the anti-CD38 antibody interferon fusion proteins by amino acid substitution or deletion of T106 resulted in an increase in anti-proliferative activity on target CD38, CD138 or HLA positive cells (1.3-12 fold).

EXAMPLE 3

ON/OFF TARGET ACTIVITY OF ANTIBODY-ATTENUATED IFN α 2b FUSION PROTEINS

[0156] The iLiteTM reporter gene assay was performed for the quantitative determination of Human Interferon Alpha (IFN α 2b) bioactivity (IU/ml) using luciferase generated-bioluminescence. The cells used in this assay express CD38 and were used to measure the 'ON-target' activity of anti-CD38-attenuated IFN α 2b fusion proteins. These cells can also be used to measure 'OFF-target' activity when CD38 is blocked with an anti-CD38 antibody recognizing the same epitope. These assays can be used to determine the Selectivity Index (SI) which is a measure of how selectively active anti-CD38 IFN fusion proteins are against CD38+ target cells and non-active on cells where CD38 is blocked (mimicking CD38⁻ cells). The larger the SI the more selective the agents are against the target, while a number close to 1 indicates that there is no selectivity against the target or non-target. Intron A was used as a positive control as it is active against cells that express interferon alpha receptors, IFNAR1/2 but not selective against other cell surface expressed antigens (i.e. CD38) having an SI of approximately 1.

Antibody-attenuated IFN constructs

[0157] The sequences for the constructs used are set out in Sequence Listing and are listed in the following Table 8.

Table 8

Antibody Constructs	Seq Id No.			
	Heavy Chain	Light Chain	IFN	VH + IFN
A10.21 IgG4 (S228P) IFN (A145D, T106T)	48	81	107	
A10.21 IgG4 (S228P) IFN (A145D, T106A)	48	81	25	87, 31
A10.21 IgG4 (S228P) IFN (A145D, Δ T106)	48	81	110	61
A10.21 IgG4 (S228P) IFN (A145D, T106S)	48	81	25	31
A10.21 IgG4 (S228P) IFN (A145D, T106V)	48	81	25	31
A10.21 IgG4 (S228P) IFN (A145D, T106G)	48	81	25	31
A10.21 IgG4 (S228P) IFN (A145D, T106E)	48	81	25	31
A10.21 IgG4 (S228P, M252Y, S254T, T256E) IFN (A145D, T106T)	49	81	107	
A10.21 IgG4 (S228P, M252Y, S254T, T256E) IFN (A145D, T106A)	49	81	25	62
A10.21 IgG4 (S228P) IFN (R144I T106T)	48	81	108	
A10.21 IgG4 (S228P) IFN (R144I, T106A)	48	81	24	63
A10.21 IgG4 (S228P) IFN (A145K, T106T)	48	81	107	
A10.21 IgG4 (S228P) IFN (A145K, T106A)	48	81	25	64
A10.21 IgG4 (S228P) IFN (A145G, T106T)	48	81	107	
A10.21 IgG4 (S228P) IFN (A145G, T106A)	48	81	25	64
A10.21 IgG4 (S228P) IFN (R33A, T106T)	48	81	109	
A10.21 IgG4 (S228P) IFN (R33A, T106A)	48	81	13	65
A10.21 IgG4 (S228P) IFN (A145Q, T106T)	48	81	107	

Antibody Constructs	Seq Id No.			
	Heavy Chain	Light Chain	IFN	VH + IFN
A10.21 IgG4 (S228P) IFN (A145Q, T106A)	48	81	25	66
A10.21 IgG4 (S228P) IFN (A145N, T106T)	48	81	107	
A10.21 IgG4 (S228P) IFN (A145N, T106A)	48	81	25	66
A10.21 IgG4 (S228P) IFN (R144N, T106T)	48	81	108	
A10.21 IgG4 (S228P) IFN (R144N, T106A)	48	81	24	67
A10.21 IgG4 (S228P) IFN (R144H, T106T)	48	81	108	
A10.21 IgG4 (S228P) IFN (R144H, T106A)	48	81	24	67
A10.21 IgG1 IFN (A145D, T106T)	50	81	107	
A10.21 IgG1 IFN (A145D, T106A)	50	81	25	68
A10.21 IgG1 IFN (A145D, ΔT106)	50	81	110	83
A10.21 IgG1 (L235A, G237A) IFN (A145D, T106T)	51	81	107	
A10.21 IgG1 (L235A, G237A) IFN (A145D, T106A)	51	81	25	69
A10.21 IgG1 (L235A, G237A, M252Y, S254T, T256E) IFN (A145D, T106T)	52	81	107	
A10.21 IgG1 (L235A, G237A, M252Y, S254T, T256E) IFN (A145D, T106A)	52	81	25	
A10.21 IgG1 (M252Y, S254T, T256E) IFN (A145D, T106T)	52	81	107	
A10.21 IgG1 (M252Y, S254T, T256E) IFN (A145D, T106A)	111	81	25	70
A10.21 IgG2 IFN (A145D, T106T)	53	81	107	
A10.21 IgG2 IFN (A145D, T106A)	53	81	25	72
A10.21 IgG2 (M252Y, S254T, T256E) IFN (A145D, T106T)	54	81	107	

Antibody Constructs	Seq Id No.			
	Heavy Chain	Light Chain	IFN	VH + IFN
A10.21 IgG2 (M252Y, S254T, T256E) IFN (A145D, T106A)	54	81	25	73
A10.43 IgG4 (S228P) IFN (A145D, T106T)	55	81	107	
A10.43 IgG4 (S228P) IFN (A145D, T106A)	55	81	25	74
R10A2 IgG4 (S228P) IFN (A145D, T106T)	75	82	107	
R10A2 IgG4 (S228P) IFN (A145D, T106A)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106R)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106N)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106D)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106C)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106E)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106Q)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106G)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106H)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106I)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106L)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106K)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106M)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106F)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106P)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106S)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106W)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106Y)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106V)	75	82	25	
A02.12 IgG4 (S228P) IFN (A145D, T106T)	58	84	107	

Antibody Constructs	Seq Id No.			
	Heavy Chain	Light Chain	IFN	VH + IFN
A02.12 IgG4 (S228P) IFN (A145D, T106A)	58	84	25	77
OPG-Fc (IgG2) IFN (A145D, T106T)	57		107	
OPG-Fc (IgG2) IFN (A145D, T106A)	57		25	78
Anti-CD138 IgG4 (S228P) IFN (A145D, T106T)	59	85	107	
Anti-CD138 IgG4 (S228P) IFN (A145D, T106A)	59	85	25	
Anti-HLA IgG4 (S228P) IFN (A145D, T106T)	60	86	107	
Anti-HLA IgG4 (S228P) IFN (A145D, T106A)	60	86	25	

[0158] INTRON® A was used as a positive control.

ON/OFF-target activity measurement

[0159] The ON/OFF-target activity was measured using the same method described above as "iLite gene reporter assay"

[0160] iLite reporter gene assay (PBL Interferon Source, Piscataway, NJ, Cat# 51100) was performed largely as described by the manufacturer, with the addition of a human IgG blocking step. The iLite cell line is described by the manufacturer as "a stable transfected cell line derived from a commercially available pro-monocytic human cell line characterized by the expression of MHC Class II antigens, in particular the human lymphocyte antigen (HLADR), on the cell surface." The cell line expresses CD38 and contains a stably transfected luciferase gene, the expression of which is driven by an interferon-response element (IRE), which allows for interferon activity to be quantified based on luminescence output.

[0161] The manufacturer supplied iLite plate (hereafter, assay plate) and diluent were removed from the -80° C freezer and allowed to equilibrate to room temperature. 50 µL of the diluent was added per well to the assay plate. The vial of manufacturer-supplied reporter cells was removed from the -80° C freezer and thawed in a 37°C water bath. 25 µL aliquots of cells were dispensed into each well of the assay plate. Next, 12.5 µL of 8 mg/mL human IgG diluted in RPMI 1640 + 10% FBS (Sigma Chemicals, St. Louis, MO; cat# I4506) was added per well. The contents were mixed and incubated at 37° C for 15 minutes. On a separate “dilution plate,” test articles were serially diluted in duplicate in RPMI 1640 + 10% FBS. Then, 12.5 µL of the test articles were transferred from the dilution plate to the assay plate. The assay plate was then incubated at 37° C with 5% CO₂ for 17 hours. The manufacturer-supplied assay buffer and substrate were removed from the -80° C freezer and allowed to equilibrate to room temperature for two hours. The manufacturer-supplied assay buffer was added to the manufacturer-supplied substrate vial and mixed well according to the manufacturer’s instructions to create the “luminescence solution.” Then, 100 µL of the luminescence solution was added to each well of the assay plate. The plate was shaken for 2 minutes. The plate was then incubated at room temperature for 5 minutes in the dark and read on a Victor 3V Multilabel Counter on a luminometry channel and the luminescence measured and presented as RLU.

[0162] To test the off-target activity of anti-CD38 antibody-IFN fusion protein constructs in the iLite assay, manufacturer-supplied diluent was supplemented with 0.25 mg/mL anti-CD38 antibody (an antibody recognizing the same epitope on CD38 as the antibody-IFN fusion protein construct being tested, to block any binding of the anti-CD38 antibody-IFN fusion protein constructs to the CD38 expressed on the iLite cells). This blocking stage was followed by treatment with anti-CD38 antibody-IFN fusion protein or IFNα2b.

[0163] Data was analyzed using Prism 5 (Graphpad, San Diego, CA) using non-linear regression and three parameter curve fit to determine the midpoint of the curve (EC50). Selectivity Index (SI) was calculated by EC50 (OFF-target activity)/ EC50 (ON-target activity). Selectivity Index (SI) is a measure of how selectively active anti-CD38 IFN constructs are against CD38-expressing cells and non-active in cells with no CD38. The

larger the number the more selective it is against the target, while a number close to 1 indicates that there is no selectivity against the target. Intron A was used as a positive control, has an SI of approximately 1.

[0164] The O-linked glycosylation site of anti-CD38 antibody attenuated interferon fusion constructs were removed by substituting threonine 106 (T106) to alanine (shown as T106A). The activity was investigated by comparing A10.21 and A10.43 anti-CD38 antibodies fused to IFN α 2b with and without O-linked glycosylation.

[0165] Removal of the O-linked glycosylation site in the attenuated IFN portion of the antibody fusion constructs (shown as T106A) resulted in slight increase in ON-target activity (Figure 3 and Table 9) as well as slight to no increase in the OFF-target activity relative to O-linked glycosylated proteins. Both O-linked glycosylated and non-glycosylated proteins showed high selectivity towards CD38+ cells, while Intron A did not show selectivity.

Table 9: EC50 and SI of anti-CD38 antibody attenuated IFN α 2b fusion proteins A10.21 and A10.43 with and without O-linked glycosylation

Test Article	EC50 (nM)		SI
	ON Target	OFF Target	
Intron A	0.00017	0.00016	0.90
A10.21 IgG4 (S228P) IFN(A145D, T106T)	0.00240	2.33	972
A10.21 IgG4 (S228P) IFN (A145D, T106A)	0.00182	2.23	1223
A10.43 IgG4 (S228P) IFN (A145D, T106T)	0.00560	2.31	412
A10.43 IgG4 (S228P) IFN (A145D, T106A)	0.00124	2.25	1822

[0166] The impact on ON/OFF target activity of the removal of the O-linked glycosylation site from the attenuated IFN of fusion proteins may also be examined in a similar manner.

[0167] The iLite™ reporter gene ON-OFF target activity assays were conducted to demonstrate the selective activity of anti-CD38 attenuated IFN fusion proteins on target CD38+ cells and the limited activity on cells when CD38 is blocked with an anti-CD38 antibody (recognizing the same epitope) mimicking the activity anticipated on target negative cells.

[0168] Removal of the O-linked glycosylation site in the attenuated IFN portion of the antibody fusion constructs (by T106A substitution) resulted in a slight increase in ON-target activity as well as slight to no increase in the OFF-target activity relative to O-linked glycosylated proteins. Both O-linked glycosylated and non-glycosylated anti-CD38 antibody attenuated interferon fusion proteins showed high selectivity towards CD38+ cells, while Intron A did not show selectivity.

[0169] To further examine the modulation in selectivity index as a result of the removal of the O-linked glycosylation site in the attenuated IFN portion of the antibody fusion constructs, ON-OFF target activity was examined in a range of constructs. The changes examined were based on the A10.21 IgG4 (S228P) IFN (A145D, T106T) construct. These included deletion of threonine 106 (Δ T106), substitution of T106 to serine (T106S), YTE substitution (YTE T106T and YTE T106A), IFN attenuation by substitution from alanine 145 to glutamine (A145Q) and varying antibody isotype to IgG1 (IgG1 T106T and IgG1 T106A).

[0170] The majority of constructs demonstrated a selectivity index >1, the magnitude of selectivity towards targeted CD38+ cells varied depending on the anti-CD38 IFN fused construct (Figure 20). The highest selectivity was observed in A10.21 IgG4 (S228P) IFN (A145D, T106A).

EXAMPLE 4

OFF-TARGET ACTIVITY OF ANTI-CD38 ANTIBODY-ATTENUATED IFN α 2b FUSION PROTEINS

[0171] HEK-Blue™ IFN- α/β cells allow the detection of bioactive human type I IFNs by monitoring the activation of the ISGF3 pathway. Stimulation of HEK-Blue™ IFN- α/β

cells with human IFN- α activates the JAK/STAT/ISGF3 pathway and subsequently induces the production of SEAP (a reporter gene under the control of the IFN- α/β inducible ISG54 promoter). Levels of SEAP in the supernatant can be easily determined with QUANTI-Blue™. The effects of removal of O-linked glycosylation from the attenuated interferon portion of the antibody interferon fusion proteins were evaluated using this reporter gene assay.

Antibody/Fc fusion protein construct production

[0172] Various transiently transfected cells expressing interferon fusion proteins were harvested and purified using a Mab Select Sure Protein A column. Samples were desalted into 200mM Arginine, 25mM Histidine pH 6.5 using a HiLoad Superdex 200 column.

Table 10

Antibody Constructs	Seq Id No.			
	Heavy Chain	Light Chain	IFN	VH + IFN
A10.21 IgG4 (S228P) IFN (A145D, T106T)	48	81	107	
A10.21 IgG4 (S228P) IFN (A145D, T106A)	48	81	25	87, 31
A10.21 IgG4 (S228P) IFN (A145D, Δ T106)	48	81	110	61
A10.21 IgG4 (S228P) IFN (A145D, T106S)	48	81	25	31
A10.21 IgG4 (S228P) IFN (A145D, T106V)	48	81	25	31
A10.21 IgG4 (S228P) IFN (A145D, T106G)	48	81	25	31
A10.21 IgG4 (S228P) IFN (A145D, T106E)	48	81	25	31
A10.21 IgG4 (S228P, M252Y, S254T, T256E) IFN (A145D, T106T)	49	81	107	
A10.21 IgG4 (S228P, M252Y, S254T, T256E) IFN (A145D, T106A)	49	81	25	62
A10.21 IgG4 (S228P) IFN (R144I T106T)	48	81	108	
A10.21 IgG4 (S228P) IFN (R144I, T106A)	48	81	24	63
A10.21 IgG4 (S228P) IFN (A145K, T106T)	48	81	107	
A10.21 IgG4 (S228P) IFN (A145K, T106A)	48	81	25	64

Antibody Constructs	Seq Id No.			
	Heavy Chain	Light Chain	IFN	VH + IFN
A10.21 IgG4 (S228P) IFN (A145G, T106T)	48	81	107	
A10.21 IgG4 (S228P) IFN (A145G, T106A)	48	81	25	64
A10.21 IgG4 (S228P) IFN (R33A, T106T)	48	81	109	
A10.21 IgG4 (S228P) IFN (R33A, T106A)	48	81	13	65
A10.21 IgG4 (S228P) IFN (A145Q, T106T)	48	81	107	
A10.21 IgG4 (S228P) IFN (A145Q, T106A)	48	81	25	66
A10.21 IgG4 (S228P) IFN (A145N, T106T)	48	81	107	
A10.21 IgG4 (S228P) IFN (A145N, T106A)	48	81	25	66
A10.21 IgG4 (S228P) IFN (R144N, T106T)	48	81	108	
A10.21 IgG4 (S228P) IFN (R144N, T106A)	48	81	24	67
A10.21 IgG4 (S228P) IFN (R144H, T106T)	48	81	108	
A10.21 IgG4 (S228P) IFN (R144H, T106A)	48	81	24	67
A10.21 IgG1 IFN (A145D, T106T)	50	81	107	
A10.21 IgG1 IFN (A145D, T106A)	50	81	25	68
A10.21 IgG1 IFN (A145D, ΔT106)	50	81	110	83
A10.21 IgG1 (L235A, G237A) IFN (A145D, T106T)	51	81	107	
A10.21 IgG1 (L235A, G237A) IFN (A145D, T106A)	51	81	25	69
A10.21 IgG1 (L235A, G237A, M252Y, S254T, T256E) IFN (A145D, T106T)	52	81	107	
A10.21 IgG1 (L235A, G237A, M252Y, S254T, T256E) IFN (A145D, T106A)	52	81	25	
A10.21 IgG1 (M252Y, S254T, T256E) IFN (A145D, T106T)	52	81	107	
A10.21 IgG1 (M252Y, S254T, T256E) IFN (A145D, T106A)		81	25	70
A10.21 IgG2 IFN (A145D, T106T)	53	81	107	

Antibody Constructs	Seq Id No.			
	Heavy Chain	Light Chain	IFN	VH + IFN
A10.21 IgG2 IFN (A145D, T106A)	53	81	25	72
A10.21 IgG2 (M252Y, S254T, T256E) IFN (A145D, T106T)	54	81	107	
A10.21 IgG2 (M252Y, S254T, T256E) IFN (A145D, T106A)	54	81	25	73
A10.43 IgG4 (S228P) IFN (A145D, T106T)	55	81	107	
A10.43 IgG4 (S228P) IFN (A145D, T106A)	55	81	25	74
R10A2 IgG4 (S228P) IFN (A145D, T106T)	75	82	107	
R10A2 IgG4 (S228P) IFN (A145D, T106A)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106R)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106N)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106D)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106C)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106E)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106Q)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106G)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106H)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106I)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106L)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106K)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106M)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106F)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106P)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106S)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106W)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106Y)	75	82	25	
R10A2 IgG4 (S228P) IFN (A145D, T106V)	75	82	25	
A02.12 IgG4 (S228P) IFN (A145D, T106T)	58	84	107	

Antibody Constructs	Seq Id No.			
	Heavy Chain	Light Chain	IFN	VH + IFN
A02.12 IgG4 (S228P) IFN (A145D, T106A)	58	84	25	77
OPG-Fc (IgG2) IFN (A145D, T106T)	57		107	
OPG-Fc (IgG2) IFN (A145D, T106A)	57		25	78
Anti-CD138 IgG4 (S228P) IFN (A145D, T106T)	59	85	107	
Anti-CD138 IgG4 (S228P) IFN (A145D, T106A)	59	85	25	
Anti-HLA IgG4 (S228P) IFN (A145D, T106T)	60	86	107	
Anti-HLA IgG4 (S228P) IFN (A145D, T106A)	60	86	25	

[0173] INTRON[®] A was used as a positive control.

Off-target activity measurement by HEK-Blue assay

[0174] Off-target activity of antibody-IFN fusion was measured using the same method as described in “HEK-Blue Off-target assay” except for the volumes of cells seeded, diluted antibodies and supernatant used. The details of the assay are as follows.

[0175] HEK-Blue Off-target assay was used to quantify the ability of antibody-IFN fusion constructs to bind interferon-alpha/ β receptor (IFNAR) using the HEK-Blue[™] IFN-alpha/ β cell line (InvivoGen, San Diego, CA). The “off -target (HB-IFN) assay” was performed largely as described by the manufacturer of the HEK-Blue IFN-alpha/ β cell line. HEK-Blue[™] IFN-alpha/ β Cells are specifically designed to monitor the activation of the JAK-STAT pathway, which is induced by type I IFNs. The cells were generated by introducing the human STAT2 and IRF9 genes into HEK293 cells to obtain a fully active type I IFN signaling pathway. The HEK-Blue[™] IFN-alpha/ β cells stably express a reporter gene, secreted embryonic alkaline phosphatase (SEAP), under the control of the ISG54 promoter. ISG54 is a well-known ISG activated through an ISRE-dependent mechanism by type I IFNs. Upon IFN-alpha or IFN β stimulation, HEK-Blue[™] IFN-alpha/ β cells

activate the JAK-STAT pathway and then the expression of the SEAP reporter gene. SEAP is secreted into the media and can be quantitated using the colorimetric reagent QUANTI-Blue™.

[0176] Briefly, HEK-Blue IFN- α/β cells (Invivogen, San Diego CA cat# hkb-ifnab) were thawed and cultured in DMEM media (Mediatech, Manassas VA, cat# 10-013-CV) + 10% FBS (Hyclone, Logan UT, cat# SH30070.03) that had been heat inactivated (HI FBS). When the cells reached 60-80% confluence, they were lifted with Cell Stripper (Mediatech, cat# 25-056-CI). Cells were washed twice in DMEM + HI FBS and counted. Cells were adjusted to 2.77×10^5 viable cells/mL in DMEM + HI FBS and was seeded at 180 μ L per well into a flat bottom 96 well tissue culture plate (hereafter, the “experimental plate”). Then, 20 μ L of IFN- α 2b or fusion protein construct, diluted into DMEM + HI FBS, was added per well. The plate was incubated at 37°C 5% CO₂ for 16-24 hours. QUANTI-Blue (Invivogen, cat# rep-qb1) was prepared according to the manufacturer’s directions. QUANTI-Blue (180 μ L) was seeded into each well of a flat bottom plate (hereafter, the “assay plate”). Then, 20 μ L supernatant per well from the experimental plate was transferred to assay plate. Assay plate was then incubated at 37°C for 1-3 hours. Assay plate absorbance at 620 nm was read on a model SpectraMaxPlus 384 Microplate Reader from Molecular Devices. The data was analyzed using Graph Pad Prism.

[0177] The impact the presence or the absence of O-linked glycosylation in IFN α 2b has on the off-target activity of the attenuated IFN fused anti-CD38 antibodies was evaluated.

[0178] The O-linked glycosylation site of an anti-CD38 antibody with attenuated interferon fusion constructs was removed by either substituting threonine 106 (T106) to alanine (shown as T106A) or deleting T106 (shown as Δ T106). The effect on off-target activity was investigated by comparing X10.21 anti-CD38 antibody fused to attenuated IFN α 2b with and without O-linked glycosylation.

[0179] Removal of the O-linked glycosylation site in the attenuated IFN portion of the antibody fusion constructs resulted in a slight increase in off-target activity relative to O-linked glycosylated proteins i.e. A10.21 IgG4 IFN (145D, T106T) and A10.21 IgG1 IFN

(145D, T106T) (Figure 5). This trend was consistent regardless of isotype (Figure 5). However IFN α 2b (A145D) is so attenuated that the level of induction of SEAP in this assay is limited even at the highest doses used. Therefore the EC50 is an approximation only.

[0180] The off-target activity of antibodies fused with attenuated IFN (R10A2 IgG4 (S228P) IFN (A145D)) possessing different amino acid substitutions for the removal of O-linked glycosylation was examined. All possible amino acid substitutions were tested and the construct are listed in Table 11.

Table 11

Construct Name	Seq Id No.		
	Heavy Chain	Light Chain	IFN
R10A2 IgG4 (S228P) IFN (A145D, T106T)	75	82	107
R10A2 IgG4 (S228P) IFN (A145D, T106A)	75	82	25
R10A2 IgG4 (S228P) IFN (A145D, T106R)	75	82	25
R10A2 IgG4 (S228P) IFN (A145D, T106N)	75	82	25
R10A2 IgG4 (S228P) IFN (A145D, T106D)	75	82	25
R10A2 IgG4 (S228P) IFN (A145D, T106C)	75	82	25
R10A2 IgG4 (S228P) IFN (A145D, T106E)	75	82	25
R10A2 IgG4 (S228P) IFN (A145D, T106Q)	75	82	25
R10A2 IgG4 (S228P) IFN (A145D, T106G)	75	82	25
R10A2 IgG4 (S228P) IFN (A145D, T106H)	75	82	25
R10A2 IgG4 (S228P) IFN (A145D, T106I)	75	82	25
R10A2 IgG4 (S228P) IFN (A145D, T106L)	75	82	25
R10A2 IgG4 (S228P) IFN (A145D, T106K)	75	82	25
R10A2 IgG4 (S228P) IFN (A145D, T106M)	75	82	25
R10A2 IgG4 (S228P) IFN (A145D, T106F)	75	82	25
R10A2 IgG4 (S228P) IFN (A145D, T106P)	75	82	25
R10A2 IgG4 (S228P) IFN (A145D, T106S)	75	82	25

Construct Name	Seq Id No.		
	Heavy Chain	Light Chain	IFN
R10A2 IgG4 (S228P) IFN (A145D, T106W)	75	82	25
R10A2 IgG4 (S228P) IFN (A145D, T106Y)	75	82	25
R10A2 IgG4 (S228P) IFN (A145D, T106V)	75	82	25

[0181] It was shown that each of these substitutions demonstrated similar or slightly less off-target activity (increased EC₅₀) relative to the O-glycosylated IFN fused antibody R10A2 IgG4 (S228P) IFN (A145D, T106T). However, IFN α 2b (A145D) is so attenuated that the level of induction of SEAP in this assay is limited even at the highest doses used. Therefore the EC₅₀ is an approximation only.

[0182] The off-target activity of another anti-CD38 antibody attenuated IFN α 2b construct and the impact of removal of O-linked glycosylation by the T106A substitution was investigated. A10.43 has 7 amino acid changes in the heavy chain compared to A10.21 while the two constructs share the same light chain sequence (see Sequence Listing). The results demonstrated that removal of the O-linked glycosylation site by T106A substitution slightly increased the off-target activity of A10.43. However IFN α 2b (A145D) is so attenuated that the level of induction of SEAP in this assay is limited even at the highest doses used. Therefore the EC₅₀ is an approximation only.

