(12) STANDARD PATENT (11) Application No. **AU 2009313551 B2**
(19) AUSTRALIAN PATENT OFFICE

(54) Title
Anti-DLL4 antibodies and uses thereof

(51) International Patent Classification(s)
C07K 16/22 (2006.01) ***C12N 15/13*** (2006.01)

(21) Application No: **2009313551** (22) Date of Filing: **2009.11.04**

(87) WIPO No: **WO10/054010**

(30) Priority Data

(31) Number	(32) Date	(33) Country
61/211,204	**2009.03.25**	**US**
61/198,764	**2008.11.07**	**US**

(43) Publication Date: **2010.05.14**
(44) Accepted Journal Date: **2015.12.17**

(71) Applicant(s)
Fabrus LLC

(72) Inventor(s)
Smider, Vaughn;Mao, Helen Hongyuan;Bentley, Cornelia A.;Chase, Tyson

(74) Agent / Attorney
Shelston IP Pty Ltd., L 21 60 Margaret St, Sydney, NSW, 2000

(56) Related Art
WO 2008/042236

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 May 2010 (14.05.2010)

PCT

(10) International Publication Number
WO 2010/054010 A1

(51) International Patent Classification:
C07K 16/22 (2006.01) *C12N 15/13* (2006.01)

(21) International Application Number:
PCT/US2009/063303

(22) International Filing Date:
4 November 2009 (04.11.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/198,764 7 November 2008 (07.11.2008) US
61/211,204 25 March 2009 (25.03.2009) US

(71) Applicant *(for all designated States except US)*: **FABRUS LLC** [US/US]; 10777 Science Center Drive, San Diego, CA 92121 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **SMIDER, Vaughn** [US/US]; 7483 Healis Place, San Diego, CA 92129 (US). **MAO, Helen, Hongyuan** [CN/US]; 3571 Overpark Road, San Diego, CA 92130 (US). **BENTLEY, Cornelia, A.** [US/US]; 4359 Robbins Street, San Diego, CA 92122 (US). **CHASE, Tyson** [US/US]; 8430 Capricorn Way, #3, San Diego, CA 92126 (US).

(74) Agents: **SEIDMAN, Stephanie, L.** et al.; K&L Gates LLP, 3580 Carmel Mountain Road, Suite 200, San Diego, CA 92130 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

— *with sequence listing part of description (Rule 5.2(a))*

WO 2010/054010 A1

(54) **Title**: ANTI-DLL4 ANTIBODIES AND USES THEREOF

(57) **Abstract**: Provided herein are anti-DLL4 antibodies and methods of using anti-DLL4 antibodies as therapeutic agents in diseases or disorders associated with DLL4.

ANTI-DLL4 ANTIBODIES AND USES THEREOF

RELATED APPLICATIONS

Benefit of priority is claimed to U.S. Provisional Application Serial No. 61/198,764, entitled "Combinatorial Antibody Libraries and Uses Thereof," filed November 07, 2008, and to U.S. Provisional Application Serial No. 61/211,204, entitled "Combinatorial Antibody Libraries and Uses Thereof," filed March 25, 2009. Where permitted, the subject matter of the above-noted applications is incorporated by reference in its entirety.

This application also is related to International PCT Application No. (Attorney Dkt. No. 3800016-00029/701PC), entitled "Combinatorial Antibody Libaries and Uses Thereof," filed the same day herewith, which claims priority to U.S. Provisional Application No. 61/198,764 and to U.S. Provisional Application No. 61/211,204.

This application also is related to U.S. Provisional Application No. (Attorney Dkt. No. 3800016-00004/p702), entitled "Methods for Affinity-Maturation-Based Antibody Optimization," filed the same day herewith.

Where permitted, the subject matter of each of the above-noted related applications is incorporated by reference in its entirety.

Incorporation by reference of Sequence Listing provided electronically

An electronic version of the Sequence Listing is filed herewith, the contents of which are incorporated by reference in their entirety. The electronic file is 742 kilobytes in size, and titled 703SEQ.PC1.txt.

FIELD OF THE INVENTION

Provided herein are anti-DLL4 antibodies and methods of using anti-DLL4 antibodies as therapeutic agents in diseases or disorders associated with DLL4.

BACKGROUND

Development of a vascular supply is a fundamental requirement for many physiological and pathological processes. For example, the process of angiogenesis, which promotes new blood vessel formation, ensures that actively growing tissues get an adequate blood supply. Angiogenesis, however, also is implicated in the pathogenesis of a variety of disorders. The process of vascular development, including endothelial cell differentiation, proliferation and migration is tightly regulated. For example, members of the Notch-signaling pathway play a role in

2009313551 23 Nov 2015

regulating processes such as cell fate determination, cellular differentiation, proliferation, survival and apoptosis, including in the vascular endothelium. The Notch ligand, Delta-like 4 (DLL4), exhibits highly selective expression in the vascular endothelium. Notch signaling also is involved in a wide variety of human diseases. Thus, there is a need to develop agents that can be used as therapeutics to regulate Notch signaling.