[0183] Removal of the O-linked glycosylation site in the attenuated IFN portion of the antibody interferon fusion constructs resulted in slight to no increase in the OFF-target activity as well as a slight increase in ON-target activity relative to O-linked glycosylated proteins. Both O-linked glycosylated and non-glycosylated anti-CD38 antibody attenuated interferon fusion proteins showed high selectivity towards CD38+ cells, while Intron A did not show selectivity.

EXAMPLE 5**EVALUATION OF HUMAN NEONATAL FC RECEPTOR (FCRN) BINDING TO ANTI-CD38-ATTENUATED IFN**

[0184] Poly-his-tagged FcRn was immobilized onto the designated active flow cells of a CM5 sensor chip in a Biacore T200 enhanced instrument using an amine coupling protocol, while a blank immobilization was performed on the reference flow cells. Pulses of poly-his-tagged FcRn were injected over the active surfaces to ensure that the solution would pre-concentrate onto the flow cell. The surfaces were then washed with 50 mM NaOH. Both the reference and active surfaces were activated for seven minutes with a mix of 50:50 EDC/NHS. This was followed by a series of pulses of poly-his-tagged FcRn at 2 µg/mL in 10 mM Sodium Acetate pH 5.0 over the active surfaces only. Once the target of 150 RU was reached, both surfaces were deactivated with 1 M ethanolamine pH 8.5 for seven minutes. This protocol resulted in the immobilization of approximately 150 RU of poly-his-tagged FcRn onto the active surfaces. Each active surface was used for one run.

[0185] The test antibodies were desalted in PBS-P running buffer (DPBS, pH 7.4 and 0.005% Tween-20 adjusted to pH 6.0 with HCl at 25°C) using Zeba Spin Desalting Column, 7K MWCO, 0.5 mL (Pierce Product # 89882). Following desalting, the concentration of each sample was adjusted to 1 mg/mL.

[0186] On the day of the assay the 1 mg/mL solutions were further diluted in running buffer to prepare the highest concentration, and then diluted 1:2 to create the concentration series. The test samples were passed over the surface using a flow rate of 50 µL/minute. The association phase was 100 seconds while the dissociation phase was 300 seconds for all concentrations tested. The active and reference surfaces were regenerated using a 60 second injection of 100 mM Tris, 50 mM NaCl at pH 8.0 to remove the test antibody. Binding constants were determined at 25°C.

[0187] The antibody poly-his-FcRn binding interaction was evaluated using the two state reaction model where the $R_{\max}$ was set to local and RI (refractive index) parameter was set to local. All data was double reference subtracted: first, the signal in the reference

cell (blank immobilization) resulting from antibody binding to the dextran matrix was subtracted, and second, the signal of 0 nM antibody on the active surface was subtracted.

[0188] Binding constants were determined on at least two separate runs for each antibody. Prolia Lot 1035726 was tested alongside the anti-CD38/IFN samples as a positive control for each run. Average values for k_{a1} , k_{d1} , k_{a2} , k_{d2} and K_D were determined.

[0189] The average kinetic and affinity values for FcRn binding for the 4 anti-CD38/IFN (A10.21 IgG4 (S228P) IFN (A145D, T106A), A10.21 IgG4 (S228P) IFN (A145D, T106T) A10.43 IgG4 (S228P) IFN (A145D, T106A) A10.43 IgG4 (S228P) IFN (A145D, T106T)) were measured. In this sample set the clone A10.21 IgG4 (S228P) IFN (A145D, T106A) displayed the highest affinity for FcRn.

EXAMPLE 6

EFFICACY OF ANTI-CD38 ANTIBODIES FUSED TO ATTENUATED INTERFERON ALPHA 2B WITH AND WITHOUT O-LINKED GLYCOSYLATION IN THE MOUSE NCI-H929 MULTIPLE MYELOMA MODEL

Drugs and Treatment:

Table 12

Gr.	N	Regimen 1			
		Agent	µg/animal	Route	Schedule
1 [#]	8	vehicle	20	ip	biwk x 5
2	8	A10.21 IgG4 (S228P) IFN (A145D, T106T)	20	ip	biwk x 5
3	8	A10.21 IgG4 (S228P) IFN (A145D, T106A)	20	ip	biwk x 5
4	8	A10.43 IgG4 (S228P) IFN (A145D, T106T)	20	ip	biwk x 5
5	8	A10.43 IgG4 (S228P) IFN (A145D, T106A)	20	ip	biwk x 5

- Control Group

Procedures:

- Set up CR female CB.17 SCID mice with 1×10^7 H929 tumor cells in 50% Matrigel sc in flank.
- Cell Injection Volume is 0.2 mL/mouse.
- Age at Start Date: 8 to 12 weeks.
- Perform a pair match when tumors reach an average size of 170 - 350 mm³, and begin treatment.
- Dosing volume = 0.2 mL/mouse. Do not adjust for body weight.
- Body Weight: qd x 5 then biwk to end
- Caliper Measurement: biwk to end
- Endpoint TGD. Animals are to be monitored individually. The endpoint of the experiment is a tumor volume of 2000 mm³ or 60 days, whichever comes first. Responders can be followed longer. When the endpoint is reached, the animals are to be euthanized per SOP #687.

[0190] The results are shown in Figure 8. Roughly equivalent efficacy was seen with and without O-linked glycosylation, with the aglycosylated form slightly more potent in impeding tumour growth.

EXAMPLE 7

[0191] In the evaluation of human neonatal Fc receptor (FcRn) binding to anti-CD38 antibodies fused to attenuated IFN with and without O-linked glycosylation the proteins without O-linked glycosylation displayed the highest affinity for FcRn. The effect of this may be evaluated in cynomolgus monkeys and humanised FcRn mice.

*Cynomolgus Monkey Study**Monkey study design- to compare +/- O-glyc*

- Single 3mg/kg intravenous infusion (1 hour) through an indwelling catheter
 - A10.21 IgG4 (S228P) IFN (145D, T106A) (n=4)
 - A10.21 IgG4 (S228P) IFN (145D, T106T) (n=4)
 - A10.21 IgG4 (S228P) IFN (145D, T106A) (n=4)
 - A10.21 IgG4 (S228P) IFN (145D, T106T) (n=4)
- Compare PK and PD (biological effect i.e. serum neopterin levels)
- PK: all monkeys, ≤ 1 ml, 11 timepoints (Pre-dose, 0 minutes (immediately post end of infusion). 2, 6, 12, 24, 48, 96, 120, 168 and at 240 hours post infusion. Samples (80) are analysed by ELISA.
- TK modelling: WinNonlin Table Assembly {non-compartmental analysis}
- Clinical pathology: Hematology and blood chemistry- all monkeys, 3 occasions (pre-treatment, 24 hours post dose and Day 8)
- Serum neopterin- all monkeys, ~ 0.5 ml 3 occasions at 5 timepoints (Predose, 12, 24, 96, 168 hours post dose)

Pharmacokinetic study in humanised FcRN mice

1. Thirty two (32) B6.Cg-*Fcgr*^{tm1Dcr}Tg(CAG-FCGRT)276Dcr/DcrJ (JAX stock# 004919) female mice are dosed on day 1 by IP injection of 1mg/kg of;

- A10.21 IgG4 (S228P) IFN (145D, T106A) (n=8)
- A10.21 IgG4 (S228P) IFN (145D, T106T) (n=8)
- A10.43 IgG4 (S228P) IFN (145D, T106A) (n=8)

– A10.43 IgG4 (S228P) IFN (145D, T106T) (n=8)

2. Body weight is measured 3 days prior to dosing, the day of dosing and then weekly.
3. Cage side observations are made daily and clinical observations made weekly.
4. Pharmacokinetic blood collection: Mice are bled (25 µl) at pre-dose 3 days and postdose 1, 12, 24, 48 and 72 hours and 5, 7, 10, and 14 days. Mice are bled in 2 cohorts (4 mice/group/cohort).
5. All mice are sacrificed on day 14. Terminal cardiocentesis is performed to collect blood.
6. Blood is collected in lithium heparin tubes and centrifuged at 10,000 rpm for 2 min at 4°C.
7. Plasma samples are diluted 1:10 in PBS and are frozen prior to analysis by binding ELISA for A10.21 IgG4 IFN(145D) A106, A10.21 IgG4 IFN(145D) T106, A10.43 IgG4 IFN(145D) A106 or A10.43 IgG4 IFN(145D) T106.

CLAIMS:

1. A fusion polypeptide comprising a first and a second domain, wherein the first domain comprises a polypeptide ligand which binds to a cell surface-associated antigen and the second domain comprises aglycosylated interferon α 2b (IFN α 2b) having a sequence of SEQ ID NO: 1 or SEQ ID NO: 2 and wherein the aglycosylated IFN α 2b further comprises one or more amino acid substitutions or deletions which attenuate the activity of the aglycosylated IFN α 2b.
2. The fusion polypeptide as claimed in claim 1 in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 in which the residue at position 106 is selected from the group consisting of A, C, D, E, F, G, H, I, K, L, M, N, P, Q, R, S, V, W and Y.
3. The fusion polypeptide as claimed in claim 1 or 2 in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 in which the residue at position 106 is A.
4. The fusion polypeptide as claimed in any one of claim 1 to 3 in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 1 modified by the attenuating mutation(s) selected from the group consisting of L15A, R22A, R23A, S25A, L26A, F27A, L30A, L30V, K31A, D32A, R33A, R33K, R33Q, H34A, Q40A, D114R, L117A, R120A, R120E, R125A, R125E, K131A, E132A, K133A, K134A, M148A, R149A, S152A, L153A, N156A, (L30A, H57Y, E58N and Q61S), (M148A, H57Y, E58N and Q61S), (L153A, H57Y, E58N and Q61S), (R144A, H57Y, E58N and Q61S), (N65A, L80A, Y85A and Y89A,) (N65A, L80A, Y85A, Y89A and D114A), (N65A, L80A, Y85A, Y89A and L117A), (N65A, L80A, Y85A, Y89A and R120A), (Y85A, Y89A and D114A), (D114A and R120A), (L117A and R120A), (L117A, R120A and K121A), (R120A and K121A), (R120E and K121E), replacement of R at position 144 with A, D, E, G, H, I, K, L, N, Q, S, T, V or Y, replacement of A at position 145 with D, E, G, H, I, K, L, M, N, Q, S, T, V or Y, and deletion of residues L161 to E165.
5. The fusion polypeptide as claimed in any one of claims 1 to 3 in which the sequence of the aglycosylated IFN α 2b is SEQ ID NO: 2 modified by the

attenuating mutation(s) selected from the group consisting of L15A, R22A, R23A, S25A, L26A, F27A, L30A, L30V, K31A, D32A, R33A, R33K, R33Q, H34A, Q40A, D113R, L116A, R119A, R119E, R124A, R124E, K130A, E131A, K132A, K133A, M147A, R148A, S149A, L152A, N155A, (L30A, H57Y, E58N and Q61S), (M147A, H57Y, E58N and Q61S), (L152A, H57Y, E58N and Q61S), (R143A, H57Y, E58N and Q61S), (N65A, L80A, Y85A and Y89A,) (N65A, L80A, Y85A, Y89A and D113A), (N65A, L80A, Y85A, Y89A and L116A), (N65A, L80A, Y85A, Y89A and R1190A), (Y85A, Y89A and D113A), (D113A and R119A), (L116A and R119A), (L116A, R119A and K120A), (R119A and K120A), (R119E and K120E), replacement of R at position 143 with A, D, E, G, H, I, K, L, N, Q, S, T, V or Y, replacement of A at position 144 with D, E, G, H, I, K, L, M, N, Q, S, T, V or Y, and deletion of residues L160 to E164.

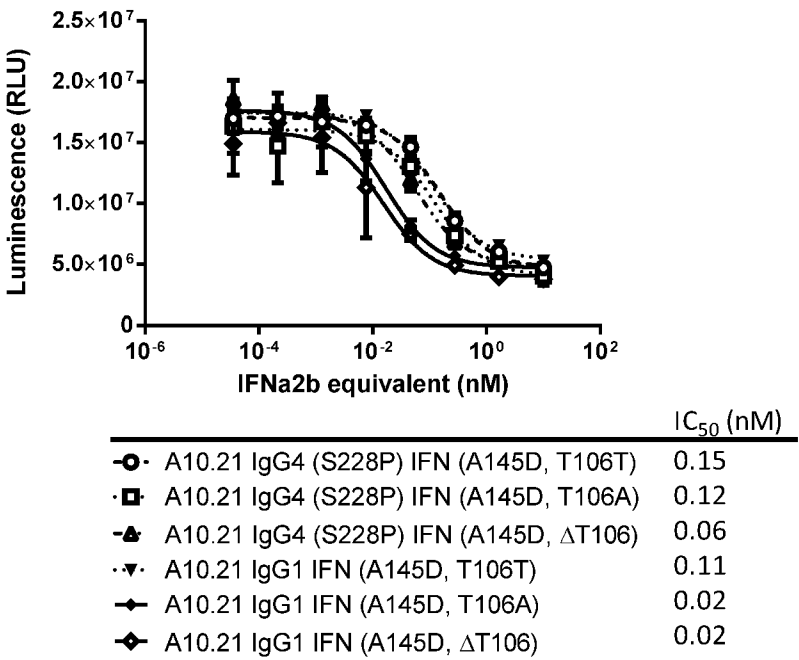
6. The fusion polypeptide as claimed in any one of claims 1 to 5 in which the sequence of the aglycosylated IFN α 2b is selected from the group consisting of SEQ ID NOs: 3 to 30 and SEQ ID NOs: 32 to 47.
7. The fusion polypeptide as claimed in any one of claims 1 to 6 in which the cell surface-associated antigen is selected from the group consisting of CD38, CD138, RANK-Ligand, HM1.24, CD56, CS1, CD20, CD74, IL-6R, Blys (BAFF), BCMA, HLA-SR, HLA-DR, Kininogen, beta2 microglobulin, FGFR3, ICAM-1, matriptase, CD52, EGFR, GM2, alpha4-integrin, IFG-1R, KIR, CD3, CD4, CD8, CD24, CD44, CD69, CD71, CD79, CD83, CD86, CD96, HLA, PD-1, ICOS, CD33, CD115, CD11c, CD19, CD52, CD14, FSP1, FAP, PDGFR alpha, PDGFR beta, ASGR1, ASGR2, FSP1, RTI140/Ti-alpha, HTI56, VEGF receptor, CD241 the product of the RCHE gene, CD117 (c-kit), CD71 (transferrin receptor), CD36 (thrombospondin receptor), CD34, CD45RO, CD45RA, CD115, CD168, CD235, CD236, CD237, CD238, CD239 and CD240.
8. The fusion polypeptide as claimed in any one of claims 1 to 7 in which the polypeptide ligand is an antibody or antigen binding portion thereof.

9. The fusion polypeptide as claimed in any one of claims 1 to 8 in which the polypeptide ligand is an antibody which binds CD38.
10. The fusion polypeptide as claimed in claim 9 in which the V_H sequence of the antibody is selected from the group consisting of SEQ ID Nos: 48 to 56 and 58.
11. The fusion polypeptide as claimed in claim 9 or claim 10 in which the V_L sequence of the antibody is selected from the group consisting of SEQ ID Nos: 81, 82 and 84.
12. The fusion polypeptide as claimed in any one of claims 1 to 11 in which the first domain is linked to the second domain via a peptide bond.
13. The fusion polypeptide as claimed in any one of claims 1 to 11 in which the first domain is linked to the second domain directly via a peptide bond.
14. The fusion polypeptide as claimed in any one of claims 1 to 11 in which the C-terminus of the first domain is linked to N-terminus of the second domain.
15. A fusion polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs: 31, 61 to 77, 83 and 87, and a sequence selected from the group consisting of SEQ ID NOs: 81, 82 and 84.
16. A fusion polypeptide comprising SEQ ID NO: 87 and SEQ ID NO: 81.
17. A composition comprising the fusion polypeptide as claimed in any one of claims 1 to 16 and a pharmaceutically acceptable carrier or diluent.
18. A method of treating a tumour in a subject comprising administering to the subject the fusion polypeptide as claimed in any one of claims 1 to 16 or the composition as claimed in claim 17 wherein the first domain of the fusion polypeptide binds to cells of the tumour.
19. A method of treating a tumour in a subject as claimed in claim 18 in which the tumour is selected from multiple myeloma or non-Hodgkin's lymphoma

20. The use of the fusion polypeptide as claimed in any one of claims 1 to 16 in the treatment of a tumour wherein the first domain of the fusion polypeptide binds to cells of the tumour.
21. The use of the fusion polypeptide as claimed in 20 in the treatment of cancer in which the cancer is multiple myeloma or non-Hodgkin's lymphoma.
22. An isolated polynucleotide(s) encoding the fusion polypeptide(s) as claimed in any one of claims 1 to 16.
23. A vector comprising one or more of the polynucleotide(s) of claim 22.
24. A transformed cell comprising the vector of claim 23.
25. A method of generating a polypeptide ligand-attenuated IFN α 2b fusion polypeptide in mammalian cells, wherein the polypeptide ligand-attenuated IFN α 2b fusion polypeptide has reduced heterogeneity and/or enhanced FcRn binding and/or enhanced target selectivity, the method comprising culturing a recombinant mammalian cell comprising one or more polynucleotides encoding the polypeptide ligand-attenuated IFN α 2b fusion polypeptide wherein T106 of the IFN α 2b sequence is replaced with another amino acid or is deleted such that on expression the IFN α 2b component of the fusion protein is aglycosylated.

Figure 1

A.



B.

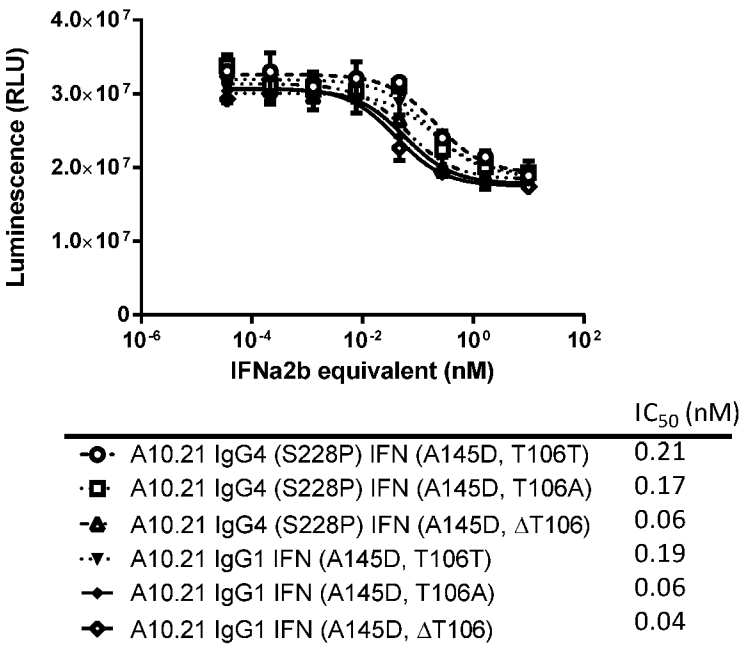
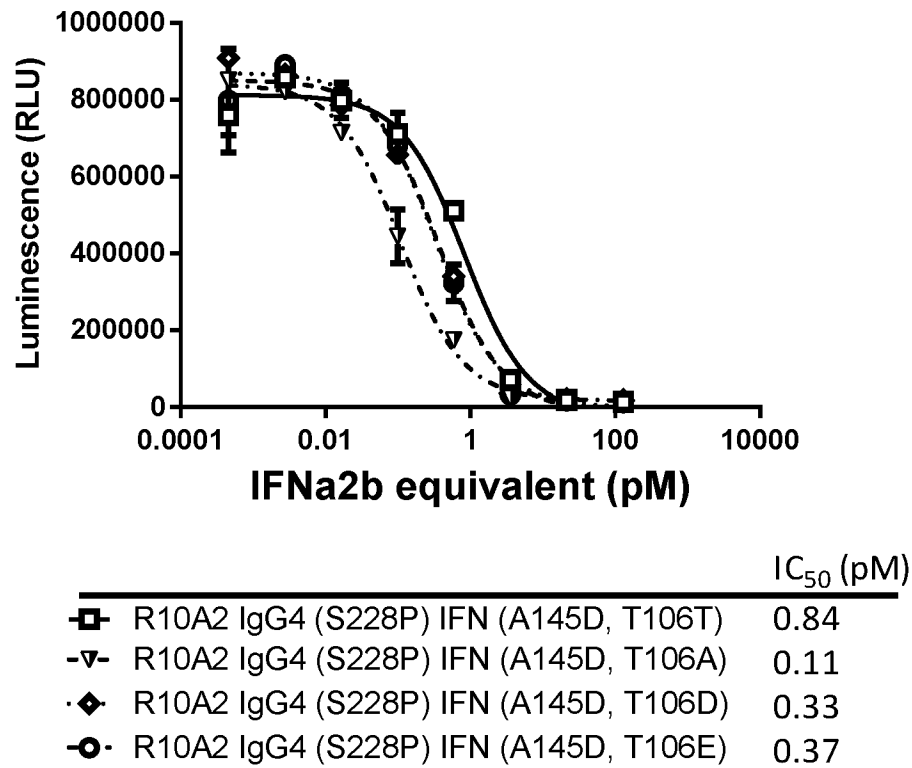


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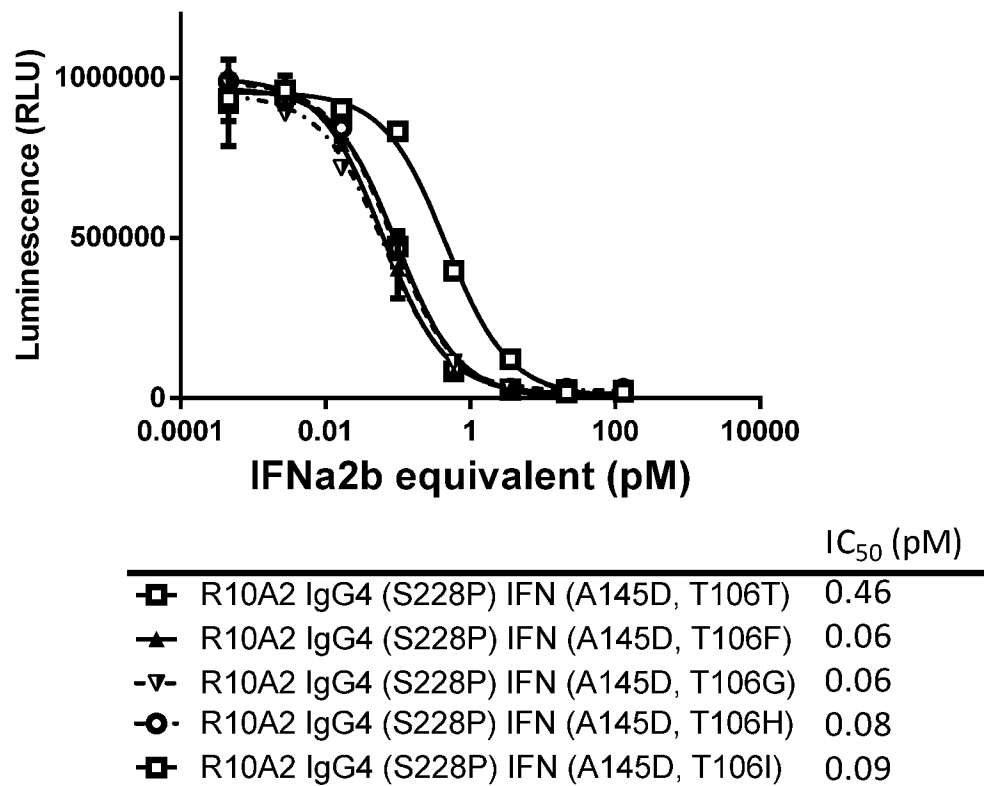
- 2/29 -

Figure 2A



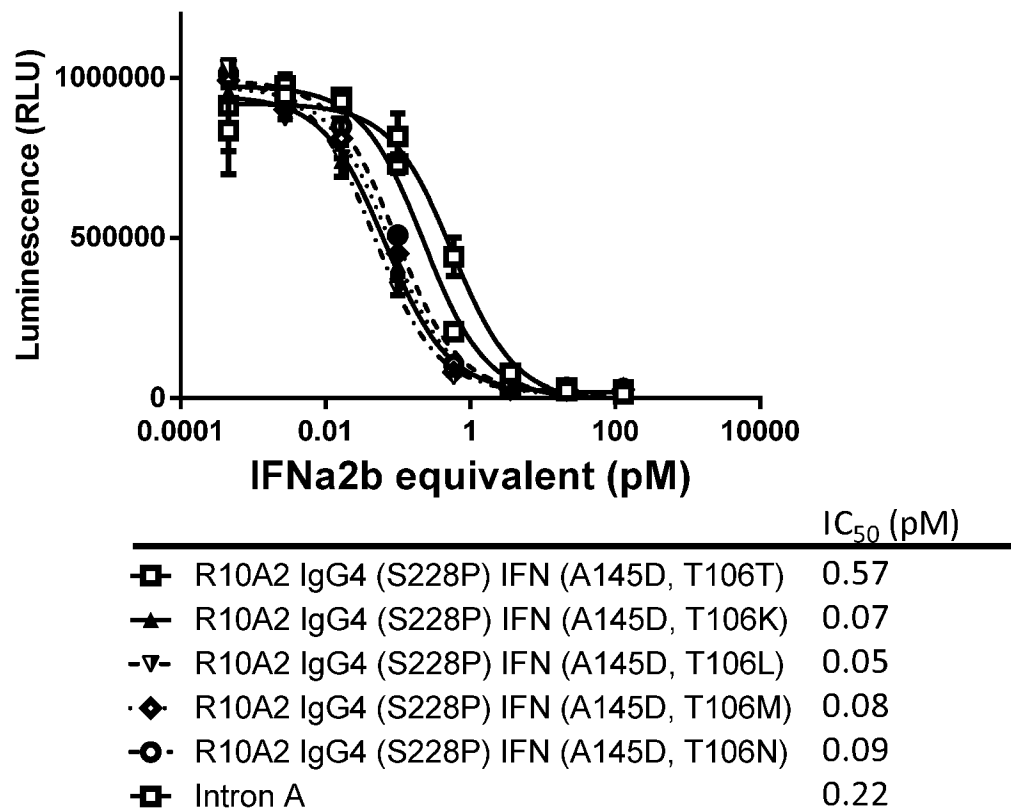
- 3/29 -

Figure 2B.



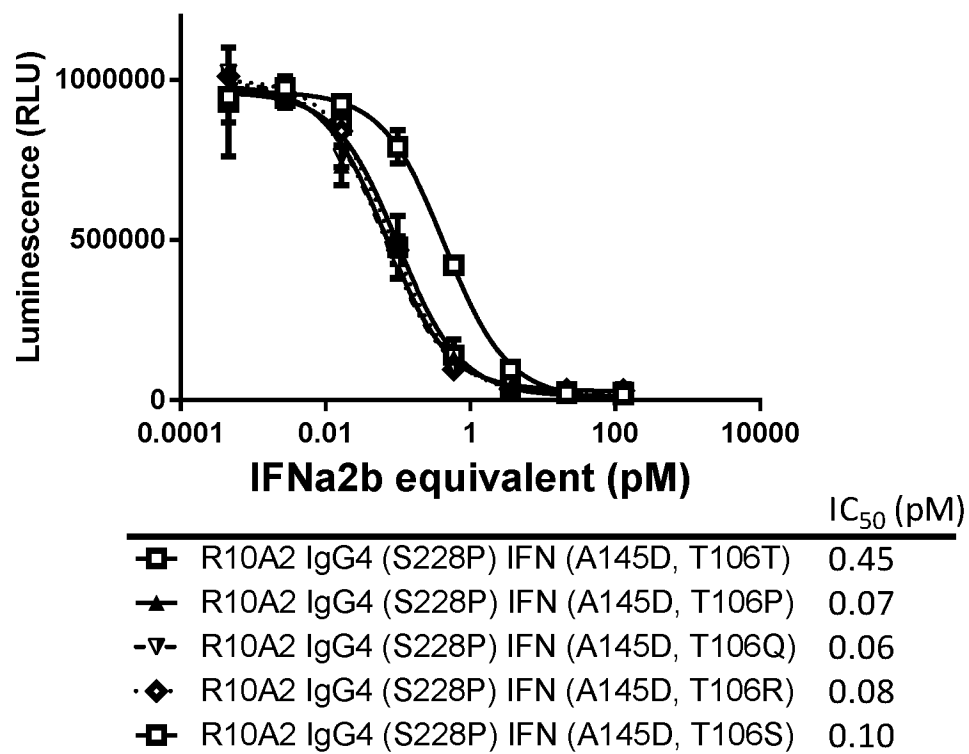
- 4/29 -

Figure 2C.



- 5/29 -

Figure 2D.



- 6/29 -

Figure 2E.

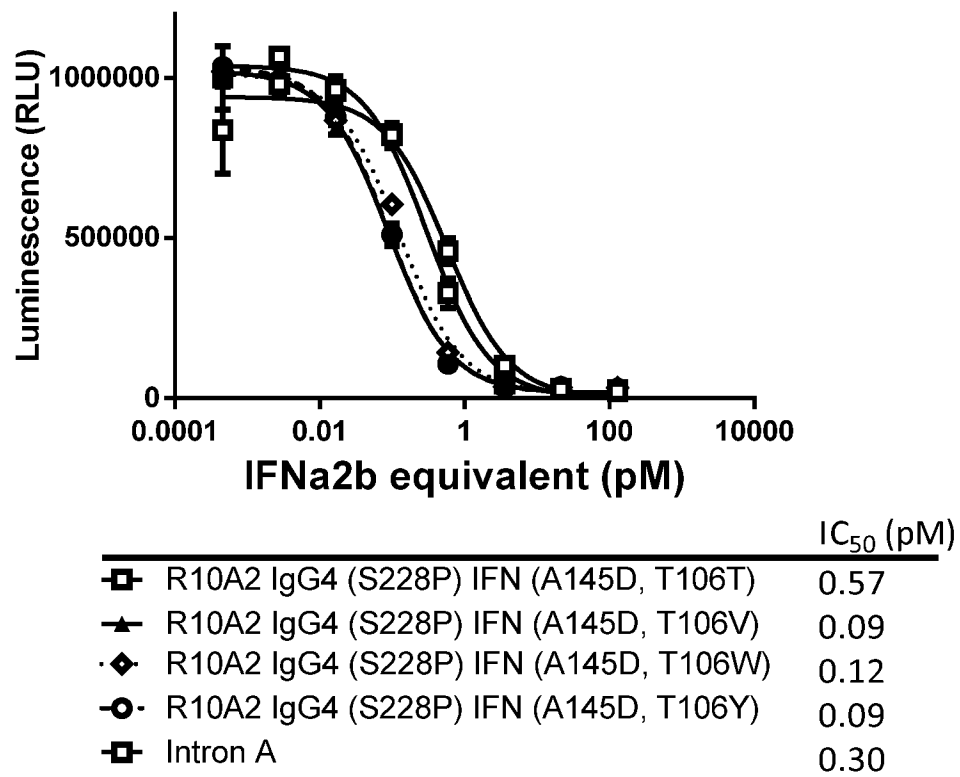
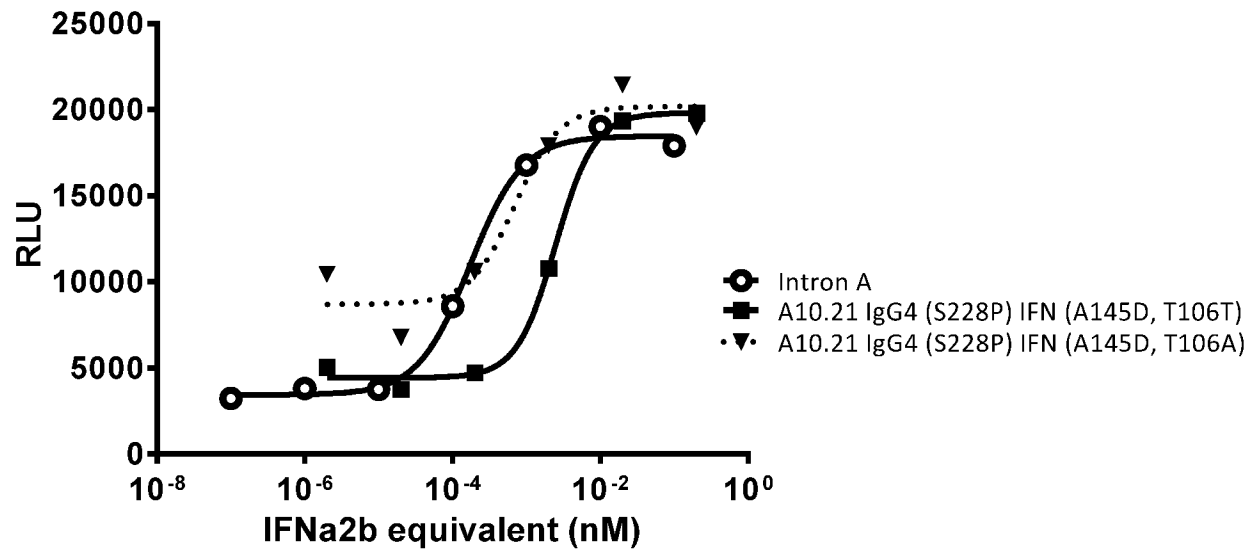
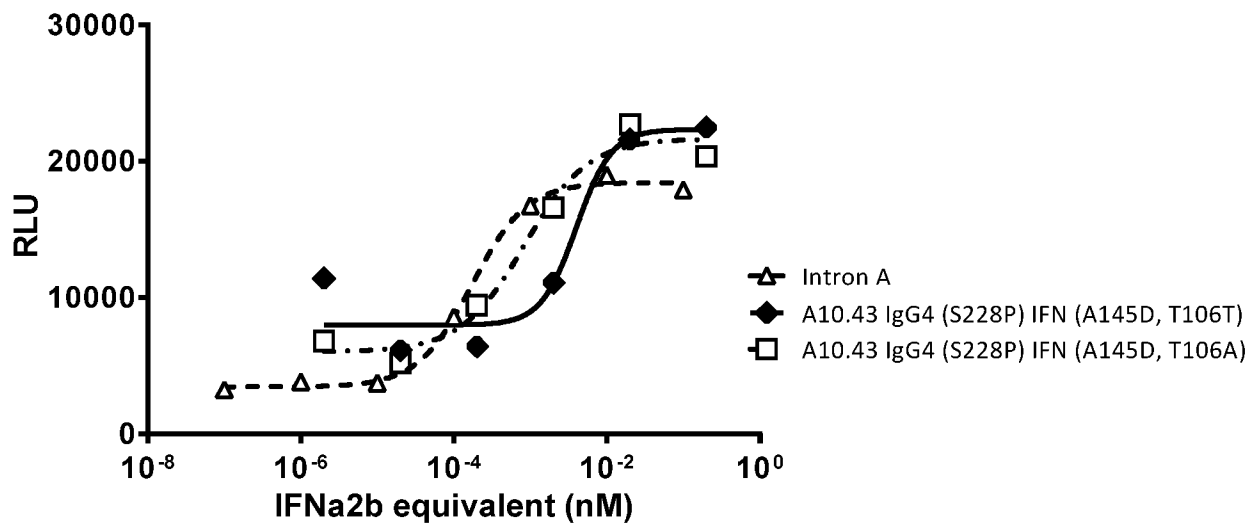


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A.



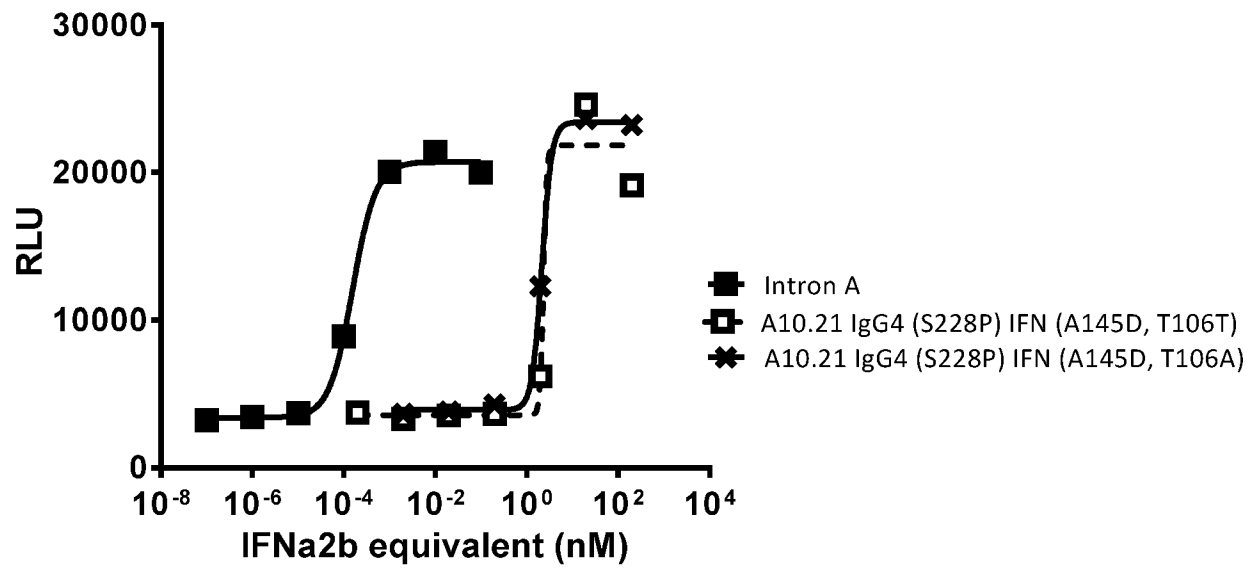
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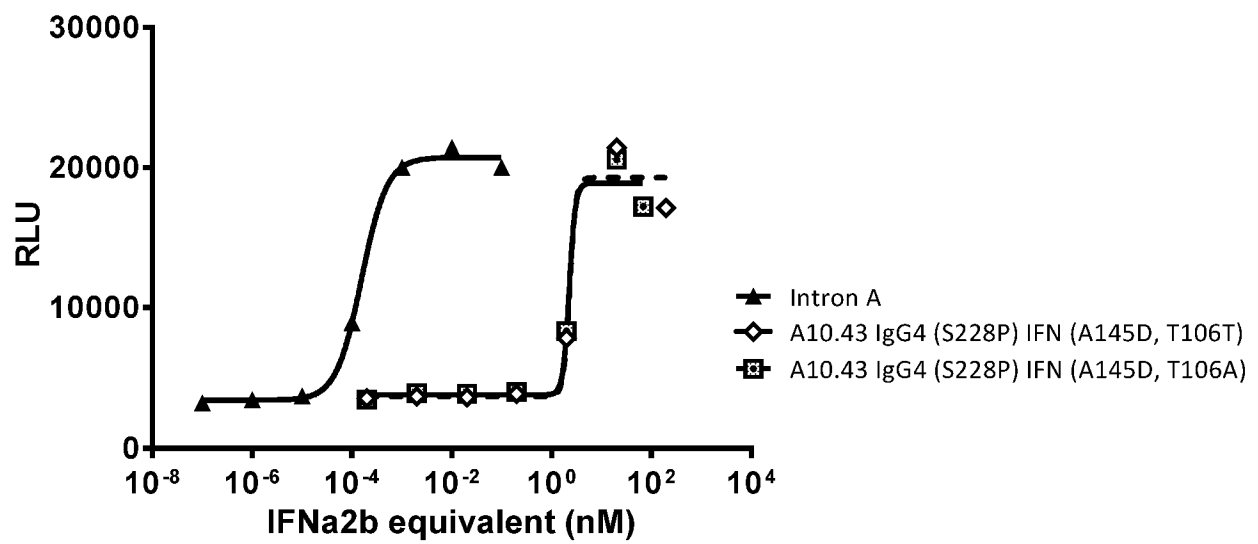
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Figure 4

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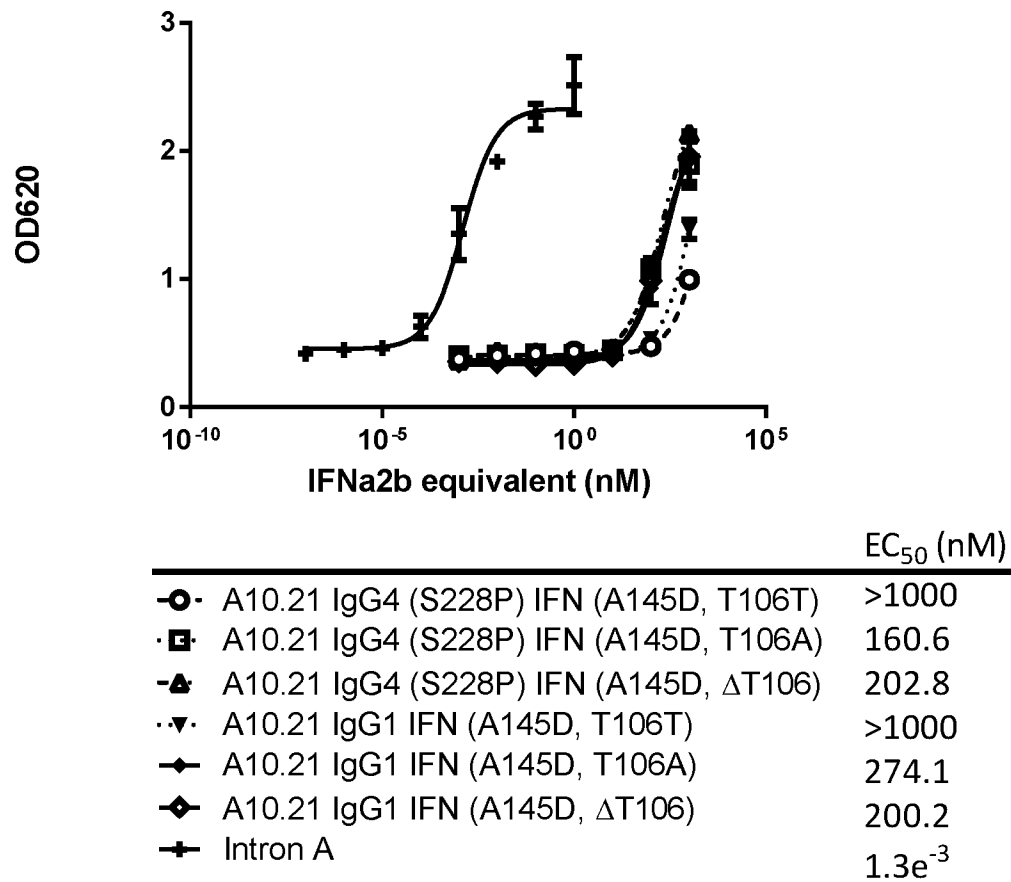


B.



- 9/29 -

Figure 5



- 10/29 -

Figure 6.

Figure 6A

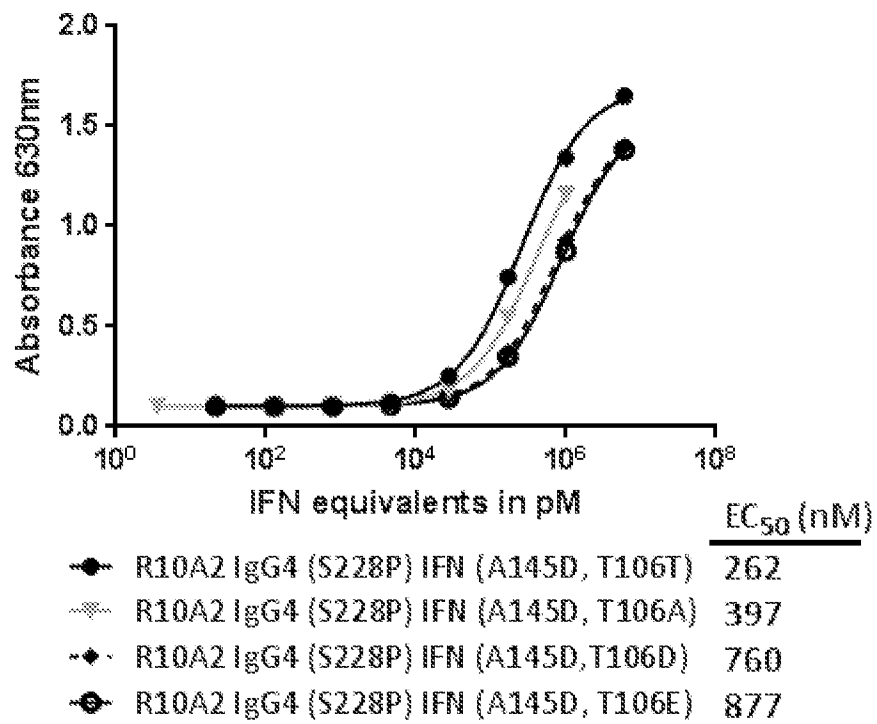
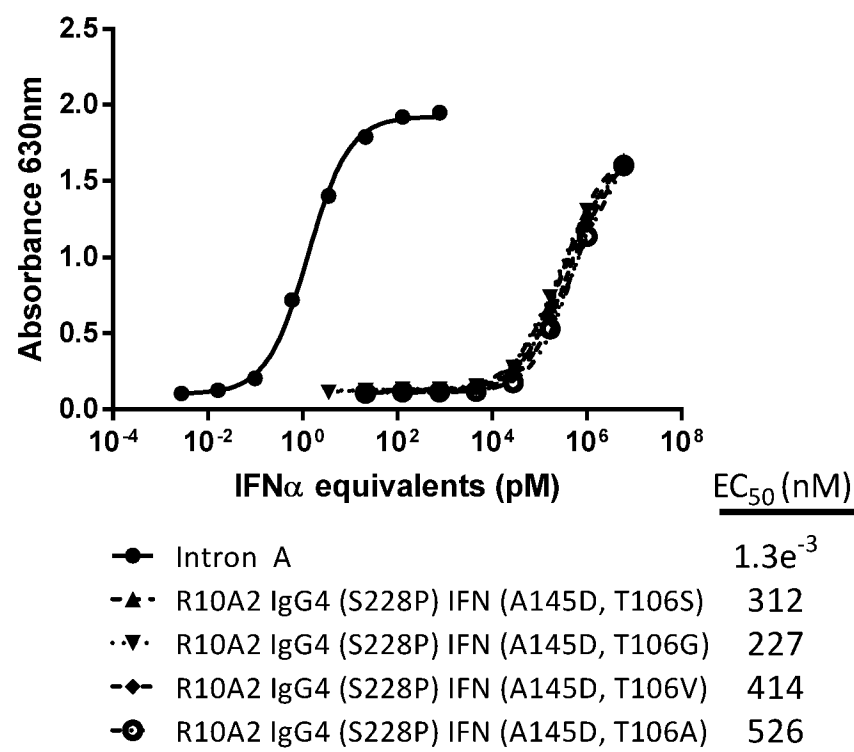
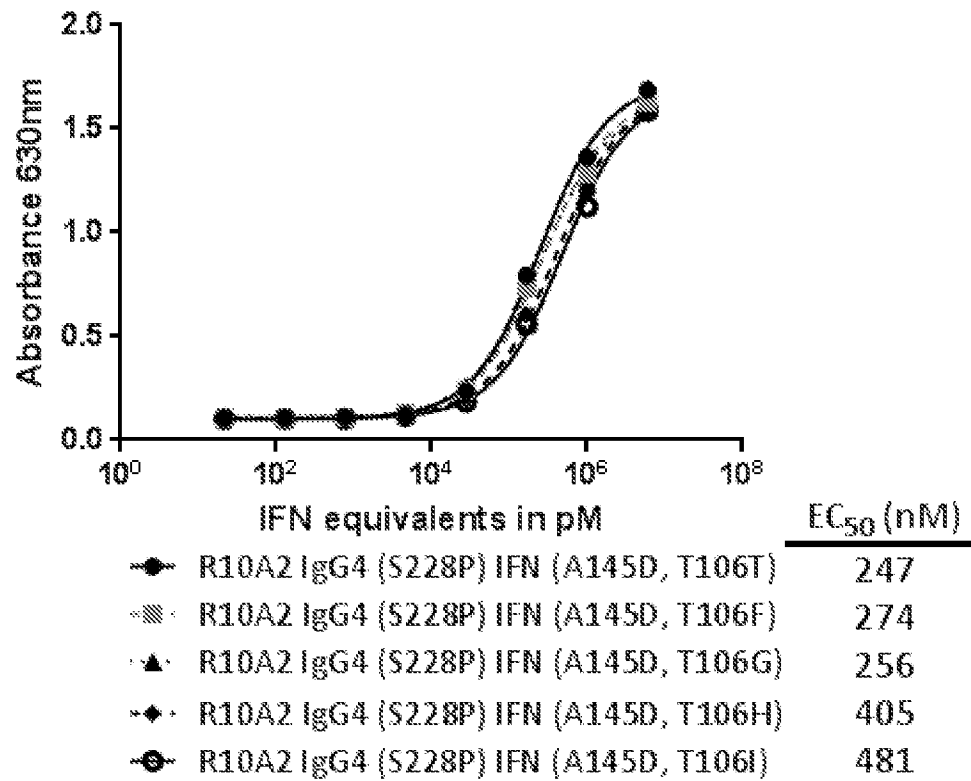


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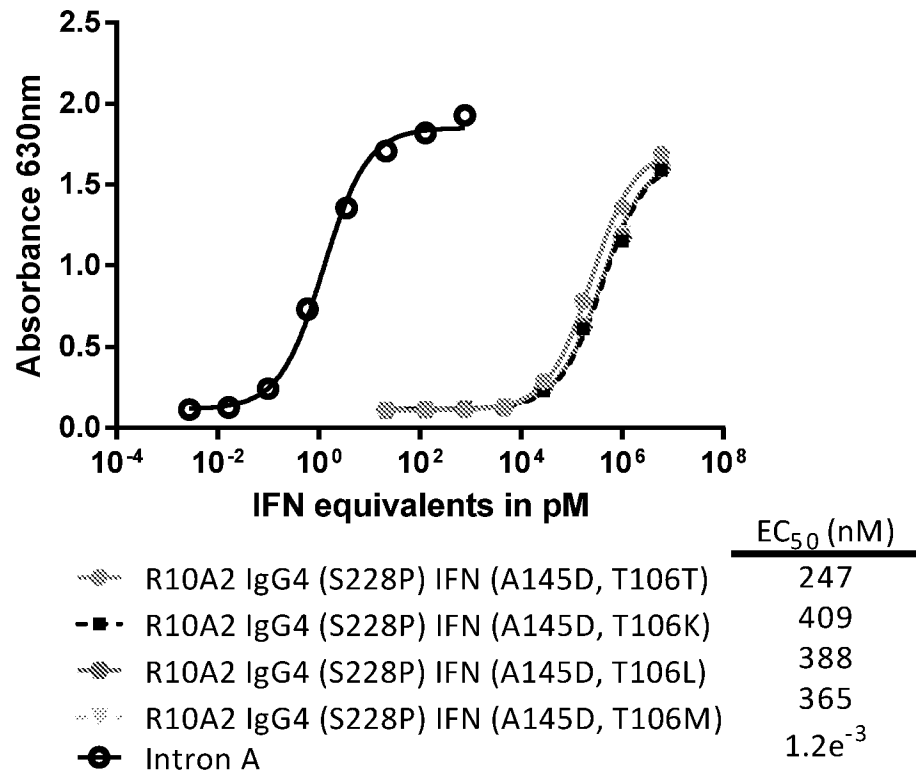
- 12/29 -