Any discussion of the prior art throughout the specification should in no way be considered as an admission that such prior art is widely known or forms part of common general knowledge in the field.

SUMMARY

According to a first aspect, the invention provides an isolated antibody that specifically binds to human DLL4 or an isolated antigen-binding fragment thereof that specifically binds to human DLL4, wherein the antibody comprises at least one heavy chain variable domain and at least one light chain variable domain, wherein each heavy chain variable domain comprises three complementarity determining regions (CDRs), CDRH1, CDRH2, and CDRH3, and each light chain variable domain comprises three CDRs, CDRL1, CDRL2, and CDRL3, wherein:

a) CDRH3 comprises an amino acid sequence of EEYSSSSAEYKQH (SEQ ID NO:851), wherein CDRH3 contains modifications of CDRH3 set forth in SEQ ID NO:851 and wherein the modifications are S98A/S99P/S100F/H102F, based on kabat numbering;

b) CDRH2 comprises an amino acid sequence of IINPSGGSTSYAQKFQG (SEQ ID NO:844), wherein CDRH2 contains modifications of CDRH2 set forth in SEQ ID NO: 844 and wherein the modifications are I51V/N52L/S53T/G55H, based on kabat numbering;

c) CDRH1 comprises an amino acid sequence of GYTFTSYYMH (SEQ ID NO: 830);

d) CDRL3 comprises an amino acid sequence of QQRSNWPPWT (SEQ ID NO:881);

e) CDRL2 comprises an amino acid sequence of DASNRAT (SEQ ID NO:871), wherein CDRL2 contains modifications of CDRL2 set forth in SEQ ID NO: 871 and wherein the modifications are S52L/A55S or S52L/A55G, based on kabat numbering; and

f) CDRL1 comprises an amino acid sequence of RASQSVSSYLA (SEQ ID NO: 861), wherein CDRL1 contains modifications of CDRL1 set forth in SEQ ID NO: 861 and wherein the modifications are S28N/S30D/S31H, based on kabat numbering.

2009313551 26 Nov 2015

According to a second aspect, the invention provides a composition comprising a carrier and an isolated antibody or antigen-binding fragment according to the invention, wherein the composition is formulated into a formulation for single dose administration or as a sustained release formulation.

According to a third aspect, the invention provides a method of making an anti-DLL4 antibody or antigen-binding fragment, comprising expressing the anti-DLL4 antibody or antigen-binding fragment using a composition comprising a first isolated or recombinant polynucleotide that comprises a coding sequence for a heavy chain variable domain of the antibody or antigen-binding fragment of the invention and a second isolated or recombinant polynucleotide that comprises a coding sequence for a light chain variable domain of the antibody or antigen-binding fragment of the invention, wherein the composition comprises at least one of the following:

a) a first vector that contains the first polynucleotide;

b) a second vector that contains the second polynucleotide;

c) a vector that contains the first and second polynucleotides;

d) a host cell stably transfected with the first polynucleotide, wherein the host cell expresses the first polynucleotide to produce a polypeptide that comprises the heavy chain variable domain of an antibody or antigen-binding fragment encoded by the first polynucleotide;

e) a host cell stably transfected with the second polynucleotide, wherein the host cell expresses the second polynucleotide to produce a polypeptide that comprises the light chain variable domain of an antibody or antigen-binding fragment encoded by the second polynucleotide; and

f) a host cell stably transfected with the first and second polynucleotides, wherein the host cell expresses the first and second polynucleotides to produce a first polypeptide that comprises the heavy chain variable domain of an antibody or antigen-binding fragment encoded by the first polynucleotide and a second polypeptide that comprises the light chain variable domain of an antibody or antigen-binding fragment encoded by the second polynucleotide, and wherein the first and second polypeptides assemble to form an antibody or antigen-binding fragment,

and recovering the antibody or antigen-binding fragment.

2009313551 26 Nov 2015

According to a fourth aspect, the invention provides a method of inhibiting Notch activation, comprising delivering an antibody or antigen-binding fragment according to the invention in an amount that inhibits Notch activation.

According to a fifth aspect, the invention provides use of the antibody or antigen-binding fragment according to the invention in the preparation of a medicament for the treatment of a disease or disorder associated with expression and/or activity of DLL4, wherein the disease or disorder is selected from the group consisting of a tumor, cancer, prostate cancer, pancreatic cancer, colon cancer, lung cancer, breast cancer, atherosclerosis, arthritis, ocular neovascularization, endometriosis, uterine fibroids, pre-eclampsia, and a cell proliferative disorder.