Figure 6C



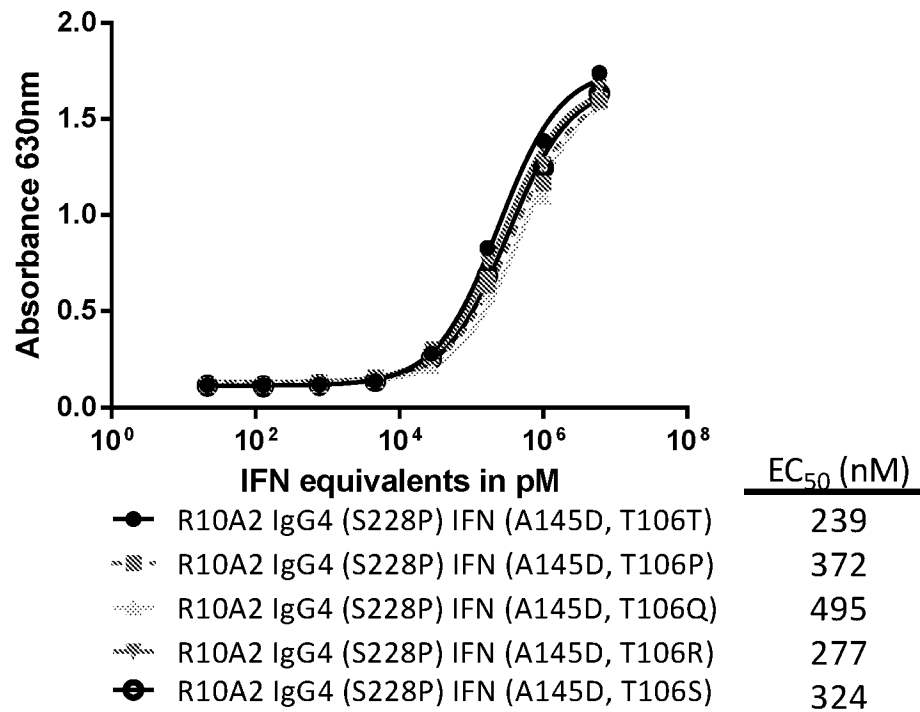
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Figure 6D



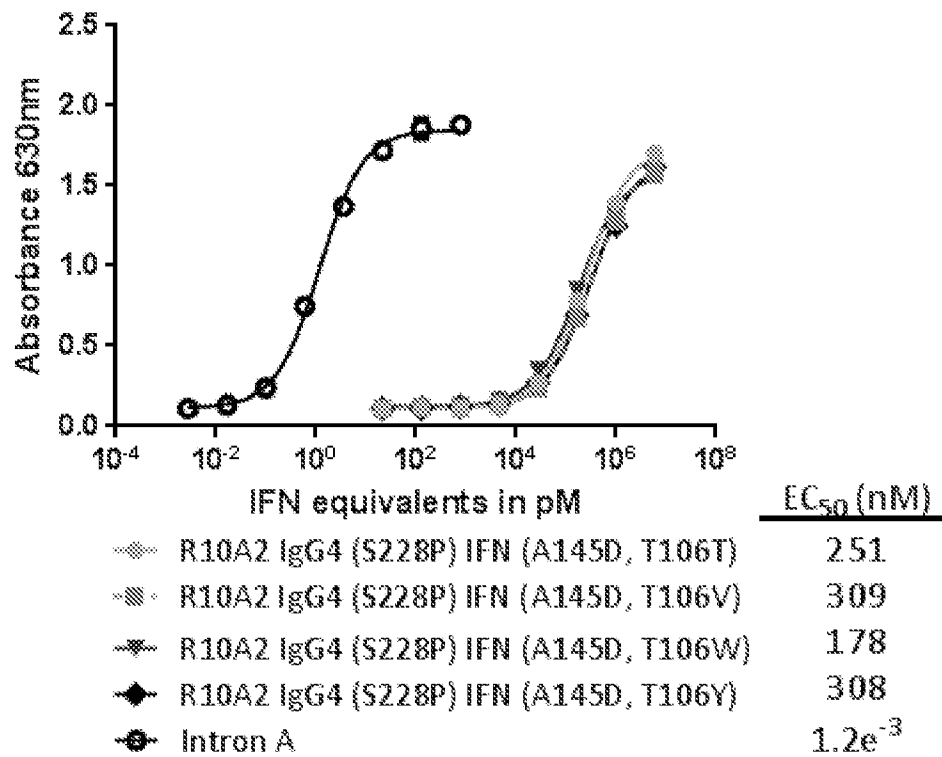
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Figure 6E



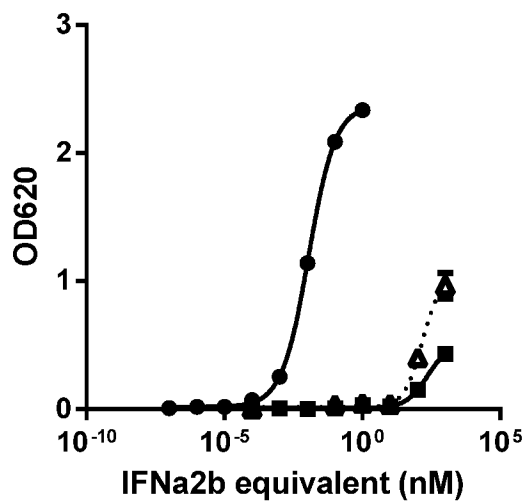
- 15/29 -

Figure 6F



- 16/29 -

Figure 7.



	EC ₅₀ (nM)
● Intron A	0.01
■ A10.43 IgG4 (S228P) IFN (A145D, T106T)	230.7
△ A10.43 IgG4 (S228P) IFN (A145D, T106A)	145.2

- 17/29 -

Figure 8.

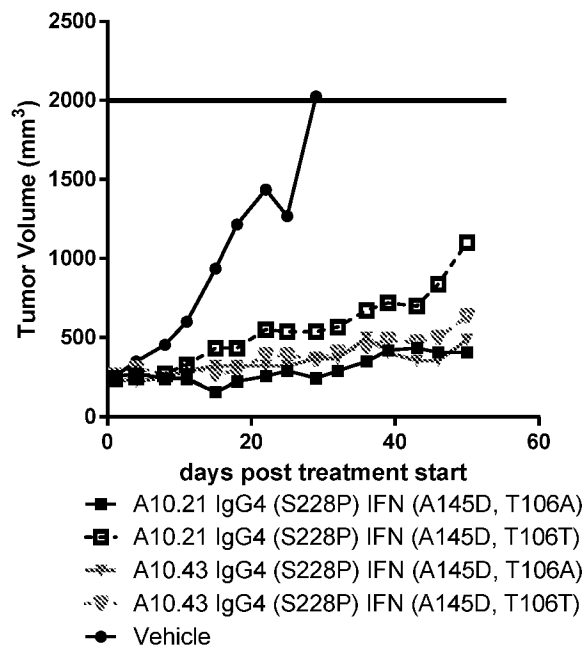
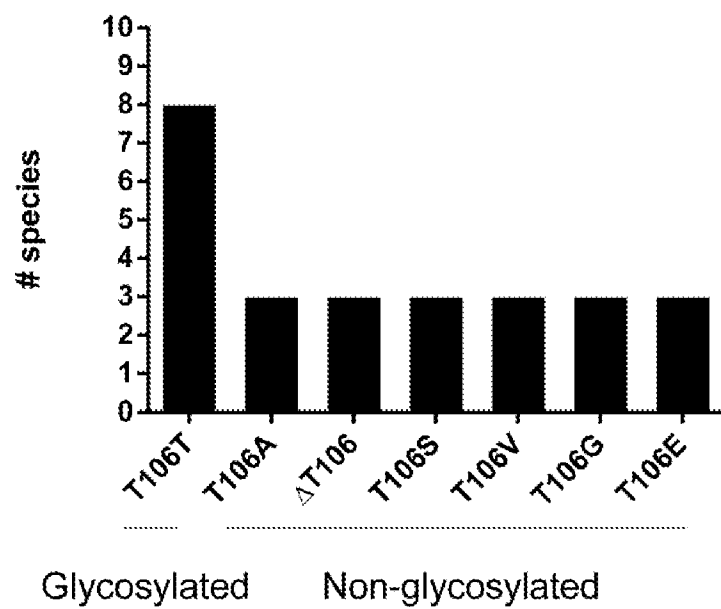
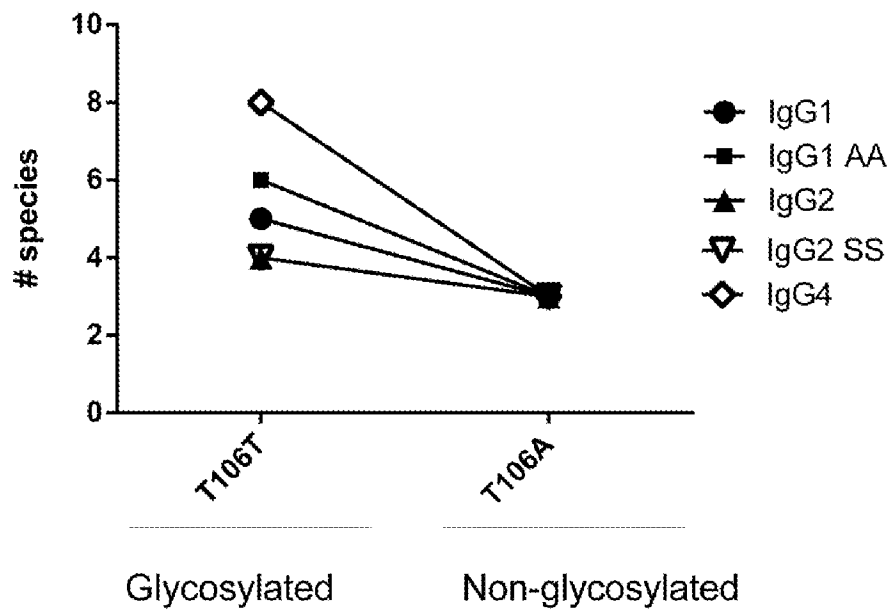


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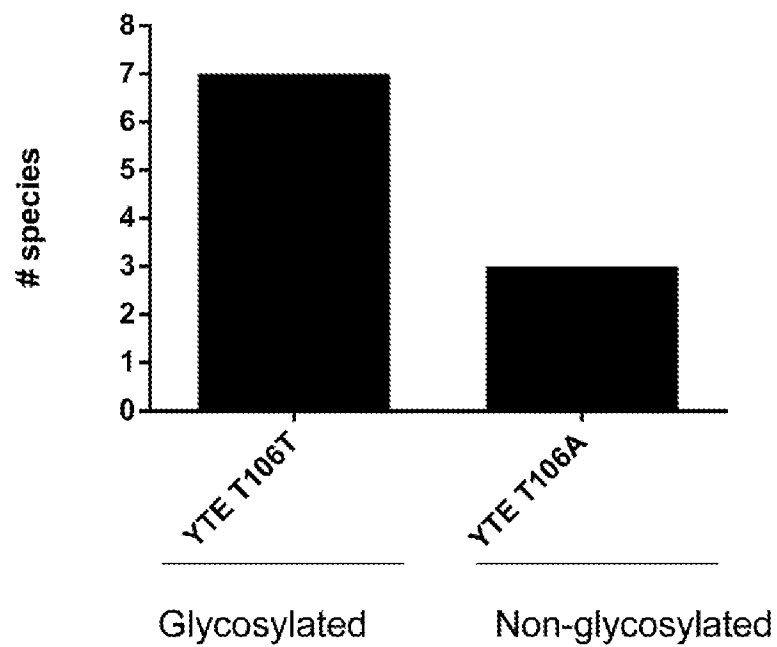
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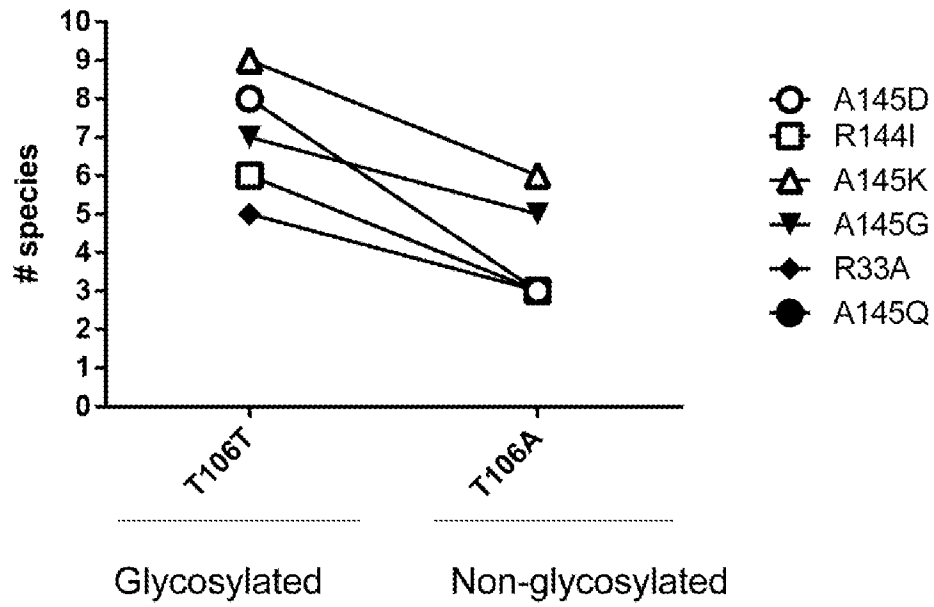
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Figure 11.



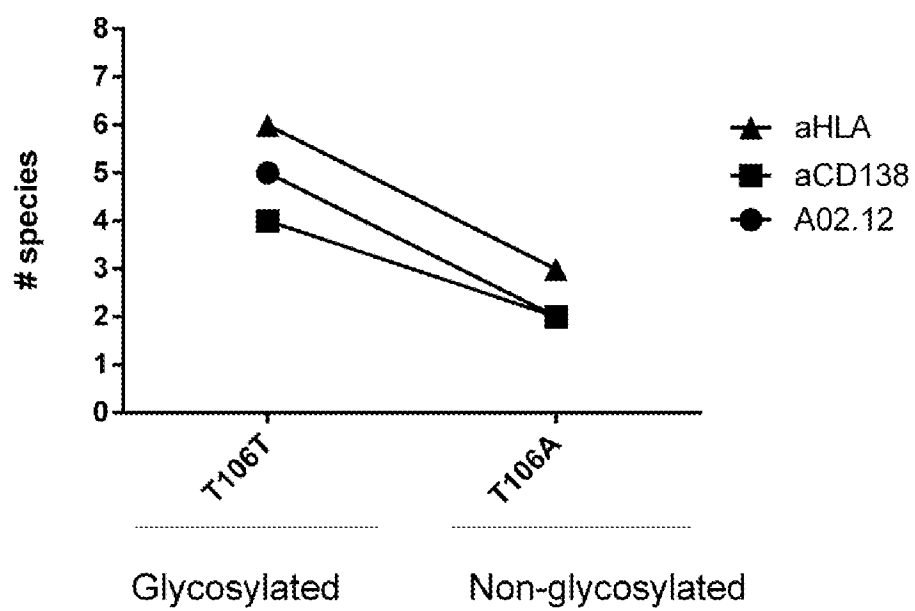
- 21/29 -

Figure 12.



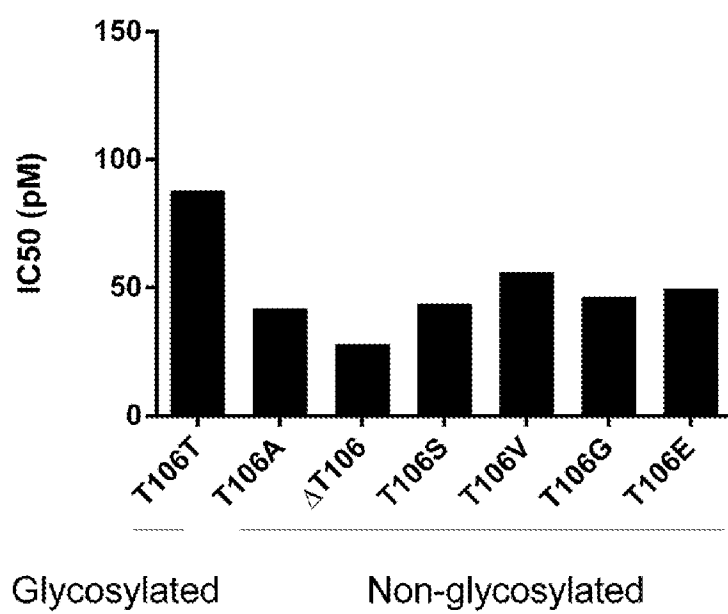
- 22/29 -

Figure 13.



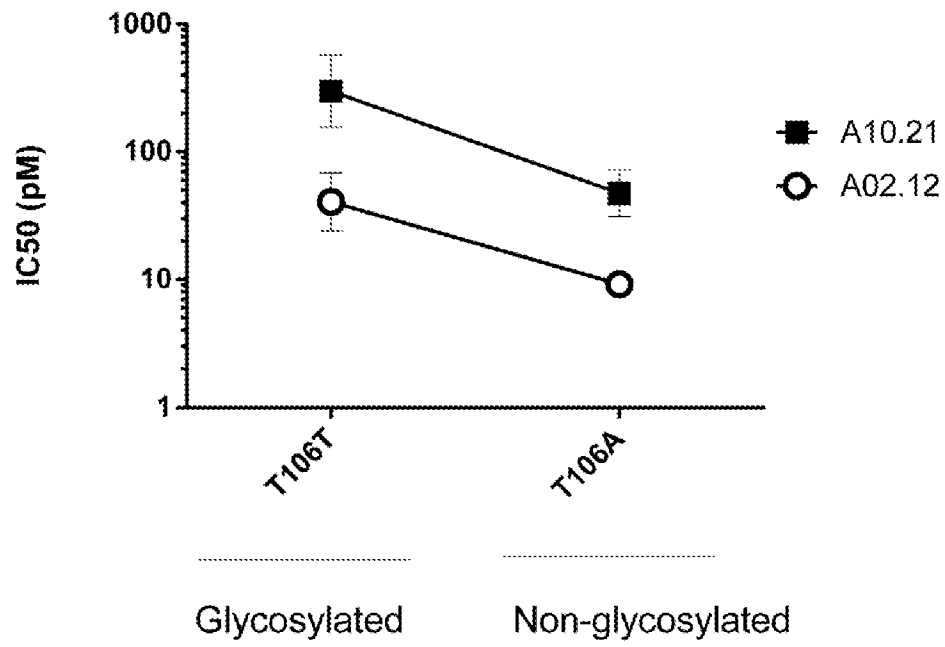
- 23/29 -

Figure 14.



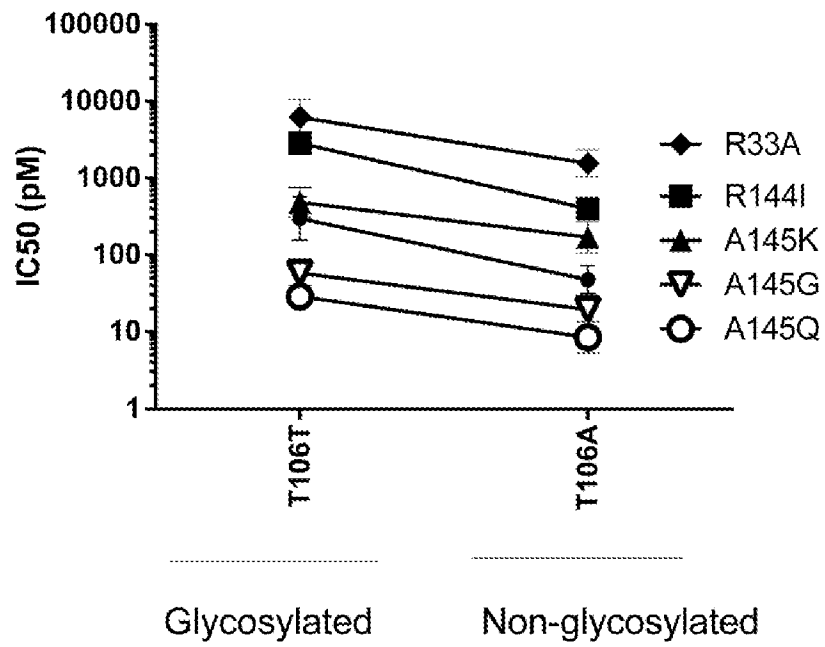
- 24/29 -

Figure 15.



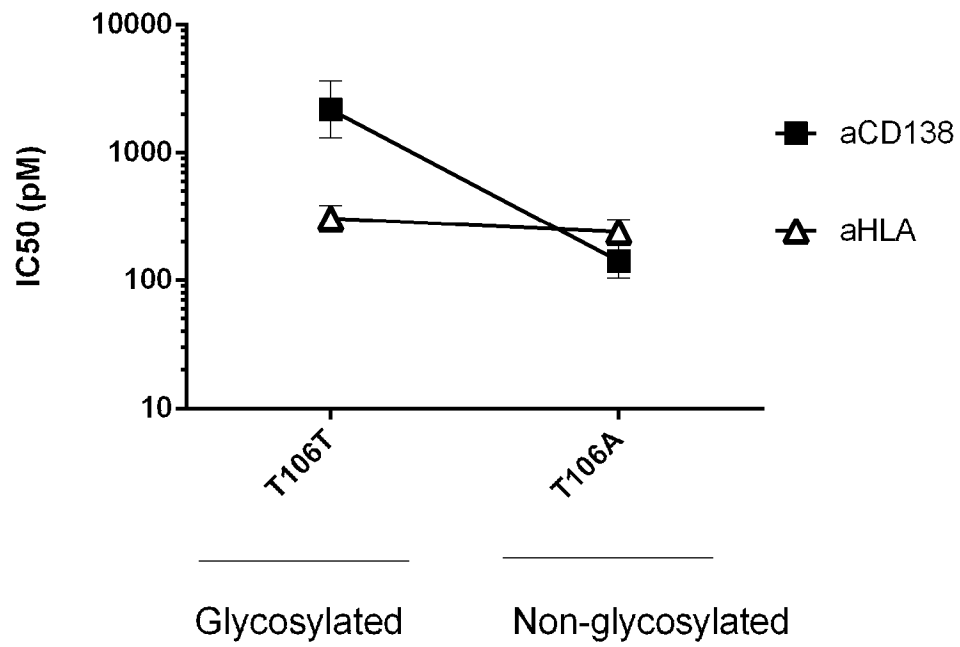
- 25/29 -

Figure 16.



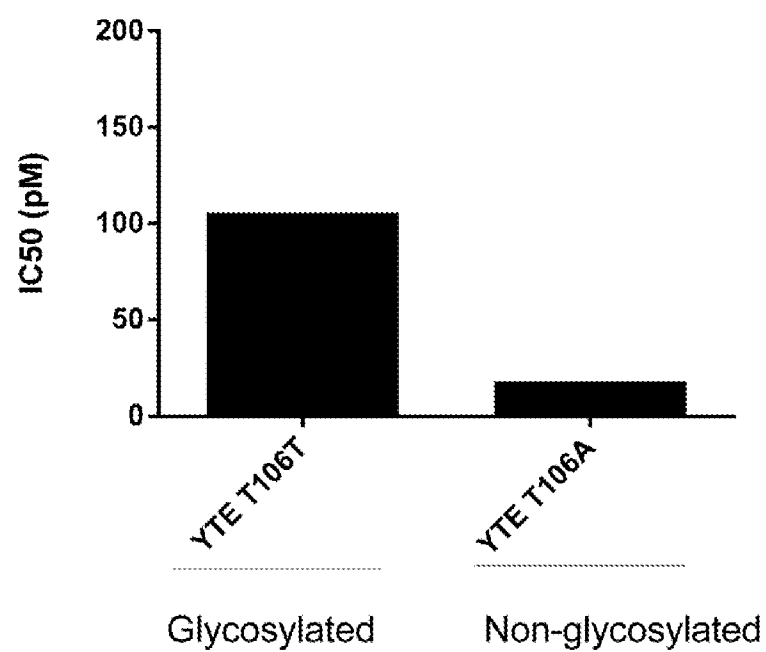
- 26/29 -

Figure 17.



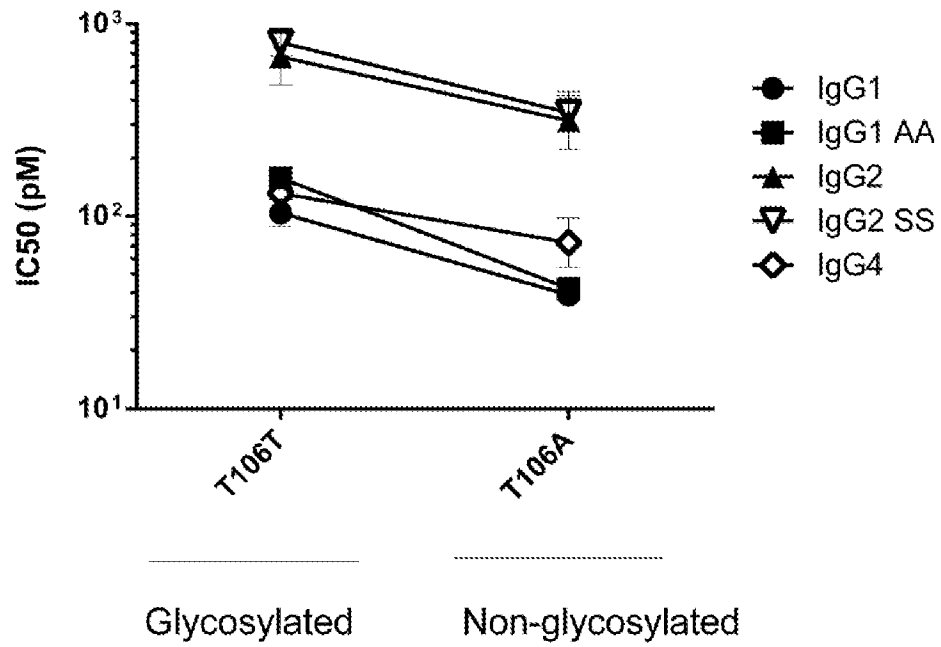
- 27/29 -

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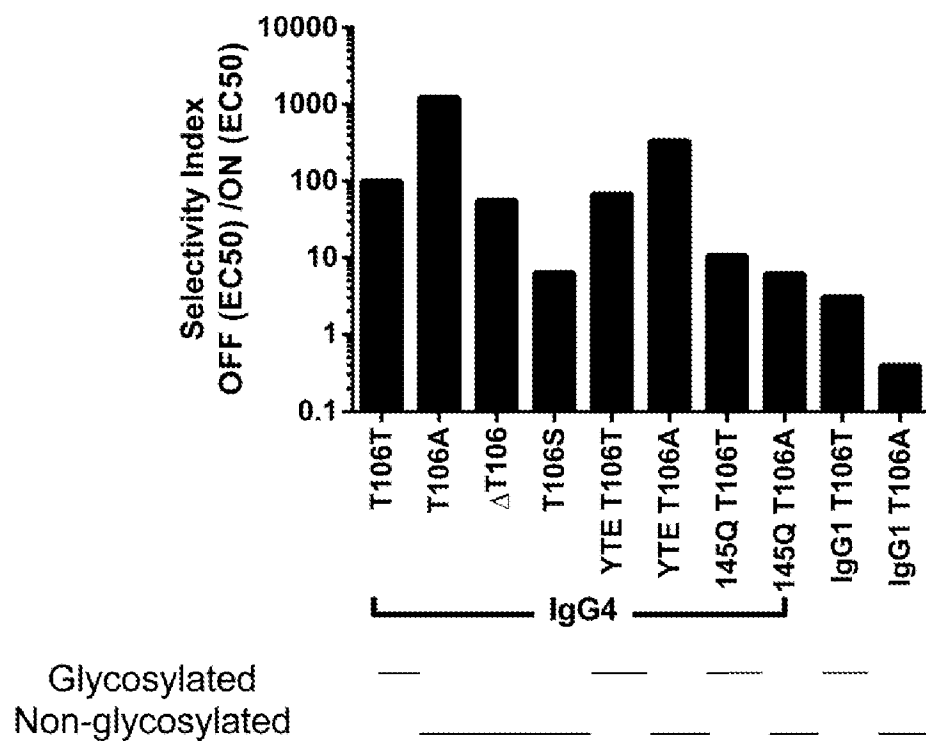
- 28/29 -

Figure 19.



- 29/29 -

Figure 20.



AU15 50654
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<220>
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 1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
 20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
 35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
 50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
 65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
 85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Xaa Glu Thr Pro Leu Met Lys
 100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
 115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
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Leu Arg Ser Lys Glu
165

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<213> Artificial

<220>
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Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Glu Thr Pro Leu Met Lys Glu
100 105 110

Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr
115 120 125

Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg Ala
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Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu
145 150 155 160

Arg Ser Lys Glu

<210> 3
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<212> PRT
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<220>
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Page 2

attenuating mutation L15A

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Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
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Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
 35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
 50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
 65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
 85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys
 100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
 115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
 130 135 140

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 145 150 155 160

Leu Arg Ser Lys Glu
 165

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Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln

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35

40

45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys
100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
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Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160

Leu Arg Ser Lys Glu
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<212> PRT

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attenuating mutation R22A

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35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

AU15 50654

Ala Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys
100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
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Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
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Leu Arg Ser Lys Glu
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Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys
100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

AU15 50654

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
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Leu Arg Ser Lys Glu
165

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<223> Aglycosylated (T106A) human interferon alpha-2-b comprising
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Leu Leu Ala Gln Met Arg Arg Ile Ala Leu Phe Ser Cys Leu Lys Asp
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35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys
100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160

Leu Arg Ser Lys Glu
165

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<223> Aglycosylated (T106A) human interferon alpha-2-b comprising attenuating mutation L26A

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 35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
 50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
 65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
 85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys
 100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
 115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
 130 135 140

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Leu Arg Ser Lys Glu
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 20 25 30

AU15 50654

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys
100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
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Leu Arg Ser Lys Glu
165

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attenuating mutation L30X, where X can be any amino acid selected
from A, V

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<223> Xaa can be any amino acid selected from A, V

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20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

AU15 50654

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys
100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
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Leu Arg Ser Lys Glu
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Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Ala Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys

100

105

110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
 115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
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Leu Arg Ser Lys Glu
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 35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
 50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
 65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
 85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys
 100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
 115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
 130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
 145 150 155 160

Leu Arg Ser Lys Glu
165

<210> 13
<211> 165
<212> PRT
<213> Artificial

<220>
<223> Aglycosylated (T106A) human interferon alpha-2-b comprising
attenuating mutation R33X, where X can be any amino acid selected
from K, A, Q

<220>
<221> VARIANT
<222> (33)..(33)
<223> Xaa can be any amino acid selected from K, A, Q

<400> 13

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Xaa His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys
100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160

Leu Arg Ser Lys Glu
165

<210> 14
 <211> 165
 <212> PRT
 <213> Artificial

<220>
 <223> Aglycosylated (T106A) human interferon alpha-2-b comprising
 attenuating mutation H34A

<400> 14

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
 1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
 20 25 30

Arg Ala Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
 35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
 50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
 65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
 85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys
 100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
 115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
 130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
 145 150 155 160

Leu Arg Ser Lys Glu
 165

<210> 15
 <211> 165
 <212> PRT
 <213> Artificial

<220>
 <223> Aglycosylated (T106A) human interferon alpha-2-b comprising
 attenuating mutation Q40A

<400> 15

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
 1 5 10 15

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Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Ala Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys
100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160

Leu Arg Ser Lys Glu
165

<210> 16

<211> 165

<212> PRT

<213> Artificial

<220>

<223> Aglycosylated (T106A) human interferon alpha-2-b comprising attenuating mutation D114R

<400> 16

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

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Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys
100 105 110

Glu Arg Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160

Leu Arg Ser Lys Glu
165

<210> 17
<211> 165
<212> PRT
<213> Artificial

<220>
<223> Aglycosylated (T106A) human interferon alpha-2-b comprising
attenuating mutation L117A

<400> 17

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys
100 105 110

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Glu Asp Ser Ile Ala Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160

Leu Arg Ser Lys Glu
165

<210> 18
<211> 165
<212> PRT
<213> Artificial

<220>
<223> Aglycosylated (T106A) human interferon alpha-2-b comprising
attenuating mutation R120X where X can be any amino acid selected
from A, E

<220>
<221> VARIANT
<222> (120)..(120)
<223> Xaa can be any amino acid selected from A, E

<400> 18

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys
100 105 110

Glu Asp Ser Ile Leu Ala Val Xaa Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
 145 150 155 160

Leu Arg Ser Lys Glu
 165

<210> 19
 <211> 165
 <212> PRT
 <213> Artificial

<220>
 <223> Aglycosylated (T106A) human interferon alpha-2-b comprising
 attenuating mutation R125X where X can be any amino acid selected
 from A, E

<220>
 <221> VARIANT
 <222> (125)..(125)
 <223> Xaa can be any amino acid selected from A, E

<400> 19

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
 1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
 20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
 35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
 50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
 65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
 85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys
 100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Xaa Ile Thr Leu
 115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
 130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
 145 150 155 160

Leu Arg Ser Lys Glu
165

<210> 20
<211> 165
<212> PRT
<213> Artificial

<220>
<223> Aglycosylated (T106A) human interferon alpha-2-b comprising
attenuating mutation K131A

<400> 20

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys
100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Ala Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160

Leu Arg Ser Lys Glu
165

<210> 21
<211> 165
<212> PRT
<213> Artificial

<220>
<223> Aglycosylated (T106A) human interferon alpha-2-b comprising
attenuating mutation E132A

<400> 21

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
 1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
 20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
 35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
 50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
 65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
 85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys
 100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
 115 120 125

Tyr Leu Lys Ala Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
 130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
 145 150 155 160

Leu Arg Ser Lys Glu
 165

<210> 22

<211> 165

<212> PRT

<213> Artificial

<220>

<223> Aglycosylated (T106A) human interferon alpha-2-b comprising
 attenuating mutation K133A

<400> 22

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
 1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
 20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
 35 40 45

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Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys
100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Lys Glu Ala Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160

Leu Arg Ser Lys Glu
165

<210> 23

<211> 165

<212> PRT

<213> Artificial

<220>

<223> Aglycosylated (T106A) human interferon alpha-2-b comprising
attenuating mutation K134A

<400> 23

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

AU15 50654

Ala Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys
100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Lys Glu Lys Ala Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160

Leu Arg Ser Lys Glu
165

<210> 24

<211> 165

<212> PRT

<213> Artificial

<220>

<223> Aglycosylated (T106A) human interferon alpha-2-b comprising
attenuating mutation R144X where X can be any amino acid selected
from A, D, E, G, H, I, K, L, N, Q, S, T, V, Y

<220>

<221> VARIANT

<222> (144)..(144)

<223> Xaa can be any amino acid selected from A, D, E, G, H, I, K, L,
N, Q, S, T, V, Y

<400> 24

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys
100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
Page 20

115

120

125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Xaa
 130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
 145 150 155 160

Leu Arg Ser Lys Glu
 165

<210> 25

<211> 165

<212> PRT

<213> Artificial

<220>

<223> Aglycosylated (T106A) human interferon alpha-2-b comprising
 attenuating mutation A145X where X can be any amino acid selected
 from D, E, G, H, I, K, L, M, N, Q, R, S, T, V, Y

<220>

<221> VARIANT

<222> (145)..(145)

<223> Xaa can be any amino acid selected from D, E, G, H, I, K, L, M,
 N, Q, R, S, T, V, Y

<400> 25

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
 1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
 20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
 35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
 50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
 65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
 85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys
 100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
 115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
 130 135 140

Xaa Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160

Leu Arg Ser Lys Glu
165

<210> 26
<211> 165
<212> PRT
<213> Artificial

<220>
<223> Aglycosylated (T106A) human interferon alpha-2-b comprising
attenuating mutation M148A

<400> 26

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys
100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Ala Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160

Leu Arg Ser Lys Glu
165

<210> 27
<211> 165
<212> PRT

<213> Artificial

<220>

<223> Aglycosylated (T106A) human interferon alpha-2-b comprising attenuating mutation R149A

<400> 27

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
 1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
 20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
 35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
 50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
 65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
 85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys
 100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
 115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
 130 135 140

Ala Glu Ile Met Ala Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
 145 150 155 160

Leu Arg Ser Lys Glu
 165

<210> 28

<211> 165

<212> PRT

<213> Artificial

<220>

<223> Aglycosylated (T106A) human interferon alpha-2-b comprising attenuating mutation S152A

<400> 28

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
 1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp

20

25

30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
 35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
 50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
 65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
 85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys
 100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
 115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
 130 135 140

Ala Glu Ile Met Arg Ser Phe Ala Leu Ser Thr Asn Leu Gln Glu Ser
 145 150 155 160

Leu Arg Ser Lys Glu
 165

<210> 29

<211> 165

<212> PRT

<213> Artificial

<220>

<223> Aglycosylated (T106A) human interferon alpha-2-b comprising
 attenuating mutation L153A

<400> 29

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
 1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
 20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
 35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
 50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
 65 70 75 80

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Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys
100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Ala Ser Thr Asn Leu Gln Glu Ser
145 150 155 160

Leu Arg Ser Lys Glu
165

<210> 30

<211> 165

<212> PRT

<213> Artificial

<220>

<223> Aglycosylated (T106A) human interferon alpha-2-b comprising
attenuating mutation N156A

<400> 30

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys
100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

AU15 50654

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Ala Leu Gln Glu Ser
145 150 155 160

Leu Arg Ser Lys Glu
165

<210> 31
<211> 612
<212> PRT
<213> Artificial

<220>
<223> A10.21 IgG4 (S228P) IFN (A592D, T553X) where X can be any amino acid selected from A, G, E, S, V

<220>
<221> VARIANT
<222> (553)..(553)
<223> Xaa can be any amino acid selected from A, G, E, S, V

<400> 31

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Ile Ser Cys Lys Val Ser Gly Tyr Thr Phe Thr Asp Ser
20 25 30

Val Met Asn Trp Val Gln Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asp Pro Glu Tyr Gly Arg Thr Asp Val Ala Glu Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Asp Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Thr Lys Tyr Asn Ser Gly Tyr Gly Phe Pro Tyr Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

AU15 50654

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro
210 215 220

Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
260 265 270

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350

Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

AU15 50654

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys Cys
435 440 445

Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met Leu
450 455 460

Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg
465 470 475 480

His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys
485 490 495

Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe Asn
500 505 510

Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu
515 520 525

Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu Ala
530 535 540

Cys Val Ile Gln Gly Val Gly Val Xaa Glu Thr Pro Leu Met Lys Glu
545 550 555 560

Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr
565 570 575

Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg Asp
580 585 590

Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu
595 600 605

Arg Ser Lys Glu
610

<210> 32
<211> 165
<212> PRT
<213> Artificial

<220>
<223> Aglycosylated (T106A) human interferon alpha-2-b comprising
attenuating mutations L30A, H57Y, E58N and Q61S

<400> 32

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Ala Lys Asp
20 25 30

AU15 50654

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu Tyr Asn Met Ile Ser Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys
100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160

Leu Arg Ser Lys Glu
165

<210> 33
<211> 165
<212> PRT
<213> Artificial

<220>
<223> Aglycosylated (T106A) human interferon alpha-2-b comprising
attenuating mutations R33A, H57Y, E58N and Q61S

<400> 33

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Ala His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu Tyr Asn Met Ile Ser Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

AU15 50654

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys
100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160

Leu Arg Ser Lys Glu
165

<210> 34
<211> 165
<212> PRT
<213> Artificial

<220>
<223> Aglycosylated (T106A) human interferon alpha-2-b comprising
attenuating mutations M148A, H57Y, E58N and Q61S

<400> 34

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu Tyr Asn Met Ile Ser Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys
100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg

130

135

140

Ala Glu Ile Ala Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
 145 150 155 160

Leu Arg Ser Lys Glu
 165

<210> 35

<211> 165

<212> PRT

<213> Artificial

<220>

<223> Aglycosylated (T106A) human interferon alpha-2-b comprising
 attenuating mutations L153A, H57Y, E58N and Q61S

<400> 35

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
 1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
 20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
 35 40 45

Lys Ala Glu Thr Ile Pro Val Leu Tyr Asn Met Ile Ser Gln Ile Phe
 50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
 65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
 85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys
 100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
 115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
 130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Ala Ser Thr Asn Leu Gln Glu Ser
 145 150 155 160

Leu Arg Ser Lys Glu
 165

<210> 36

<211> 165

<212> PRT
 <213> Artificial

<220>
 <223> Aglycosylated (T106A) human interferon alpha-2-b comprising
 attenuating mutations R144A, H57Y, E58N and Q61S

<400> 36

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
 1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
 20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
 35 40 45

Lys Ala Glu Thr Ile Pro Val Leu Tyr Asn Met Ile Ser Gln Ile Phe
 50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
 65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
 85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys
 100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
 115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Ala
 130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
 145 150 155 160

Leu Arg Ser Lys Glu
 165

<210> 37
 <211> 165
 <212> PRT
 <213> Artificial

<220>
 <223> Aglycosylated (T106A) human interferon alpha-2-b comprising
 attenuating mutations N65A, L80A, Y85A, Y89A

<400> 37

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
 1 5 10 15

AU15 50654

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Ala Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Ala
65 70 75 80

Leu Asp Lys Phe Ala Thr Glu Leu Ala Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys
100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160

Leu Arg Ser Lys Glu
165

<210> 38

<211> 165

<212> PRT

<213> Artificial

<220>

<223> Aglycosylated (T106A) human interferon alpha-2-b comprising
attenuating mutations N65A, L80A, Y85A, Y89A and D114A

<400> 38

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Ala Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Ala

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160

Leu Arg Ser Lys Glu
165

<210> 40
<211> 165
<212> PRT
<213> Artificial

<220>
<223> Aglycosylated (T106A) human interferon alpha-2-b comprising
attenuating mutations N65A,L80A, Y85A, Y89A and R120A

<400> 40

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Ala Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Ala
65 70 75 80

Leu Asp Lys Phe Ala Thr Glu Leu Ala Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys
100 105 110

Glu Asp Ser Ile Leu Ala Val Ala Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160

Leu Arg Ser Lys Glu
165

<210> 41
 <211> 165
 <212> PRT
 <213> Artificial

<220>
 <223> Aglycosylated (T106A) human interferon alpha-2-b comprising attenuating mutations Y85A, Y89A and R120A

<400> 41

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
 1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
 20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
 35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
 50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
 65 70 75 80

Leu Asp Lys Phe Ala Thr Glu Leu Ala Gln Gln Leu Asn Asp Leu Glu
 85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys
 100 105 110

Glu Asp Ser Ile Leu Ala Val Ala Lys Tyr Phe Gln Arg Ile Thr Leu
 115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
 130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
 145 150 155 160

Leu Arg Ser Lys Glu
 165

<210> 42
 <211> 165
 <212> PRT
 <213> Artificial

<220>
 <223> Aglycosylated (T106A) human interferon alpha-2-b comprising attenuating mutations D114A, R120A

<400> 42

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met

1					5					10					15				
Leu	Leu	Ala	Gln 20	Met	Arg	Arg	Ile	Ser 25	Leu	Phe	Ser	Cys	Leu 30	Lys	Asp				
Arg	His	Asp 35	Phe	Gly	Phe	Pro	Gln 40	Glu	Glu	Phe	Gly	Asn 45	Gln	Phe	Gln				
Lys	Ala 50	Glu	Thr	Ile	Pro	Val 55	Leu	His	Glu	Met	Ile 60	Gln	Gln	Ile	Phe				
Asn 65	Leu	Phe	Ser	Thr	Lys 70	Asp	Ser	Ser	Ala	Ala 75	Trp	Asp	Glu	Thr	Leu 80				
Leu	Asp	Lys	Phe	Tyr 85	Thr	Glu	Leu	Tyr	Gln 90	Gln	Leu	Asn	Asp	Leu 95	Glu				
Ala	Cys	Val	Ile 100	Gln	Gly	Val	Gly	Val 105	Ala	Glu	Thr	Pro	Leu 110	Met	Lys				
Glu	Ala	Ser 115	Ile	Leu	Ala	Val	Ala 120	Lys	Tyr	Phe	Gln	Arg 125	Ile	Thr	Leu				
Tyr	Leu 130	Lys	Glu	Lys	Lys	Tyr 135	Ser	Pro	Cys	Ala	Trp 140	Glu	Val	Val	Arg				
Ala 145	Glu	Ile	Met	Arg	Ser 150	Phe	Ser	Leu	Ser	Thr 155	Asn	Leu	Gln	Glu	Ser 160				
Leu	Arg	Ser	Lys	Glu 165															

<210>	43
<211>	165
<212>	PRT
<213>	Artificial

<220>
<223> Aglycosylated (T106A) human interferon alpha-2-b comprising
attenuating mutations L117A,R120A

<400> 43

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

AU15 50654

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys
100 105 110

Glu Asp Ser Ile Ala Ala Val Ala Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160

Leu Arg Ser Lys Glu
165

<210> 44
<211> 165
<212> PRT
<213> Artificial

<220>
<223> Aglycosylated (T106A) human interferon alpha-2-b comprising
attenuating mutations L117A,R120A,K121A

<400> 44

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys
100 105 110

AU15 50654

Glu Asp Ser Ile Ala Ala Val Ala Ala Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160

Leu Arg Ser Lys Glu
165

<210> 45

<211> 165

<212> PRT

<213> Artificial

<220>

<223> Aglycosylated (T106A) human interferon alpha-2-b comprising
attenuating mutations R120A,K121A

<400> 45

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys
100 105 110

Glu Asp Ser Ile Leu Ala Val Ala Ala Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160

Leu Arg Ser Lys Glu
165

<210> 46
<211> 165
<212> PRT
<213> Artificial

<220>
<223> Aglycosylated (T106A) human interferon alpha-2-b comprising
attenuating mutations R120E,K121E

<400> 46

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys
100 105 110

Glu Asp Ser Ile Leu Ala Val Glu Glu Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160

Leu Arg Ser Lys Glu
165

<210> 47
<211> 160
<212> PRT
<213> Artificial

<220>
<223> Aglycosylated (T106A) human interferon alpha-2-b comprising
attenuating deletion of residues L161-E165

AU15 50654

<400> 47

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys
100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160

<210> 48

<211> 447

<212> PRT

<213> Artificial

<220>

<223> VH sequence of 10.21 formatted as IgG4 incorporating hinge stabilisation substitution S228P

<400> 48

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Ile Ser Cys Lys Val Ser Gly Tyr Thr Phe Thr Asp Ser
20 25 30

Val Met Asn Trp Val Gln Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asp Pro Glu Tyr Gly Arg Thr Asp Val Ala Glu Lys Phe
50 55 60

AU15 50654

Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Asp Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Thr Lys Tyr Asn Ser Gly Tyr Gly Phe Pro Tyr Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro
210 215 220

Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
260 265 270

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
325 330 335

AU15 50654

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350

Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
435 440 445

<210> 49
<211> 447
<212> PRT
<213> Artificial

<220>
<223> VH sequence of 10.21 formatted as an IgG4 incorporating hinge
stabilisation substitution S228P and YTE residues substituted in
positions 252, 254, 256 respectively

<400> 49

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Ile Ser Cys Lys Val Ser Gly Tyr Thr Phe Thr Asp Ser
20 25 30

Val Met Asn Trp Val Gln Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asp Pro Glu Tyr Gly Arg Thr Asp Val Ala Glu Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Asp Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Thr Lys Tyr Asn Ser Gly Tyr Gly Phe Pro Tyr Trp Gly Gln
100 105 110

AU15 50654

Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro
210 215 220

Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Tyr Ile Thr Arg Glu
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
260 265 270

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350

Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

AU15 50654

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
435 440 445

<210> 50

<211> 450

<212> PRT

<213> Artificial

<220>

<223> VH sequence of 10.21 formatted as an IgG1

<400> 50

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Ile Ser Cys Lys Val Ser Gly Tyr Thr Phe Thr Asp Ser
20 25 30

Val Met Asn Trp Val Gln Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asp Pro Glu Tyr Gly Arg Thr Asp Val Ala Glu Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Asp Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Thr Lys Tyr Asn Ser Gly Tyr Gly Phe Pro Tyr Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
 180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
 195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
 210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
 225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
 245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
 260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
 275 280 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
 290 295 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
 305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
 325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
 340 345 350

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
 355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
 370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
 385 390 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
 405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
 420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
 Page 46

435

440

445

Gly Lys
450

<210> 51
<211> 450
<212> PRT
<213> Artificial

<220>
<223> VH sequence of 10.21 formatted as an IgG1 incorporating
substitutions L238A and G240A to reduce effector function

<400> 51

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Ile Ser Cys Lys Val Ser Gly Tyr Thr Phe Thr Asp Ser
20 25 30

Val Met Asn Trp Val Gln Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asp Pro Glu Tyr Gly Arg Thr Asp Val Ala Glu Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Asp Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Thr Lys Tyr Asn Ser Gly Tyr Gly Phe Pro Tyr Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

AU15 50654

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Ala Gly Ala
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
290 295 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly Lys
450

<210> 52
<211> 450

<212> PRT
 <213> Artificial

<220>
 <223> VH sequence of 10.21 formatted as an IgG1 incorporating
 substitutions L235A and G237A (reduce effector function) and
 M255Y, S257T, T259E

<400> 52

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1 5 10 15

Thr Val Lys Ile Ser Cys Lys Val Ser Gly Tyr Thr Phe Thr Asp Ser
 20 25 30

Val Met Asn Trp Val Gln Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
 35 40 45

Gly Trp Ile Asp Pro Glu Tyr Gly Arg Thr Asp Val Ala Glu Lys Phe
 50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Asp Thr Ala Tyr
 65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Thr Lys Tyr Asn Ser Gly Tyr Gly Phe Pro Tyr Trp Gly Gln
 100 105 110

Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
 115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
 130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
 145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
 165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
 180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
 195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
 210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Ala Gly Ala
 225 230 235 240

AU15 50654

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Tyr Ile
245 250 255

Thr Arg Glu Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
290 295 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly Lys
450

<210> 53
<211> 446
<212> PRT
<213> Artificial

<220>
<223> VH sequence of 10.21 formatted onto an IgG2 backbone

<400> 53

AU15 50654

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1 5 10 15
 Thr Val Lys Ile Ser Cys Lys Val Ser Gly Tyr Thr Phe Thr Asp Ser
 20 25 30
 Val Met Asn Trp Val Gln Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
 35 40 45
 Gly Trp Ile Asp Pro Glu Tyr Gly Arg Thr Asp Val Ala Glu Lys Phe
 50 55 60
 Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Asp Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Thr Lys Tyr Asn Ser Gly Tyr Gly Phe Pro Tyr Trp Gly Gln
 100 105 110
 Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
 115 120 125
 Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
 130 135 140
 Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
 145 150 155 160
 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
 165 170 175
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
 180 185 190
 Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys
 195 200 205
 Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val
 210 215 220
 Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe
 225 230 235 240
 Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
 245 250 255
 Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
 260 265 270

AU15 50654

Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val
290 295 300

Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 54

<211> 446

<212> PRT

<213> Artificial

<220>

<223> VH sequence of 10.21 formatted onto an IgG2 backbone
incorporating substitutions M251Y, S253T and T255E

<400> 54

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Ile Ser Cys Lys Val Ser Gly Tyr Thr Phe Thr Asp Ser
20 25 30

Val Met Asn Trp Val Gln Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asp Pro Glu Tyr Gly Arg Thr Asp Val Ala Glu Lys Phe
Page 52

50

55

Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Asp Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Thr Lys Tyr Asn Ser Gly Tyr Gly Phe Pro Tyr Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val
210 215 220

Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Tyr Ile Thr Arg Glu Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val
290 295 300

Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser

325

330

335

Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
 340 345 350

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
 355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
 370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp
 385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
 405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
 420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 435 440 445

<210> 55

<211> 447

<212> PRT

<213> Artificial

<220>

<223> VH sequence of 10.43 formatted onto an IgG4 backbone
 incorporating the hinge stabilisation substitution S228P

<400> 55

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1 5 10 15

Ser Val Lys Val Ser Cys Lys Val Ser Gly Tyr Thr Leu Thr Asp Ser
 20 25 30

Val Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
 35 40 45

Gly Trp Ile Asp Pro Glu Tyr Gly Arg Thr Asp Val Ala Gln Lys Phe
 50 55 60

Gln Gly Arg Val Thr Met Thr Ala Asp Thr Ser Thr Asp Thr Ala Tyr
 65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Thr Lys Tyr Asn Ser Gly Tyr Gly Phe Pro Tyr Trp Gly Gln
 100 105 110

Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
 115 120 125
 Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
 130 135 140
 Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
 145 150 155 160
 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
 165 170 175
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
 180 185 190
 Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys
 195 200 205
 Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro
 210 215 220
 Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val
 225 230 235 240
 Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
 245 250 255
 Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
 260 265 270
 Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
 275 280 285
 Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
 290 295 300
 Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
 305 310 315 320
 Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
 325 330 335
 Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
 340 345 350
 Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
 355 360 365
 Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
 370 375 380

AU15 50654

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
435 440 445

<210> 56

<211> 447

<212> PRT

<213> Artificial

<220>

<223> VH sequence of 10.152 formatted as an IgG4 incorporating the hinge stabilisation substitution S228P

<400> 56

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Ile Ser Cys Lys Val Ser Gly Tyr Thr Phe Thr Asp Ser
20 25 30

Val Met Asn Trp Val Gln Gln His Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asp Pro Glu Tyr Gly Arg Thr Asp Val Ala Glu Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Asp Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Thr Lys Tyr Asn Ser Gly Tyr Gly Phe Pro Tyr Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

AU15 50654

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro
210 215 220

Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
260 265 270

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350

Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

AU15 50654

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
 435 440 445

<210> 57
 <211> 401
 <212> PRT
 <213> Artificial

<220>
 <223> OPG-Fc construct

<400> 57

Glu Thr Phe Pro Pro Lys Tyr Leu His Tyr Asp Glu Glu Thr Ser His
 1 5 10 15

Gln Leu Leu Cys Asp Lys Cys Pro Pro Gly Thr Tyr Leu Lys Gln His
 20 25 30

Cys Thr Ala Lys Trp Lys Thr Val Cys Ala Pro Cys Pro Asp His Tyr
 35 40 45

Tyr Thr Asp Ser Trp His Thr Ser Asp Glu Cys Leu Tyr Cys Ser Pro
 50 55 60

Val Cys Lys Glu Leu Gln Tyr Val Lys Gln Glu Cys Asn Arg Thr His
 65 70 75 80

Asn Arg Val Cys Glu Cys Lys Glu Gly Arg Tyr Leu Glu Gly Glu Phe
 85 90 95

Cys Leu Lys His Arg Ser Cys Pro Pro Gly Phe Gly Val Val Gln Ala
 100 105 110

Gly Thr Pro Glu Arg Asn Thr Val Cys Lys Arg Cys Pro Asp Gly Phe
 115 120 125

Phe Ser Asn Glu Thr Ser Ser Lys Ala Pro Cys Arg Lys His Thr Asn
 130 135 140

Cys Ser Val Phe Gly Leu Leu Leu Thr Gln Lys Gly Asn Ala Thr His
 145 150 155 160

Asp Asn Ile Cys Ser Gly Asn Ser Glu Ser Thr Gln Lys Glu Arg Lys
 165 170 175

Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro
 180 185 190

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
 195 200 205

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp

AU15 50654
220

210

215

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
225 230 235 240

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val
245 250 255

Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu
260 265 270

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys
275 280 285

Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
290 295 300

Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
305 310 315 320

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
325 330 335

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu
340 345 350

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
355 360 365

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
370 375 380

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
385 390 395 400

Lys

<210> 58
<211> 448
<212> PRT
<213> Artificial

<220>
<223> X2.12 VH sequence formatted as an IgG4 (S228P)

<400> 58

Gln Leu Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Ser
20 25 30

AU15 50654

Ser Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
35 40 45

Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Asn Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65 70 75 80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95

Cys Ala Arg Val Gly Gly Ala Gly Gly Trp Pro Leu Asp Val Trp Gly
100 105 110

Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
115 120 125

Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala
130 135 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190

Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His
195 200 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly
210 215 220

Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser
225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
245 250 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro
260 265 270

Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val
290 295 300

AU15 50654

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr
325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
340 345 350

Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385 390 395 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser
405 410 415

Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
435 440 445

<210> 59

<211> 449

<212> PRT

<213> Artificial

<220>

<223> Anti-CD138 VH sequence formatted onto an IgG4 (S228P) backbone

<400> 59

Gln Val Gln Leu Gln Gln Ser Gly Ser Glu Leu Met Met Pro Gly Ala
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Ala Thr Gly Tyr Thr Phe Ser Asn Tyr
20 25 30

Trp Ile Glu Trp Val Lys Gln Arg Pro Gly His Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Leu Pro Gly Thr Gly Arg Thr Ile Tyr Asn Glu Lys Phe
50 55 60

Lys Gly Lys Ala Thr Phe Thr Ala Asp Ile Ser Ser Asn Thr Val Gln
65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys

Ala Arg Arg Asp Tyr Tyr Gly Asn Phe Tyr Tyr Ala Met Asp Tyr Trp
 100 105 110

Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
 115 120 125

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
 130 135 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
 145 150 155 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
 165 170 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
 180 185 190

Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp
 195 200 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
 210 215 220

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro
 225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
 245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
 260 265 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
 275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val
 290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
 305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
 325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
 340 345 350

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr

355

360

365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
 370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
 385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys
 405 410 415

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
 420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
 435 440 445

Lys

<210> 60

<211> 447

<212> PRT

<213> Artificial

<220>

<223> Anti-HLA VH sequence formatted onto IgG4 incorporating the hinge
 stabilising substitution S228P

<400> 60

Gln Val Gln Leu Lys Gln Ser Gly Pro Gly Leu Val Gln Pro Ser Gln
 1 5 10 15

Ser Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Ser Tyr
 20 25 30

Gly Val His Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu
 35 40 45

Gly Val Ile Trp Ser Gly Gly Ser Thr Asp Tyr Asn Ala Ala Phe Ile
 50 55 60

Ser Arg Leu Ser Ile Arg Lys Asp Asn Ser Lys Ser Gln Val Phe Phe
 65 70 75 80

Lys Met Asn Ser Leu Gln Ala Asp Asp Thr Ala Ile Tyr Tyr Cys Ala
 85 90 95

Arg Thr Phe Thr Thr Ser Thr Ser Ala Trp Phe Ala Tyr Trp Gly Gln
 100 105 110

Gly Thr Leu Val Thr Val Ser Ala Ala Ser Thr Lys Gly Pro Ser Val
 115 120 125

AU15 50654

Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
 130 135 140
 Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
 145 150 155 160
 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
 165 170 175
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
 180 185 190
 Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys
 195 200 205
 Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro
 210 215 220
 Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val
 225 230 235 240
 Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
 245 250 255
 Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
 260 265 270
 Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
 275 280 285
 Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
 290 295 300
 Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
 305 310 315 320
 Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
 325 330 335
 Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
 340 345 350
 Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
 355 360 365
 Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
 370 375 380
 Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
 385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg
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Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
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<212> PRT
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<223> A10.21VH sequence formatted onto IgG4 backbone incorporating hinge stabilisation substitution S228P and the deletion of Threonine residue at position 553 (ie:T106 in interferon sequence)

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Thr Val Lys Ile Ser Cys Lys Val Ser Gly Tyr Thr Phe Thr Asp Ser
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Val Met Asn Trp Val Gln Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asp Pro Glu Tyr Gly Arg Thr Asp Val Ala Glu Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Asp Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Thr Lys Tyr Asn Ser Gly Tyr Gly Phe Pro Tyr Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
 180 185 190

Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys
 195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro
 210 215 220

Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val
 225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
 245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
 260 265 270

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
 275 280 285

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
 290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
 305 310 315 320

Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
 325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
 340 345 350

Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
 355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
 370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
 385 390 400

Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg
 405 410 415

Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
 420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys Cys

435

440

445

Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met Leu
 450 455 460

Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg
 465 470 475 480

His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys
 485 490 495

Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe Asn
 500 505 510

Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu
 515 520 525

Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu Ala
 530 535 540

Cys Val Ile Gln Gly Val Gly Val Glu Thr Pro Leu Met Lys Glu Asp
 545 550 555 560

Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr Leu
 565 570 575

Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg Asp Glu
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Ser Lys Glu
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Val Met Asn Trp Val Gln Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
 35 40 45

AU15 50654

Gly Trp Ile Asp Pro Glu Tyr Gly Arg Thr Asp Val Ala Glu Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Asp Thr Ala Tyr
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Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Thr Lys Tyr Asn Ser Gly Tyr Gly Phe Pro Tyr Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro
210 215 220

Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Tyr Ile Thr Arg Glu
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
260 265 270

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

AU15 50654

Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
 325 330 335
 Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
 340 345 350
 Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
 355 360 365
 Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
 370 375 380
 Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
 385 390 395 400
 Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg
 405 410 415
 Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
 420 425 430
 His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys Cys
 435 440 445
 Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met Leu
 450 455 460
 Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg
 465 470 475 480
 His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys
 485 490 495
 Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe Asn
 500 505 510
 Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu
 515 520 525
 Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu Ala
 530 535 540
 Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys Glu
 545 550 555 560
 Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr
 565 570 575
 Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg Asp
 580 585 590

AU15 50654

Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu
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Arg Ser Lys Glu
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35 40 45

Gly Trp Ile Asp Pro Glu Tyr Gly Arg Thr Asp Val Ala Glu Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Asp Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Thr Lys Tyr Asn Ser Gly Tyr Gly Phe Pro Tyr Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys
Page 70

195							200								205
Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr	Gly	Pro
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Pro	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Phe	Leu	Gly	Gly	Pro	Ser	Val
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Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr
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Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	Gln	Glu	Asp	Pro	Glu
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Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys
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Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser
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Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys
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Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	Ser	Ser	Ile	Glu	Lys	Thr	Ile
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Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro
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Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu
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Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn
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Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser
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Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Arg	Leu	Thr	Val	Asp	Lys	Ser	Arg
				405					410					415	
Trp	Gln	Glu	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu
			420					425					430		
His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Leu	Gly	Lys	Cys
		435					440					445			
Asp	Leu	Pro	Gln	Thr	His	Ser	Leu	Gly	Ser	Arg	Arg	Thr	Leu	Met	Leu
	450					455					460				
Leu	Ala	Gln	Met	Arg	Arg	Ile	Ser	Leu	Phe	Ser	Cys	Leu	Lys	Asp	Arg

465 470 475 480

His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys
485 490 495

Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe Asn
500 505 510

Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu
515 520 525

Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu Ala
530 535 540

Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys Glu
545 550 555 560

Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr
565 570 575

Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Ile Ala
580 585 590

Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu
595 600 605

Arg Ser Lys Glu
610

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Val Met Asn Trp Val Gln Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asp Pro Glu Tyr Gly Arg Thr Asp Val Ala Glu Lys Phe
Page 72

50

55

Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Asp Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Thr Lys Tyr Asn Ser Gly Tyr Gly Phe Pro Tyr Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro
210 215 220

Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
260 265 270

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile

325

330

335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
 340 345 350

Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
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Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
 370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
 385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg
 405 410 415

Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
 420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys Cys
 435 440 445

Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met Leu
 450 455 460

Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg
 465 470 475 480

His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys
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Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe Asn
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Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu
 515 520 525

Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu Ala
 530 535 540

Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys Glu
 545 550 555 560

Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr
 565 570 575

Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg Xaa
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Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu

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Arg Ser Lys Glu
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Val Met Asn Trp Val Gln Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asp Pro Glu Tyr Gly Arg Thr Asp Val Ala Glu Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Asp Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Thr Lys Tyr Asn Ser Gly Tyr Gly Phe Pro Tyr Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
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Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys
195 200 205

AU15 50654

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro
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Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val
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Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
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Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
260 265 270

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350

Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
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His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys Cys
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Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met Leu
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Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp Ala
465 470 475 480

AU15 50654

His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys
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Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe Asn
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Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu
515 520 525

Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu Ala
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Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys Glu
545 550 555 560

Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr
565 570 575

Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg Ala
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Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu
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Arg Ser Lys Glu
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Gly Trp Ile Asp Pro Glu Tyr Gly Arg Thr Asp Val Ala Glu Lys Phe
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AU15 50654

Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Asp Thr Ala Tyr
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Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
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Ala Arg Thr Lys Tyr Asn Ser Gly Tyr Gly Phe Pro Tyr Trp Gly Gln
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Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
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Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro
210 215 220

Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
260 265 270

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
325 330 335

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Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350

Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys Cys
435 440 445

Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met Leu
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Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg
465 470 475 480

His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys
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Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe Asn
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Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu
515 520 525

Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu Ala
530 535 540

Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys Glu
545 550 555 560

Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr
565 570 575

Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg Xaa
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Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu
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Arg Ser Lys Glu
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Gly Trp Ile Asp Pro Glu Tyr Gly Arg Thr Asp Val Ala Glu Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Asp Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Thr Lys Tyr Asn Ser Gly Tyr Gly Phe Pro Tyr Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

AU15 50654

Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro
210 215 220

Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
260 265 270

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
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Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
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Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350

Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
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Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys Cys
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Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met Leu
450 455 460

AU15 50654

Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg
465 470 475 480

His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys
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Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe Asn
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Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu
515 520 525

Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu Ala
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Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys Glu
545 550 555 560

Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr
565 570 575

Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Xaa Ala
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35 40 45

Gly Trp Ile Asp Pro Glu Tyr Gly Arg Thr Asp Val Ala Glu Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Asp Thr Ala Tyr
Page 82

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Met	Glu	Leu	Ser	Ser 85	Leu	Arg	Ser	Glu	Asp 90	Thr	Ala	Val	Tyr	Tyr 95	Cys				
Ala	Arg	Thr	Lys 100	Tyr	Asn	Ser	Gly	Tyr 105	Gly	Phe	Pro	Tyr	Trp 110	Gly	Gln				
Gly	Thr	Thr 115	Val	Thr	Val	Ser	Ser 120	Ala	Ser	Thr	Lys	Gly 125	Pro	Ser	Val				
Phe	Pro 130	Leu	Ala	Pro	Ser	Ser 135	Lys	Ser	Thr	Ser	Gly 140	Gly	Thr	Ala	Ala				
Leu 145	Gly	Cys	Leu	Val	Lys 150	Asp	Tyr	Phe	Pro	Glu 155	Pro	Val	Thr	Val	Ser 160				
Trp	Asn	Ser	Gly	Ala 165	Leu	Thr	Ser	Gly	Val 170	His	Thr	Phe	Pro	Ala 175	Val				
Leu	Gln	Ser	Ser 180	Gly	Leu	Tyr	Ser	Leu 185	Ser	Ser	Val	Val	Thr 190	Val	Pro				
Ser	Ser	Ser 195	Leu	Gly	Thr	Gln	Thr 200	Tyr	Ile	Cys	Asn	Val 205	Asn	His	Lys				
Pro	Ser 210	Asn	Thr	Lys	Val	Asp 215	Lys	Lys	Val	Glu	Pro 220	Lys	Ser	Cys	Asp				
Lys 225	Thr	His	Thr	Cys	Pro 230	Pro	Cys	Pro	Ala	Pro 235	Glu	Leu	Leu	Gly	Gly 240				
Pro	Ser	Val	Phe	Leu 245	Phe	Pro	Pro	Lys	Pro 250	Lys	Asp	Thr	Leu	Met 255	Ile				
Ser	Arg	Thr	Pro 260	Glu	Val	Thr	Cys	Val 265	Val	Val	Asp	Val	Ser 270	His	Glu				
Asp	Pro	Glu 275	Val	Lys	Phe	Asn	Trp 280	Tyr	Val	Asp	Gly	Val 285	Glu	Val	His				
Asn	Ala 290	Lys	Thr	Lys	Pro	Arg 295	Glu	Glu	Gln	Tyr	Asn 300	Ser	Thr	Tyr	Arg				
Val 305	Val	Ser	Val	Leu	Thr 310	Val	Leu	His	Gln	Asp 315	Trp	Leu	Asn	Gly	Lys 320				
Glu	Tyr	Lys	Cys	Lys 325	Val	Ser	Asn	Lys	Ala 330	Leu	Pro	Ala	Pro	Ile 335	Glu				
Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr				

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345

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Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
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Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
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Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
 385 390 395 400

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Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
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Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
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Gly Lys Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr
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 565 570 575

Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val
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Gly Trp Ile Asp Pro Glu Tyr Gly Arg Thr Asp Val Ala Glu Lys Phe
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Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Asp Thr Ala Tyr
 65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
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Ala Arg Thr Lys Tyr Asn Ser Gly Tyr Gly Phe Pro Tyr Trp Gly Gln
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Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
 115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
 130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
 145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
 165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
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Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
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Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
 210 215 220

AU15 50654

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Ala Gly Ala
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 Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
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 260 265 270
 Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
 275 280 285
 Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
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 Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
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 Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
 325 330 335
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 355 360 365
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 405 410 415
 Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
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 Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
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 Gly Lys Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr
 450 455 460
 Leu Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu
 465 470 475 480
 Lys Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln
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AU15 50654

Phe Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln
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Leu Glu Ala Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu
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Met Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile
565 570 575

Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val
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Glu Ser Leu Arg Ser Lys Glu
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Gly Trp Ile Asp Pro Glu Tyr Gly Arg Thr Asp Val Ala Glu Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Asp Thr Ala Tyr
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Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
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Ala Arg Thr Lys Tyr Asn Ser Gly Tyr Gly Phe Pro Tyr Trp Gly Gln
Page 87

100

105

110

Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
 115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
 130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
 145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
 165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
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Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
 195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
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Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
 225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Tyr Ile
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Thr Arg Glu Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
 260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
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Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
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Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
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Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
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 Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
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 Gly Lys Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr
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 Lys Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln
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 Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val
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Gly Trp Ile Asp Pro Glu Tyr Gly Arg Thr Asp Val Ala Glu Lys Phe
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Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Asp Thr Ala Tyr
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Ala Arg Thr Lys Tyr Asn Ser Gly Tyr Gly Phe Pro Tyr Trp Gly Gln
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Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
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Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
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Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Ala Gly Ala
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Tyr Ile
245 250 255

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Thr Arg Glu Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
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Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
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Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
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Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
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355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
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Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
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Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
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Gly Lys Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr
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Leu Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu
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Lys Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln
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Phe Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln
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515 520 525

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Met Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile
565 570 575

Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val
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Gly Trp Ile Asp Pro Glu Tyr Gly Arg Thr Asp Val Ala Glu Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Asp Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
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Ala Arg Thr Lys Tyr Asn Ser Gly Tyr Gly Phe Pro Tyr Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
Page 92

130 135 140
 Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
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 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
 165 170 175
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
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 Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val
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 Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe
 225 230 235 240
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 Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
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 Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
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Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Cys Asp
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Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met Leu Leu
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Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg His
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Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe Asn Leu
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Ser Lys Glu
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Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Asp Thr Ala Tyr
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Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
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Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
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Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
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180 185 190

Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val
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Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Tyr Ile Thr Arg Glu Pro
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Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
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Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

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 Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
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 Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
 355 360 365
 Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
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 Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp
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 Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
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 Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg His
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 Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys Ala
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 Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe Asn Leu
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 Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu Asp
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 545 550 555 560

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565 570 575

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Ala Arg Thr Lys Tyr Asn Ser Gly Tyr Gly Phe Pro Tyr Trp Gly Gln
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Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
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Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
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Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
Page 97

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
 180 185 190

Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys
 195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro
 210 215 220

Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val
 225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
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Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
 260 265 270

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
 275 280 285

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
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Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
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Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
 340 345 350

Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
 355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
 370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
 385 390 400

Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg
 405 410 415

Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
 420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys Cys

AU15 50654

435

440

445

Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met Leu
450 455 460

Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg
465 470 475 480

His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys
485 490 495

Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe Asn
500 505 510

Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu
515 520 525

Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu Ala
530 535 540

Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys Glu
545 550 555 560

Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr
565 570 575

Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg Asp
580 585 590

Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu
595 600 605

Arg Ser Lys Glu
610

<210> 75
<211> 612
<212> PRT
<213> Artificial

<220>
<223> R10A2 IgG4 IFN

<220>
<221> VARIANT
<222> (553)..(553)
<223> Where Xaa can be any amino acid selected from A, C, D, E, F, G,
H, I, L, K, M, N, P, Q, R, S, V, W, Y

<400> 75

Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Val Gly Arg Pro Gly Ser
1 5 10 15

AU15 50654

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Ser
20 25 30

Val Met Asn Trp Val Lys Gln Ser Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Trp Ile Asp Pro Glu Tyr Gly Arg Thr Asp Val Ala Glu Lys Phe
50 55 60

Lys Lys Lys Ala Thr Leu Thr Ala Asp Ser Ser Ser Thr Ala Tyr
65 70 75 80

Ile Tyr Leu Ser Gly Leu Thr Ser Glu Asp Thr Ala Thr Tyr Phe Cys
85 90 95

Ala Arg Thr Lys Tyr Asn Ser Gly Tyr Gly Phe Pro Tyr Trp Gly Gln
100 105 110

Gly Ser Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro
210 215 220

Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
260 265 270

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

AU15 50654

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350

Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys Cys
435 440 445

Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met Leu
450 455 460

Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg
465 470 475 480

His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys
485 490 495

Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe Asn
500 505 510

Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu
515 520 525

Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu Ala
530 535 540

Cys Val Ile Gln Gly Val Gly Val Xaa Glu Thr Pro Leu Met Lys Glu
545 550 555 560

Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr
 565 570 575

Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg Asp
 580 585 590

Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu
 595 600 605

Arg Ser Lys Glu
 610

<210> 76
 <211> 612
 <212> PRT
 <213> Artificial

<220>
 <223> A10.152 IgG4 IFN

<400> 76

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1 5 10 15

Thr Val Lys Ile Ser Cys Lys Val Ser Gly Tyr Thr Phe Thr Asp Ser
 20 25 30

Val Met Asn Trp Val Gln Gln His Pro Gly Lys Gly Leu Glu Trp Met
 35 40 45

Gly Trp Ile Asp Pro Glu Tyr Gly Arg Thr Asp Val Ala Glu Lys Phe
 50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Asp Thr Ala Tyr
 65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Thr Lys Tyr Asn Ser Gly Tyr Gly Phe Pro Tyr Trp Gly Gln
 100 105 110

Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
 115 120 125

Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
 130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
 145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
 165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
 180 185 190
 Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys
 195 200 205
 Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro
 210 215 220
 Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val
 225 230 235 240
 Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
 245 250 255
 Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
 260 265 270
 Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
 275 280 285
 Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
 290 295 300
 Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
 305 310 315 320
 Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
 325 330 335
 Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
 340 345 350
 Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
 355 360 365
 Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
 370 375 380
 Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
 385 390 395 400
 Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg
 405 410 415
 Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
 420 425 430
 His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys Cys
 435 440 445

AU15 50654

Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met Leu
450 455 460

Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg
465 470 475 480

His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys
485 490 495

Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe Asn
500 505 510

Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu
515 520 525

Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu Ala
530 535 540

Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys Glu
545 550 555 560

Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr
565 570 575

Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg Asp
580 585 590

Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu
595 600 605

Arg Ser Lys Glu
610

<210> 77
<211> 613
<212> PRT
<213> Artificial

<220>
<223> A02.12 IgG4 IFN

<400> 77

Gln Leu Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Ser
20 25 30

Ser Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
35 40 45

AU15 50654

Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Asn Tyr Asn Pro Ser
 50 55 60

Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
 65 70 75 80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
 85 90 95

Cys Ala Arg Val Gly Gly Ala Gly Gly Trp Pro Leu Asp Val Trp Gly
 100 105 110

Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
 115 120 125

Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala
 130 135 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
 145 150 155 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
 165 170 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
 180 185 190

Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His
 195 200 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly
 210 215 220

Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser
 225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
 245 250 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro
 260 265 270

Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
 275 280 285

Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val
 290 295 300

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
 305 310 315 320

AU15 50654

Lys Cys Lys Val Ser₃₂₅ Asn Lys Gly Leu Pro₃₃₀ Ser Ser Ile Glu Lys₃₃₅ Thr
Ile Ser Lys Ala₃₄₀ Lys Gly Gln Pro Arg₃₄₅ Glu Pro Gln Val Tyr₃₅₀ Thr Leu
Pro Pro Ser₃₅₅ Gln Glu Glu Met Thr₃₆₀ Lys Asn Gln Val Ser₃₆₅ Leu Thr Cys
Leu Val₃₇₀ Lys Gly Phe Tyr Pro₃₇₅ Ser Asp Ile Ala Val₃₈₀ Glu Trp Glu Ser
Asn Gly Gln Pro Glu Asn₃₉₀ Asn Tyr Lys Thr Thr₃₉₅ Pro Pro Val Leu Asp₄₀₀
Ser Asp Gly Ser Phe₄₀₅ Phe Leu Tyr Ser Arg₄₁₀ Leu Thr Val Asp Lys₄₁₅ Ser
Arg Trp Gln Glu₄₂₀ Gly Asn Val Phe Ser₄₂₅ Cys Ser Val Met His₄₃₀ Glu Ala
Leu His Asn₄₃₅ His Tyr Thr Gln Lys₄₄₀ Ser Leu Ser Leu Ser₄₄₅ Leu Gly Lys
Cys Asp₄₅₀ Leu Pro Gln Thr His₄₅₅ Ser Leu Gly Ser Arg₄₆₀ Arg Thr Leu Met
Leu Leu Ala Gln Met Arg₄₇₀ Arg Ile Ser Leu Phe₄₇₅ Ser Cys Leu Lys Asp₄₈₀
Arg His Asp Phe Gly₄₈₅ Phe Pro Gln Glu Glu₄₉₀ Phe Gly Asn Gln Phe₄₉₅ Gln
Lys Ala Glu Thr₅₀₀ Ile Pro Val Leu His₅₀₅ Glu Met Ile Gln Gln₅₁₀ Ile Phe
Asn Leu Phe₅₁₅ Ser Thr Lys Asp Ser₅₂₀ Ser Ala Ala Trp Asp₅₂₅ Glu Thr Leu
Leu Asp₅₃₀ Lys Phe Tyr Thr Glu₅₃₅ Leu Tyr Gln Gln Leu₅₄₀ Asn Asp Leu Glu
Ala Cys Val Ile Gln Gly₅₅₀ Val Gly Val Ala Glu₅₅₅ Thr Pro Leu Met Lys₅₆₀
Glu Asp Ser Ile Leu₅₆₅ Ala Val Arg Lys Tyr₅₇₀ Phe Gln Arg Ile Thr₅₇₅ Leu
Tyr Leu Lys Glu₅₈₀ Lys Lys Tyr Ser Pro₅₈₅ Cys Ala Trp Glu Val₅₉₀ Val Arg

AU15 50654

Asp Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
595 600 605

Leu Arg Ser Lys Glu
610

<210> 78
<211> 566
<212> PRT
<213> Artificial

<220>
<223> OPG-Fc (IgG2) IFN

<400> 78

Glu Thr Phe Pro Pro Lys Tyr Leu His Tyr Asp Glu Glu Thr Ser His
1 5 10 15

Gln Leu Leu Cys Asp Lys Cys Pro Pro Gly Thr Tyr Leu Lys Gln His
20 25 30

Cys Thr Ala Lys Trp Lys Thr Val Cys Ala Pro Cys Pro Asp His Tyr
35 40 45

Tyr Thr Asp Ser Trp His Thr Ser Asp Glu Cys Leu Tyr Cys Ser Pro
50 55 60

Val Cys Lys Glu Leu Gln Tyr Val Lys Gln Glu Cys Asn Arg Thr His
65 70 75 80

Asn Arg Val Cys Glu Cys Lys Glu Gly Arg Tyr Leu Glu Gly Glu Phe
85 90 95

Cys Leu Lys His Arg Ser Cys Pro Pro Gly Phe Gly Val Val Gln Ala
100 105 110

Gly Thr Pro Glu Arg Asn Thr Val Cys Lys Arg Cys Pro Asp Gly Phe
115 120 125

Phe Ser Asn Glu Thr Ser Ser Lys Ala Pro Cys Arg Lys His Thr Asn
130 135 140

Cys Ser Val Phe Gly Leu Leu Leu Thr Gln Lys Gly Asn Ala Thr His
145 150 155 160

Asp Asn Ile Cys Ser Gly Asn Ser Glu Ser Thr Gln Lys Glu Arg Lys
165 170 175

Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro
180 185 190

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
195 200 205

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
 210 215 220
 Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
 225 230 235 240
 Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val
 245 250 255
 Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu
 260 265 270
 Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys
 275 280 285
 Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
 290 295 300
 Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
 305 310 315 320
 Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
 325 330 335
 Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu
 340 345 350
 Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
 355 360 365
 Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
 370 375 380
 Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
 385 390 395 400
 Lys Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu
 405 410 415
 Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys
 420 425 430
 Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe
 435 440 445
 Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile
 450 455 460
 Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr
 465 470 475 480

AU15 50654

Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu
485 490 495

Glu Ala Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met
500 505 510

Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr
515 520 525

Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val
530 535 540

Arg Asp Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu
545 550 555 560

Ser Leu Arg Ser Lys Glu
565

<210> 79
<211> 614
<212> PRT
<213> Artificial

<220>
<223> Anti-CD138 IgG4 IFN

<400> 79

Gln Val Gln Leu Gln Gln Ser Gly Ser Glu Leu Met Met Pro Gly Ala
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Ala Thr Gly Tyr Thr Phe Ser Asn Tyr
20 25 30

Trp Ile Glu Trp Val Lys Gln Arg Pro Gly His Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Leu Pro Gly Thr Gly Arg Thr Ile Tyr Asn Glu Lys Phe
50 55 60

Lys Gly Lys Ala Thr Phe Thr Ala Asp Ile Ser Ser Asn Thr Val Gln
65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Asp Tyr Tyr Gly Asn Phe Tyr Tyr Ala Met Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
115 120 125

AU15 50654

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
130 135 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145 150 155 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
165 170 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
180 185 190

Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp
195 200 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
210 215 220

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro
225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
260 265 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385 390 395 400

AU15 50654

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys
405 410 415

Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
435 440 445

Lys Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu
450 455 460

Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys
465 470 475 480

Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe
485 490 495

Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile
500 505 510

Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr
515 520 525

Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu
530 535 540

Glu Ala Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met
545 550 555 560

Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr
565 570 575

Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val
580 585 590

Arg Asp Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu
595 600 605

Ser Leu Arg Ser Lys Glu
610

<210> 80
<211> 612
<212> PRT
<213> Artificial

<220>
<223> Anti-HLA IgG4 IFN

<400> 80

Gln Val Gln Leu Lys Gln Ser Gly Pro Gly Leu Val Gln Pro Ser Gln
1 5 10 15

Ser Leu Ser Leu₂₀ Thr Cys Thr Val Ser₂₅ Gly Phe Ser Leu₃₀ Thr Ser Tyr
 Gly Val His₃₅ Trp Val Arg Gln₄₀ Pro Gly Lys Gly₄₅ Leu Glu Trp Leu
 Gly Val Ile Trp Ser Gly₅₅ Gly Ser Thr Asp Tyr Asn₆₀ Ala Ala Phe Ile
 Ser Arg Leu Ser Ile Arg₇₀ Lys Asp Asn Ser Lys₇₅ Ser Gln Val Phe Phe₈₀
 Lys Met Asn Ser Leu₈₅ Gln Ala Asp Asp Thr₉₀ Ala Ile Tyr Tyr Cys₉₅ Ala
 Arg Thr Phe Thr₁₀₀ Thr Ser Thr Ser Ala₁₀₅ Trp Phe Ala Tyr Trp₁₁₀ Gly Gln
 Gly Thr Leu₁₁₅ Val Thr Val Ser Ala₁₂₀ Ala Ser Thr Lys Gly₁₂₅ Pro Ser Val
 Phe Pro₁₃₀ Leu Ala Pro Cys Ser₁₃₅ Arg Ser Thr Ser Glu₁₄₀ Ser Thr Ala Ala
 Leu Gly Cys Leu Val Lys₁₅₀ Asp Tyr Phe Pro Glu₁₅₅ Pro Val Thr Val Ser₁₆₀
 Trp Asn Ser Gly Ala₁₆₅ Leu Thr Ser Gly Val₁₇₀ His Thr Phe Pro Ala Val₁₇₅
 Leu Gln Ser Ser₁₈₀ Gly Leu Tyr Ser Leu₁₈₅ Ser Ser Val Val Thr₁₉₀ Val Pro
 Ser Ser Ser₁₉₅ Leu Gly Thr Lys Thr₂₀₀ Tyr Thr Cys Asn Val₂₀₅ Asp His Lys
 Pro Ser₂₁₀ Asn Thr Lys Val Asp₂₁₅ Lys Arg Val Glu Ser₂₂₀ Lys Tyr Gly Pro
 Pro Cys Pro Pro Cys Pro₂₃₀ Ala Pro Glu Phe Leu Gly Gly Pro Ser Val₂₄₀
 Phe Leu Phe Pro₂₄₅ Lys Pro Lys Asp Thr₂₅₀ Leu Met Ile Ser Arg₂₅₅ Thr
 Pro Glu Val Thr₂₆₀ Cys Val Val Val Asp₂₆₅ Val Ser Gln Glu Asp₂₇₀ Pro Glu
 Val Gln Phe Asn Trp Tyr Val Asp₂₈₀ Gly Val Glu Val His₂₈₅ Asn Ala Lys

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
 290 295 300
 Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
 305 310 315 320
 Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
 325 330 335
 Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
 340 345 350
 Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
 355 360 365
 Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
 370 375 380
 Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
 385 390 395 400
 Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg
 405 410 415
 Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
 420 425 430
 His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys Cys
 435 440 445
 Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met Leu
 450 455 460
 Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg
 465 470 475 480
 His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys
 485 490 495
 Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe Asn
 500 505 510
 Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu
 515 520 525
 Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu Ala
 530 535 540
 Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys Glu
 545 550 555 560

AU15 50654

Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr
565 570 575

Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg Asp
580 585 590

Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu
595 600 605

Arg Ser Lys Glu
610

<210> 81
<211> 214
<212> PRT
<213> Artificial

<220>
<223> A10.21 and A10.43 light chain

<400> 81

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asn Val Asp Ser Asp
20 25 30

Val Asp Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Lys Ala Ser Asn Asp Tyr Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Ile Ala Thr Tyr Tyr Cys Met Gln Ser Asn Thr His Pro Arg
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

AU15 50654

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 82
<211> 214
<212> PRT
<213> Artificial

<220>
<223> R10A2 light chain

<400> 82

Asp Ile Val Met Thr Gln Ser Pro Thr Ser Ile Ser Ile Ser Val Gly
1 5 10 15

Glu Arg Val Thr Met Asn Cys Lys Ala Ser Gln Asn Val Asp Ser Asp
20 25 30

Val Asp Trp Tyr Gln Gln Lys Thr Gly Gln Ser Pro Lys Leu Leu Ile
35 40 45

Tyr Lys Ala Ser Asn Arg Tyr Thr Gly Val Pro Asp Arg Phe Thr Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Asn Met Gln Ala
65 70 75 80

Glu Asp Leu Ala Val Tyr Tyr Cys Met Gln Ser Asn Thr His Pro Arg
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Leu Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr₁₈₀ Leu Ser Lys Ala Asp₁₈₅ Tyr Glu Lys His Lys₁₉₀ Val Tyr

Ala Cys Glu₁₉₅ Val Thr His Gln Gly₂₀₀ Leu Ser Ser Pro Val₂₀₅ Thr Lys Ser

Phe Asn Arg Gly Glu Cys
210

<210> 83
<211> 614
<212> PRT
<213> Artificial

<220>
<223> A10.21 IgG1 IFN

<400> 83

Glu Val Gln Leu₅ Val Gln Ser Gly Ala Glu₁₀ Val Lys Lys Pro Gly₁₅ Ala

Thr Val Lys Ile₂₀ Ser Cys Lys Val Ser₂₅ Gly Tyr Thr Phe Thr₃₀ Asp Ser

Val Met Asn₃₅ Trp Val Gln Gln Ala₄₀ Pro Gly Lys Gly Leu₄₅ Glu Trp Met

Gly Trp₅₀ Ile Asp Pro Glu Tyr₅₅ Gly Arg Thr Asp Val₆₀ Ala Glu Lys Phe

Gln Gly Arg Val Thr Ile₇₀ Thr Ala Asp Thr Ser₇₅ Thr Asp Thr Ala Tyr₈₀

Met Glu Leu Ser Ser₈₅ Leu Arg Ser Glu Asp₉₀ Thr Ala Val Tyr Tyr₉₅ Cys

Ala Arg Thr Lys₁₀₀ Tyr Asn Ser Gly Tyr₁₀₅ Gly Phe Pro Tyr Trp₁₁₀ Gly Gln

Gly Thr Thr₁₁₅ Val Thr Val Ser Ser₁₂₀ Ala Ser Thr Lys Gly₁₂₅ Pro Ser Val

Phe Pro₁₃₀ Leu Ala Pro Ser Ser₁₃₅ Lys Ser Thr Ser Gly₁₄₀ Gly Thr Ala Ala

Leu Gly Cys Leu Val Lys₁₅₀ Asp Tyr Phe Pro Glu₁₅₅ Pro Val Thr Val Ser₁₆₀

Trp Asn Ser Gly Ala₁₆₅ Leu Thr Ser Gly Val₁₇₀ His Thr Phe Pro Ala₁₇₅ Val

AU15 50654

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
290 295 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

AU15 50654

Gly Lys Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr
450 455 460

Leu Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu
465 470 475 480

Lys Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln
485 490 495

Phe Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln
500 505 510

Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu
515 520 525

Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp
530 535 540

Leu Glu Ala Cys Val Ile Gln Gly Val Gly Val Glu Thr Pro Leu Met
545 550 555 560

Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr
565 570 575

Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val
580 585 590

Arg Asp Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu
595 600 605

Ser Leu Arg Ser Lys Glu
610

<210> 84
<211> 222
<212> PRT
<213> Artificial

<220>
<223> A02.12 lambda light chain

<400> 84

Gln Ala Val Leu Thr Gln Pro Ala Ser Leu Ser Ala Ser Pro Gly Glu
1 5 10 15

Ser Ala Arg Leu Thr Cys Thr Leu Pro Ser Asp Ile Asn Val Arg Tyr
20 25 30

Tyr Asn Ile Tyr Trp Tyr Gln Gln Lys Pro Gly Ser Pro Pro Arg Tyr
35 40 45

Leu Leu Tyr Tyr Tyr Ser Asp Ser His Lys Gly Gln Gly Ser Gly Val
50 55 60

AU15 50654

Pro Ser Arg Phe Ser Gly Ser Lys Asp Val Ser Thr Asn Ser Gly Ile
65 70 75 80

Leu Leu Ile Ser Gly Leu Gln Ser Glu Asp Ile Ala Thr Tyr Tyr Cys
85 90 95

Met Thr Trp Ser Ser Asn Gly Ser Gly Val Phe Gly Gly Gly Thr Gln
100 105 110

Leu Thr Val Leu Gly Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe
115 120 125

Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys
130 135 140

Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala
145 150 155 160

Asp Ser Ser Pro Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys
165 170 175

Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro
180 185 190

Glu Gln Trp Lys Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu
195 200 205

Gly Ser Thr Val Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
210 215 220

<210> 85
<211> 214
<212> PRT
<213> Artificial

<220>
<223> Anti-CD138 light chain

<400> 85

Asp Ile Gln Met Thr Gln Ser Thr Ser Ser Leu Ser Ala Ser Leu Gly
1 5 10 15

Asp Arg Val Thr Ile Ser Cys Ser Ala Ser Gln Gly Ile Asn Asn Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Glu Leu Leu Ile
35 40 45

Tyr Tyr Thr Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

AU15 50654

Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Pro
65 70 75 80

Glu Asp Ile Gly Thr Tyr Tyr Cys Gln Gln Tyr Ser Lys Leu Pro Arg
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 86
<211> 215
<212> PRT
<213> Artificial

<220>
<223> Anti-HLA light chain

<400> 86

Ser Ile Val Met Thr Gln Thr Pro Lys Phe Leu Leu Val Ser Ala Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser Val Ser Asn Asp
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
35 40 45

Tyr Tyr Ala Ser Asn Arg Tyr Thr Gly Val Pro Asp Arg Phe Thr Gly
50 55 60

Ser Gly Tyr Gly Thr Asp Phe Thr Phe Thr Ile Ser Thr Val Gln Ala
65 70 75 80

AU15 50654

Glu Asp Leu Ala Val Tyr Phe Cys Gln Gln Asp Tyr Ser Ser Pro Pro
85 90 95

Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Arg Arg Thr Val Ala
100 105 110

Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
115 120 125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
130 135 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145 150 155 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
165 170 175

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
180 185 190

Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
195 200 205

Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 87
<211> 612
<212> PRT
<213> Artificial

<220>
<223> A10.21 IgG4 (S228P) IFN (A145D, T106A)

<400> 87

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Ile Ser Cys Lys Val Ser Gly Tyr Thr Phe Thr Asp Ser
20 25 30

Val Met Asn Trp Val Gln Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asp Pro Glu Tyr Gly Arg Thr Asp Val Ala Glu Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Asp Thr Ala Tyr
65 70 75 80

AU15 50654

Met Glu Leu Ser Ser₈₅ Leu Arg Ser Glu Asp₉₀ Thr Ala Val Tyr Tyr₉₅ Cys

Ala Arg Thr Lys₁₀₀ Tyr Asn Ser Gly Tyr₁₀₅ Gly Phe Pro Tyr Trp₁₁₀ Gly Gln

Gly Thr Thr₁₁₅ Val Thr Val Ser Ser₁₂₀ Ala Ser Thr Lys Gly₁₂₅ Pro Ser Val

Phe Pro₁₃₀ Leu Ala Pro Cys Ser₁₃₅ Arg Ser Thr Ser Glu₁₄₀ Ser Thr Ala Ala

Leu Gly Cys Leu Val Lys₁₅₀ Asp Tyr Phe Pro Glu₁₅₅ Pro Val Thr Val Ser₁₆₀

Trp Asn Ser Gly Ala₁₆₅ Leu Thr Ser Gly Val₁₇₀ His Thr Phe Pro Ala₁₇₅ Val

Leu Gln Ser Ser₁₈₀ Gly Leu Tyr Ser Leu₁₈₅ Ser Ser Val Val Thr₁₉₀ Val Pro

Ser Ser Ser₁₉₅ Leu Gly Thr Lys Thr₂₀₀ Tyr Thr Cys Asn Val₂₀₅ Asp His Lys

Pro Ser₂₁₀ Asn Thr Lys Val Asp₂₁₅ Lys Arg Val Glu Ser₂₂₀ Lys Tyr Gly Pro

Pro Cys Pro Pro Cys Pro₂₃₀ Ala Pro Glu Phe Leu₂₃₅ Gly Gly Pro Ser Val₂₄₀

Phe Leu Phe Pro Pro₂₄₅ Lys Pro Lys Asp Thr₂₅₀ Leu Met Ile Ser Arg₂₅₅ Thr

Pro Glu Val Thr₂₆₀ Cys Val Val Val Asp₂₆₅ Val Ser Gln Glu Asp₂₇₀ Pro Glu

Val Gln Phe Asn Trp Tyr Val Asp₂₈₀ Gly Val Glu Val His₂₈₅ Asn Ala Lys

Thr Lys₂₉₀ Pro Arg Glu Glu Gln₂₉₅ Phe Asn Ser Thr Tyr₃₀₀ Arg Val Val Ser

Val Leu Thr Val Leu His₃₁₀ Gln Asp Trp Leu Asn₃₁₅ Gly Lys Glu Tyr Lys₃₂₀

Cys Lys Val Ser Asn₃₂₅ Lys Gly Leu Pro Ser₃₃₀ Ser Ile Glu Lys Thr₃₃₅ Ile

Ser Lys Ala Lys₃₄₀ Gly Gln Pro Arg Glu₃₄₅ Pro Gln Val Tyr Thr₃₅₀ Leu Pro

AU15 50654

Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys Cys
435 440 445

Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met Leu
450 455 460

Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg
465 470 475 480

His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys
485 490 495

Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe Asn
500 505 510

Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu
515 520 525

Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu Ala
530 535 540

Cys Val Ile Gln Gly Val Gly Val Ala Glu Thr Pro Leu Met Lys Glu
545 550 555 560

Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr
565 570 575

Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg Asp
580 585 590

Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu
595 600 605

Arg Ser Lys Glu
610

<210> 88
 <211> 495
 <212> DNA
 <213> Artificial

<220>
 <223> IFN alpha-2-beta

<400> 88
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 atgaggagaa tctctctttt ctctgcttg aaggacagac atgacttttg atttccccag 120
 gaggagtgtt gcaaccagtt ccaaaaggct gaaaccatcc ctgtcctcca tgagatgatc 180
 cagcagatct tcaatctctt cagcacaaag gactcatctg ctgcttggga tgagaccctc 240
 ctagacaaat tctacactga actctaccag cagctgaatg acctggaagc ctgtgtgata 300
 caggggggtg ggggtgacaga gactcccctg atgaaggagg actccattct ggctgtgagg 360
 aaatacttcc aaagaatcac tctctatctg aaagagaaga aatacagccc ttgtgcctgg 420
 gaggttgtca gagcagaaat catgagatct ttttctttgt caacaaactt gcaagaaagt 480
 ttaagaagta aggaa 495

<210> 89
 <211> 1341
 <212> DNA
 <213> Artificial

<220>
 <223> Polynucleotide of 10.21 as an IgG2 incorporating S228P

<400> 89
 gaagtgcagc tgggtgcagtc tggcgccgaa gtgaagaaac ccggcgctac cgtgaagatc 60
 tcctgcaagg tgtccggcta caccttcacc gactccgtga tgaactgggt gcagcaggcc 120
 cctggcaagg gcctggaatg gatgggctgg atcgaccccg agtacggcag aaccgacgtg 180
 gccgagaagt tccagggcag agtgaccatc accgccgaca cctccaccga caccgcctac 240
 atggaactgt cctccctgcg gagcgaggac accgccgtgt actactgcg cgggaccaag 300
 tacaactccg gctacggctt cccctactgg ggccagggca ccaccgtgac cgtgtcctcc 360
 gcctccacca agggcccctc cgtgttcctt ctggcccctt gctcccggtc cacctccgag 420
 tctaccgccg ctctgggctg cctgggtcaag gactacttcc ccgagcctgt gacagtgtcc 480
 tggaactctg gcgccctgac ctccggcgtg cacaccttcc ctgccgtgct gcagtcctcc 540
 ggcctgtact ccctgtcctc cgtcgtgacc gtgccttcca gctccctggg caccaagacc 600
 tacacctgta acgtggacca caagccctcc aacaccaagg tggacaagcg ggtggaatct 660
 aagtacggcc ctccctgccc cccctgccct gccctgaat ttctgggcgg accttccgtg 720
 ttctgttcc ccccaaagcc caaggacacc ctgatgatct cccggacccc cgaagtgacc 780
 tgcgtgggtg tggacgtgtc ccaagaggac cccgaggtgc agttcaattg gtacgtggac 840
 ggcgtggaag tgcacaacgc caagaccaag cccagagagg aacagttcaa ctccacctac 900
 cgggtggtgt ccgtgctgac cgtgctgcac caggactggc tgaacggcaa agaatacaag 960

AU15 50654

tgcaaagtct ccaacaaggg cctgccctcc agcatcgaaa agaccatctc caaggccaag	1020
ggacagcccc gcgagcccca ggtgtacacc ctgcccccta gccaagagga aatgaccaag	1080
aaccaggtgt ccctgacctg cctcgtgaag ggcttctacc cctccgatat cgccgtggaa	1140
tgggagtcca acggccagcc cgagaacaac tacaagacca cccccctgt gctggactcc	1200
gacggctcct tcttcctgta ctctcggtg accgtggaca agtcccgtg gcaagagggc	1260
aacgtgttct cctgctccgt gatgcacgag gccctgcaca accactacac ccagaagtcc	1320
ctgtccctga gcctgggcaa g	1341

<210> 90
 <211> 1341
 <212> DNA
 <213> Artificial

<220>
 <223> Polynucleotide sequence of 10.43 as an IgG4 incorporating S228P

<400> 90	
caggtgcagc tgggtgcagtc tggcgccgaa gtgaagaaac ctggcgccctc cgtgaagggtg	60
tcctgcaagg tgtccggcta caccctgacc gactccgtga tgaactgggt ccgacaggcc	120
cctggcaagg gcctggaatg gatgggctgg atcgaccccg agtacggcag aaccgacgtg	180
gcccagaaat tccagggcag agtgaccatg accgccgaca cctccaccga caccgcctac	240
atggaactgt cctccctgcg gagcgaggac accgccgtgt actactgcg cgggaccaag	300
tacaactccg gctacggctt cccctactgg ggccagggca ccaccgtgac cgtgtcctct	360
gcttccacca agggcccctc cgtgttcct ctggcccctt gctcccggtc cacctccgag	420
tctaccgccg ctctgggctg cctgggtcaag gactacttcc ccgagcctgt gacagtgtcc	480
tggaaactctg gcgccctgac ctccggcggtg cacaccttcc ctgccgtgct gcagtccctc	540
ggcctgtact ccctgtcctc cgtcgtgacc gtgccttcca gctccctggg caccaagacc	600
tacacctgta acgtggacca caagccctcc aacaccaagg tggacaagcg ggtggaatct	660
aagtacggcc ctccctgccc cccctgccct gccctgaat ttctgggagg accttccgtg	720
ttcctgttcc ccccaaagcc caaggacacc ctgatgatct cccggacccc cgaagtgacc	780
tgcgtggtgg tggacgtgtc ccaagaggac ccgaggtgc agttcaattg gtacgtggac	840
ggcgtggaag tgcacaacgc caagaccaag ccagagagg aacagttcaa ctccacctac	900
cgggtggtgt ccgtgctgac cgtgctgcac caggactggc tgaacggcaa agaatacaag	960
tgcaaagtct ccaacaaggg cctgccctcc agcatcgaaa agaccatctc caaggccaag	1020
ggacagcccc gcgagcccca ggtgtacacc ctgcccccta gccaagagga aatgaccaag	1080
aaccaggtgt ccctgacctg cctcgtgaag ggcttctacc cctccgatat cgccgtggaa	1140
tgggagtcca acggccagcc cgagaacaac tacaagacca cccccctgt gctggactcc	1200
gacggctcct tcttcctgta ctctcggtg accgtggaca agtcccgtg gcaagagggc	1260
aacgtgttct cctgctccgt gatgcacgag gccctgcaca accactacac ccagaagtcc	1320

ctgtccctga gcctgggcaa g

1341

<210> 91
 <211> 1344
 <212> DNA
 <213> Artificial

<220>

<223> Polynucleotide of 2.12 formatted an an IgG4 incorporating S228P

<400> 91

cagctgcagc tgcaggaatc tggccctggc ctcgtgaagc ccagcgagac actgagcctg	60
acctgtaccg tgtccggcgg cagcatcagc agcagctcct actactggtc ctggatcaga	120
cagcaccctg gcaagggcct ggaatggatc ggctacatct actacagcgg cagcaccaac	180
tacaacccca gcctgaagtc cagagtgacc atcagcgtgg acaccagcaa gaaccagttc	240
tccctgaagc tgagcagcgt gacagccgcc gataccgccg tgtactactg tgccagagtg	300
ggcggagctg gcggctggcc tctggatgtg tggggacagg gcaccaccgt gacagtgtcc	360
tcagctagca ccaagggccc cagcgtgttc cctctggccc cttgtagcag aagcaccagc	420
gagtctacag ccgccctggg ctgcctcgtg aaggactact ttcccagacc cgtcaccgtg	480
tcctggaact ctggcgctct gacaagcggc gtgcacacct ttccagccgt gctgcagagc	540
agcggcctgt actctctgag cagcgtcgtg accgtgcccc gctctagcct gggcaccaag	600
acctacacct gtaacgtgga ccacaagccc agcaacacca aggtggacaa gcgggtggaa	660
tctaagtacg gccctccctg ccctccttgc ccagcccctg aatttctggg cggaccctcc	720
gtgttcctgt tcccccaaa gcccaaggac accctgatga tcagccggac ccccgaagtg	780
acctgcgtgg tgggtggatgt gtcccaggaa gatcccaggg tgcagttcaa ttggtacgtg	840
gacggcgtgg aagtgcacaa cgccaagacc aagcccagag aggaacagtt caacagcacc	900
taccgggtgg tgtccgtgct gacagtgtg caccaggact ggctgaacgg caaagagtac	960
aagtgcagg tgtccaacaa gggcctgcct agcagcatcg agaaaaccat cagcaaggcc	1020
aagggccagc cccgcgaacc tcaggtgtac aactgcccc ctagccagga agagatgacc	1080
aagaaccagg tgtccctgac ctgtctcgtg aaaggcttct acccctccga tatcgccgtg	1140
gaatgggaga gcaacggcca gcccgagaac aactacaaga ccaccccccc tgtgctggac	1200
agcgacggct cattcttcct gtacagcaga ctgaccgtgg acaagagccg gtggcaggaa	1260
ggcaacgtgt tcagctgcag cgtgatgcac gaggccctgc acaaccacta caccagaag	1320
tccctgtccc tgtctctggg caag	1344

<210> 92
 <211> 1341
 <212> DNA
 <213> Artificial

<220>

<223> Polynucleotide of R10A2 formatted as an IgG4 incorporating S228P

AU15 50654

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<400> 92
gaagtccagc tgcagcagtc tggccccgaa gtgggcagac ctggctcctc cgtgaagatc      60
tcctgcaagg cctccggcta caccttcacc gactccgtga tgaactgggt caagcagtct      120
cccggccagg gcctggaatg gatcggatgg atcgaccccc agtacggcag aaccgacgtg      180
gccgagaagt tcaagaagaa ggccaccctg accgccgact cctccagctc caccgcctac      240
atctacctgt ccggcctgac ctccgaggac accgccacct acttttgcg cccggaccaag      300
tacaacagcg gctacggctt cccctactgg ggacagggct ctctcgtgac agtgtcctca      360
gcctccacca agggcccctc cgtgttcctt ctggcccctt gctcccggtc cacctccgag      420
tctaccgccg ctctgggctg cctgggtgaaa gactacttcc ccgagcctgt gaccgtgagc      480
tggaactctg gcgccctgac ctccggcgtg cacaccttcc ctgccgtgct gcagtcctcc      540
ggcctgtact ccctgtcctc cgtggtgaca gtgccctcct ccagcctggg caccaagacc      600
tacacctgta acgtggacca caagccctcc aacaccaagg tggacaagcg ggtggaatct      660
aagtacggcc ctccctgccc cccctgccct gccctgaat ttctgggctg accttccgtg      720
tttctgttcc ccccaaagcc caaggacacc ctgatgatct cccggacccc cgaagtgacc      780
tgcgtggtgg tggacgtgtc ccaggaagat ccagaggtgc agttcaattg gtacgtggac      840
ggcgtggaag tgcacaacgc caagaccaag cccagagagg aacagttcaa ctccacctac      900
cgggtggtgt ccgtgctgac cgtgctgcac caggactggc tgaacggcaa agagtacaag      960
tgcaagggtg ccaacaaggg cctgccctcc agcatcgaaa agaccatctc caaggccaag     1020
ggccagcccc gcgagcccca ggtgtacacc ctgcccccta gccaggaaga gatgaccaag     1080
aaccagggtg ccctgacctg tctgggtgaaa ggcttctacc cctccgacat tgccgtggaa     1140
tgggagtcca acggccagcc cgagaacaac tacaagacca cccccctgt gctggactcc     1200
gacggctcct tcttctgtga ctctcggtg acagtggata agtcccgggtg gcaggaaggg     1260
aacgtgttct cctgcagcgt gatgcacgag gccctgcaca accactatac ccagaagtcc     1320
ctgtccctga gcctgggcaa g                                     1341

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<210> 93
<211> 642
<212> DNA
<213> Artificial

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<220>
<223> Polynucleotide sequence of R10A2 VK

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<400> 93
gacatcgtga tgaccagag ccccacctcc atctccatca gcgtgggcga gcgcgtgacc      60
atgaactgca aggcctccca gaacgtggac agcgacgtgg actggtatca gcagaaaacc     120
ggccagtccc ccaagctgct gatctacaag gccagcaaca gataaccgg cgtgcccgcac     180
aggttcaccg gctctggctc tggaaccgac ttcaccttca ccatcagcaa catgcaggcc     240
gaggatctgg ccgtgtacta ctgtatgcag tccaacaccc acccccggac cttcggcgga     300
ggcaccaaac tggaactgaa gcggaccgtg gccgtccca gcgtgttcat cttccccccc     360

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AU15 50654

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ccccgggagg ccaaggtgca gtggaaggtg gacaacgccc tgcagtctgg caacagccag	480
gaaagcgtca ccgagcagga cagcaaggat agcacctaca gcctgagcag caccctgacc	540
ctgagcaagg ccgactacga gaagcacaag gtgtacgcct gcgaggtcac ccaccagggc	600
ctgtctagcc ccgtcaccaa gagcttcaac cggggcgagt gc	642

<210> 94
 <211> 642
 <212> DNA
 <213> Artificial

<220>
 <223> Polynucleotide sequence of VK used to generate antibody 10.21 and antibody 10.43

<400> 94	
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ggcaaggccc ccaagctgct gatctacaag gcctccaacg actacaccgg cgtgccctcc	180
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ggcaccaagg tggaaatcaa gcggaaccgtg gccgtccct ccgtgttcat cttccacccc	360
tccgacgagc agctgaagtc cggcaccgcc tccgtcgtgt gcctgctgaa caacttctac	420
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gagtcctgta ccgagcagga ctccaaggac agcacctact ccctgtcctc caccctgacc	540
ctgtccaagg ccgactacga gaagcacaag gtgtacgcct gcgaagtgcac ccaccagggc	600
ctgtccagcc ccgtgaccaa gtccttcaac cggggcgagt gc	642

<210> 95
 <211> 1341
 <212> DNA
 <213> Artificial

<220>
 <223> Polynucleotide sequence of 10.152 formatted as an IgG4 incorporating S228P

<400> 95	
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tcctgcaagg tgtccggcta caccttcacc gactccgtga tgaactgggt gcagcagcat	120
cccggcaagg gcctggaatg gatgggctgg atcgaccccg agtacggcag aaccgacgtg	180
gccgagaagt tccagggcag agtgaccatc accgccgaca cctccaccga caccgcctac	240
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tacaactccg gctacggctt cccctactgg ggccagggca ccaccgtgac cgtgtcctct	360
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AU15 50654

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ggcctgtact ccctgtcctc cgtcgtgacc gtgccttcca gctccctggg caccaagacc	600
tacacctgta acgtggacca caagccctcc aacaccaagg tggacaagcg ggtggaatct	660
aagtacggcc ctccctgccc cccctgccct gcccttgaat ttctgggcgg accttccgtg	720
ttcctgttcc ccccaaagcc caaggacacc ctgatgatct cccggacccc cgaagtgacc	780
tgcgtggtgg tggacgtgtc ccaagaggac cccgaggtgc agttcaattg gtacgtggac	840
ggcgtggaag tgcacaacgc caagaccaag cccagagagg aacagttcaa ctccacctac	900
cgggtggtgt ccgtgctgac cgtgctgcac caggactggc tgaacggcaa agaatacaag	960
tgcaaagtct ccaacaaggg cctgccctcc agcatcgaaa agaccatctc caaggccaag	1020
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gacggctcct tcttctgta ctctcggctg accgtggaca agtcccgggtg gcaagagggc	1260
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ctgtccctga gcctgggcaa g	1341

<210> 96
 <211> 214
 <212> PRT
 <213> Artificial

<220>
 <223> Amino acid sequence of 10.152 light chain

<400> 96

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Asp	Arg	Val	Thr	Ile	Thr	Cys	Gln	Ala	Ser	Gln	Asn	Val	Asp	Ser	Asp
			20					25					30		

Val	Asp	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
		35					40					45			

Tyr	Lys	Ala	Ser	Asn	Asp	Tyr	Thr	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
	50					55					60				

Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Phe	Thr	Ile	Ser	Ser	Leu	Gln	Pro
65					70					75					80

Glu	Asp	Ile	Ala	Thr	Tyr	Tyr	Cys	Ala	Gln	Ser	Asn	Thr	His	Pro	Arg
				85					90					95	

AU15 50654

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 97
<211> 642
<212> DNA
<213> Artificial

<220>
<223> Polynucleotide sequence of 10.152 light chain

<400> 97
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gggaaagcgc ccaagctgct gatctacaag gcctccaatg attacactgg agtgcctagc 180
cggttcagcg gatcagggtc gggaacggac ttcactttta ccacttcaag cctccaacca 240
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ccccgcgagg ccaaggtgca gtggaaggtg gacaacgccc tgcagagcgg caacagccag 480
gaaagcgtga ccgagcagga cagcaaggac tccacctaca gcctgagcag caccctgacc 540
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ctgtccagcc ccgtgaccaa gagcttcaac cggggcgagt gc 642

<210> 98
<211> 666
<212> DNA
<213> Artificial

<220>

<223> Polynucleotide sequence of 2.12 light chain

<400> 98

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acctgcaccc tgccctccga catcaacgtg cggtactaca acatctactg gtatcagcag	120
aagcccggca gccccccag atacctgctg tactactact ccgactccca caagggccag	180
ggctccggcg tgccctccag attctccggc tccaaggacg tgtccaccaa ctccggcatc	240
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agcaacggca gcggcgtgtt cggcggaggc acccagctga ccgtcctagg tcagcccaag	360
gccgctccca gcgtgaccct gttcccccca agcagcgagg aactgcaggc caacaaggcc	420
accctggtgt gcctgatcag cgacttctac cctggggccg tgaccgtggc ctggaaggcc	480
gatagcagcc ctgtgaaggc cggcgtggaa accaccaccc cctccaagca gagcaacaac	540
aaatacgccg ccagcagcta cctgtccctg acccccgagc agtggaagtc ccaccggtcc	600
tacagctgcc aggtgacaca cgagggcagc accgtggaaa agaccgtggc cccaccgag	660
tgcagc	666

<210> 99

<211> 642

<212> DNA

<213> Artificial

<220>

<223> Polynucleotide sequence of Anti-CD138 kappa light chain

<400> 99

gacatccaga tgaccagag cacatcctct ctgagcgcct ccctgggcca tcgcgtgact	60
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gacggaaccg tcgagctgct catctattac acatctacgc tgcaaagcgg cgtgccttcc	180
aggttctcag ggagcggttc cggaactgat tactctctga ccattagcaa tctcgaacca	240
gaagacatcg gcacatatta ctgtcagcag tactccaagc tgccccggac ttttggggga	300
ggcaccaaac tggagatcaa gcgtacggtg gcggcgccca gcgtgttcat cttcccaccc	360
agcgacgagc agctgaagtc cggcacagcc agcgtggtgt gcctgctgaa caacttctac	420
ccccgcgagg ccaaggtgca gtggaaggtg gacaacgccc tgcaagcgg caacagccag	480
gaaagcgtga ccgagcagga cagcaaggac tccacctaca gcctgagcag caccctgacc	540
ctgagcaagg ccgactacga gaagcacaag gtgtacgcct gcgaagtgac ccaccagggc	600
ctgtccagcc ccgtgaccaa gagcttcaac cggggcgagt gc	642

<210> 100

<211> 1347

<212> DNA

<213> Artificial

<220>

AU15 50654

<223> Polynucleotide sequence of Anti-CD138 IgG4 (S228P)

<400> 100
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tcctgcaaag ctaccggcta cacattcagc aactattgga ttgagtgggt gaagcagcgc 120
ccagggcacg gtctggagtg gatcggagag atcctgccag gcaccgggag gactattttac 180
aatgaaaagt ttaaaggaaa ggccacattc accgcagaca tctctagcaa cactgttcaa 240
atgcagctct cctctctgac ctccgaggat agcgccgtgt attactgtgc tcggagagac 300
tactatggca atttttacta tgctatggat tactggggac agggcacatc tgtgaccgtc 360
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aagacctaca cctgtaacgt ggaccacaag cccagcaaca ccaaggtgga caagcgggtg 660
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gacagcgacg gcagcttctt cctgtactcc cggctgaccg tggacaagag ccggtggcag 1260
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aagtcctga gcctgagcct gggcaag 1347

<210> 101
<211> 1341
<212> DNA
<213> Artificial

<220>
<223> Polynucleotide sequence of Anti-HLA IgG4 (S228P)

<400> 101
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acttgaccg tgtccggatt cagcctgacc tcatacggag tgcattgggt gcggcagcct 120
cccgggaaag gactggagtg gctcggagtc atttgggtccg gtggatcaac tgactacaat 180
gccgctttca tcagcaggct gagcattcgg aaggacaact ctaagagcca agtgttcttc 240
aagatgaact cactccaggc cgatgacacc gccatctact attgtgccag aaccttcacc 300

AU15 50654

accagcacct	ctgcatggtt	tgcatactgg	ggccagggca	ctcttgtgac	cgtgtcagct	360
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agcacagccg	ccctgggctg	cctgggtgaaa	gactacttcc	ccgagcccgt	caccgtgtcc	480
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cgggtggtgt	ccgtgctgac	cgtgctgcac	caggactggc	tgaacggcaa	agagtacaag	960
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<210> 102
 <211> 645
 <212> DNA
 <213> Artificial

<220>
 <223> Polynucleotide sequence of Anti-HLA VK

<400> 102	
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cccgaagttc	ctcctggtgt
cagctggtga	tcgggtgacc
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120	
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gctacaccgg	cgtgcccgac
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gccaccctg	gactttcggg
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gtccggcaca	gccagcgtgg
tgtgcctgct	gaacaacttc
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ggacagcaag	gactccacct
acagcctgag	cagcaccctg
540	
accctgagca	aggccgacta
cgagaagcac	aaggtgtacg
cctgcgaagt	gaccaccag
600	
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caagagcttc	aaccggggcg
agtgc	
645	

<210> 103
 <211> 1203
 <212> DNA
 <213> Artificial

<220>
 <223> Polynucleotide sequence of OPG-Fc

<400> 103
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 ccgaaagata ccctgatgat tagccgcacc ccggaagtga cctgcgtggt ggtggatgtg 660
 agcatgaag atccggaagt gcagtttaac tggatatgtg atggcgtgga agtgcataac 720
 gcgaaaacca aaccgcgcga agaacagttt aacagcacct ttcgcgtggt gagcgtgctg 780
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 ccggaaaaca actataaaac caccgcccg atgctggata gcgatggcag cttttttctg 1080
 tatagcaaac tgaccgtgga taaaagccgc tggcagcagg gcaacgtgtt tagctgcagc 1140
 gtgatgcatg aagcgtgca taaccattat acccagaaaa gcctgagcct gagcccgggc 1200
 aaa 1203

<210> 104
 <211> 1350
 <212> DNA
 <213> Artificial

<220>
 <223> Polynucleotide sequence of 10.21 formatted as an IgG1

<400> 104
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 agctgcaagg tgtccggcta caccttcacc gacagcgtga tgaactgggt gcagcaggcc 120
 cctggcaagg gcctggaatg gatgggatgg atcgaccccg agtacggcag aaccgacgtg 180

AU15 50654

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tacaacagcg	gctacggctt	cccctactgg	ggccagggca	caaccgtgac	agtgtcctca	360
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cagcagggca	acgtgttcag	ctgcagcgtg	atgcacgagg	ccctgcacaa	ccactacacc	1320
cagaagtccc	tgagcctgag	ccccggcaag				1350

<210> 105
 <211> 1338
 <212> DNA
 <213> Artificial

<220>
 <223> Polynucleotide sequence of 10.21 IgG2

<400> 105						
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cctggcaagg	gcctggaatg	gatgggatgg	atcgaccccc	agtacggcag	aaccgacgtg	180
gccgagaagt	tccagggcag	agtgaccatc	accgccgaca	ccagcaccga	caccgcctac	240
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tacaacagcg	gctacggctt	cccctactgg	ggccagggca	caaccgtgac	agtgtcctca	360
gccagcacca	agggccccag	cgtgttcccc	ctggccccct	gcagcagaag	caccagcgag	420
agcacagccg	ccctgggctg	cctggtgaag	gactacttcc	ccgagcccgt	gacagtgagc	480
tggaacagcg	gagccctgac	ctccggtgta	cacaccttcc	ccgccgtgct	gcagagcagc	540

AU15 50654

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aagtgtgctg	tggagtgtccc	cccctgtccc	gccccccag	tggccggacc	ctccgtgttt	720
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aaggtctcca	acaagggcct	gccagcccc	atcgagaaaa	ccatcagcaa	gaccaagggc	1020
cagccacggg	agccccaagt	gtataccctg	ccccccagcc	gggaggagat	gaccaagaac	1080
caggtgtccc	tgacctgtct	ggtgaagggc	ttctacccca	gcgacatcgc	cgtggagtgg	1140
gagagcaacg	gccagcccga	gaacaactac	aagaccaccc	cccccatgct	ggacagcgac	1200
ggcagcttct	tcctgtactc	caagctgaca	gtggacaagt	ccaggtggca	gcagggcaac	1260
gtgttcagct	gcagcgtgat	gcacgaggcc	ctgcacaacc	actacacca	gaagagcctg	1320
agcctgtccc	ccggcaag					1338

<210> 106
 <211> 1491
 <212> DNA
 <213> Artificial

<220>
 <223> Polynucleotide sequence of 10.21 IgG3

<400> 106		
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cgtgaagatc		60
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caccttcacc	gacagcgtga	
tgaactgggt	gcagcaggcc	120
cctggcaagg	gcctggaatg	
gatgggatgg	atcgaccccg	
agtacggcag	aaccgacgtg	180
gccgagaagt	tccagggcag	
agtgaccatc	accgccgaca	
ccagcaccga	caccgcctac	240
atggaactga	gcagcctgcg	
gagcgaggac	accgccgtgt	
actactgtgc	ccggaccaag	300
tacaacagcg	gctacggctt	
cccctactgg	ggccagggca	
caaccgtgac	agtgtcctca	360
gcgagcacca	aaggcccag	
cgtgtttccg	ctggcgccgt	
gcagccgcag	caccagcggc	420
ggcaccgcgg	cgctgggctg	
cctggtgaaa	gattattttc	
cggaaccggt	gaccgtgagc	480
tggaacagcg	gcgcgctgac	
cagcggcgctg	catacctttc	
cggcggtgct	gcagagcagc	540
ggcctgtata	gcctgagcag	
cgtggtgacc	gtgccgagca	
gcagcctggg	cacccagacc	600
tataacctgca	acgtgaacca	
taaaccgagc	aacaccaaag	
tggataaacg	cgtggaactg	660
aaaacccccgc	tgggcgatac	
caccataacc	tgcccgcgct	
gcccggaacc	gaaaagctgc	720
gataccccgc	cgccgtgccc	
gcgctgccc	gaaccgaaaa	
gctgcgatac	cccgccgccg	780
tgcccgcgct	gcccggaacc	
gaaaagctgc	gataccccgc	
cgccgtgccc	gcgctgccc	840
gcgcccgaac	tgctgggcgg	
cccagcgtg	tttctgtttc	
cgccgaaacc	gaaagatacc	900

AU15 50654

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ctgatgatta gccgcacccc ggaagtgacc tgcgtggtgg tggatgtgag ccatgaagat      960
ccggaagtgc agtttaaagt gtatgtggat ggcgtggaag tgcataacgc gaaaacacaaa    1020
ccgcgcgaag aacagtttaa cagcaccttt cgcgtggtga gcgtgctgac cgtgctgcat      1080
caggattggc tgaacggcaa agaataataa tgcaaagtga gcaacaaagc gctgccggcg      1140
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accgtggata aaagccgctg gcagcagggc aacattttta gctgcagcgt gatgcatgaa      1440
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<210> 107
 <211> 165
 <212> PRT
 <213> Artificial

<220>
 <223> Glycosylated (T106T) human interferon alpha-2-b comprising
 attenuating mutation A145X where X can be any amino acid selected
 from D, E, G, H, I, K, L, M, N, Q, R, S, T, V, Y

<220>
 <221> VARIANT
 <222> (145)..(145)
 <223> Xaa can be any amino acid selected from D, E, G, H, I, K, L, M,
 N, Q, R, S, T, V, Y

<400> 107

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
 1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
 20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
 35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
 50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
 65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
 85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
 100 105 110

AU15 50654

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Xaa Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160

Leu Arg Ser Lys Glu
165

<210> 108
<211> 165
<212> PRT
<213> Artificial

<220>
<223> Glycosylated (T106T) human interferon alpha-2-b comprising
attenuating mutation R144X where X can be any amino acid selected
from A, D, E, G, H, I, K, L, N, Q, S, T, V, Y

<220>
<221> VARIANT
<222> (144)..(144)
<223> Xaa can be any amino acid selected from A, D, E, G, H, I, K, L,
N, Q, S, T, V, Y

<400> 108

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

AU15 50654

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Xaa
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160

Leu Arg Ser Lys Glu
165

<210> 109
<211> 165
<212> PRT
<213> Artificial

<220>
<223> Glycosylated (T106T) human interferon alpha-2-b comprising
attenuating mutation R33X, where X can be any amino acid selected
from K, A, Q

<220>
<221> VARIANT
<222> (33)..(33)
<223> Xaa can be any amino acid selected from K, A, Q

<400> 109

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Xaa His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160

Leu Arg Ser Lys Glu
165

<210> 110
<211> 164
<212> PRT
<213> Artificial

<220>
<223> Human interferon alpha-2-b comprising with deletion of amino acid at position 106 and comprising attenuating mutation A144X where X, can be any amino acid selected from D, E, G, H, I, K, L, M, N, Q, R, S, T, V, Y

<220>
<221> VARIANT
<222> (144)..(144)
<223> Xaa can be any amino acid selected from D, E, G, H, I, K, L, M, N, Q, R, S, T, V, Y

<400> 110

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Glu Thr Pro Leu Met Lys Glu
100 105 110

Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr
115 120 125

Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg Xaa
130 135 140

Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu
145 150 155 160

Arg Ser Lys Glu

<210> 111
 <211> 450
 <212> PRT
 <213> Artificial

<220>
 <223> VH sequence of 10.21 formatted as an IgG1 incorporating
 substitutions M255Y, S257T, T259E

<400> 111

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1 5 10 15

Thr Val Lys Ile Ser Cys Lys Val Ser Gly Tyr Thr Phe Thr Asp Ser
 20 25 30

Val Met Asn Trp Val Gln Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
 35 40 45

Gly Trp Ile Asp Pro Glu Tyr Gly Arg Thr Asp Val Ala Glu Lys Phe
 50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Asp Thr Ala Tyr
 65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Thr Lys Tyr Asn Ser Gly Tyr Gly Phe Pro Tyr Trp Gly Gln
 100 105 110

Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
 115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
 130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
 145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
 165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
 180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
 195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
 210 215 220

AU15 50654

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Tyr Ile
245 250 255

Thr Arg Glu Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
290 295 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly Lys
450

<210> 112
<211> 446
<212> PRT
<213> Artificial

<220>
<223> VH sequence of 10.21 formatted onto an IgG2 backbone
Page 142

AU15 50654
incorporating substitutions A330S and P331S

<400> 112

Glu	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala	1	5	10	15
Thr	Val	Lys	Ile	Ser	Cys	Lys	Val	Ser	Gly	Tyr	Thr	Phe	Thr	Asp	Ser	20	25	30	
Val	Met	Asn	Trp	Val	Gln	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Met	35	40	45	
Gly	Trp	Ile	Asp	Pro	Glu	Tyr	Gly	Arg	Thr	Asp	Val	Ala	Glu	Lys	Phe	50	55	60	
Gln	Gly	Arg	Val	Thr	Ile	Thr	Ala	Asp	Thr	Ser	Thr	Asp	Thr	Ala	Tyr	65	70	75	80
Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	85	90	95	
Ala	Arg	Thr	Lys	Tyr	Asn	Ser	Gly	Tyr	Gly	Phe	Pro	Tyr	Trp	Gly	Gln	100	105	110	
Gly	Thr	Thr	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	115	120	125	
Phe	Pro	Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	130	135	140	
Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	145	150	155	160
Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	165	170	175	
Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	180	185	190	
Ser	Ser	Asn	Phe	Gly	Thr	Gln	Thr	Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	195	200	205	
Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Thr	Val	Glu	Arg	Lys	Cys	Cys	Val	210	215	220	
Glu	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Pro	Val	Ala	Gly	Pro	Ser	Val	Phe	225	230	235	240
Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	245	250	255	

AU15 50654

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val
290 295 300

Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser
325 330 335

Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445