According to a sixth aspect, the invention provides an anti-DLL4 antibody or antigen-binding fragment thereof when produced by the method according to the invention.

According to a seventh aspect, the invention provides a method of treating a disease or disorder associated with expression and/or activity of DLL4, said method comprising administering the antibody or antigen-binding fragment according to the invention, wherein the disease or disorder is selected from the group consisting of a tumor, cancer, prostate cancer, pancreatic cancer, colon cancer, lung cancer, breast cancer, atherosclerosis, arthritis, ocular neovascularization, endometriosis, uterine fibroids, pre-eclampsia, and a cell proliferative disorder.

Unless the context clearly requires otherwise, throughout the description and the claims, the words “comprise”, “comprising”, and the like are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense; that is to say, in the sense of “including, but not limited to”.

Provided herein are anti-DLL4 antibodies or antigen-binding fragments thereof that specifically bind to human DLL4. Anti-DLL4 antibodies include antibodies that have at least one complementarity determining region (CDR) that is a CDRH1, a CDRH2, a CDRH3, a CDRL1, a CDRL2 or a CDRL3. For example, the antibody can contain a heavy chain CDR3 (CDRH3) that has a sequence of amino acids set forth as EEYSSSSAEYKQH (SEQ ID NO:851); RGYSYGYDYFDY (SEQ ID NO:852); EYYDFWSGYYTDYFDY (SEQ ID NO:853); EGYSSSWYDYFDY (SEQ ID NO:854); ANWGDYFDY (SEQ ID NO:855); DDYGGNSDYFDY (SEQ ID NO:856); EGYCSGGSCYS (SEQ ID NO:857); EYYYGSGSYYNDYFDY (SEQ ID NO:858); GCYCSSTSCYADYYYYYGMDV (SEQ ID NO:859); GSCYSYWYFDL (SEQ ID NO:860); or a sequence of amino acids that exhibits at

2009313551 26 Nov 2015

least 65% sequence identity to the sequence of amino acids set forth in any of SEQ ID NOS: 851-860. The antibody can contain a heavy chain CDR2 (CDRH2) that has a sequence of amino acids set forth as IINPSGGSTSYAQKFQG (SEQ ID NO:844); IIYPGDSDTRYSPSFQG (SEQ ID NO:845); RTYYRSKWYNDYAVSVKS (SEQ ID NO:846); EINHSGSTNYNPSLKS (SEQ ID NO:847); INSNAGNGNTKYSQEFQG (SEQ ID NO: 848); WMNPNS GNTGYAQKFQG (SEQ ID NO:849); YIYYSGSTYYNPSLKS (SEQ ID NO:850); or a sequence of amino acids that exhibits at least 65% sequence identity to the sequence of amino acids set forth in any of SEQ ID NOS: 844-850. The antibody can contain a heavy chain CDR1 (CDRH1) that has a sequence of amino acids set forth as GYTFTSYYMH (SEQ ID NO: 830); GYSFTSYWIG (SEQ ID NO:831); GDSVSSNSAA (SEQ ID NO:832); GGSFSGYYWS (SEQ ID NO:833); GYTFTSYAMH (SEQ ID NO:834); GYTFTSYAIN (SEQ ID NO:835); GGSISSGGYY (SEQ ID NO: 836); or a sequence of amino acids that exhibits at least

65% sequence identity to a sequence of amino acids set forth in any of SEQ ID NOS: 831-836, with the proviso that the sequence of amino acids is not GYTFTSYVIN (SEQ ID NO:904); and a sequence of amino acids that exhibits at least 72% sequence identity to the sequence of amino acids set forth in SEQ ID NO:830. The antibody can contain a light chain CDR3 (CDRL3) that has a sequence of amino acids set forth as QQRSNWPPWT (SEQ ID NO:881); VLYMGSGISYV (SEQ ID NO:882); MIWHSSASFV (SEQ ID NO: 883); QQYNNWPPWT (SEQ ID NO: 884); QANSFPPWT (SEQ ID NO:885); QQYGSSPPWT (SEQ ID NO: 886); QQYNSYSPWT (SEQ ID NO:887); MQRIEFPSWT (SEQ ID NO: 888); SSYTSSSTLFV (SEQ ID NO: 889); and QVYESSANFV (SEQ ID NO: 890); and a sequence of amino acids that exhibits at least 65% sequence identity to the sequence of amino acids set forth in any of SEQ ID NOS: 881-890. The antibody can contain a light chain CDR2 (CDRL2) is selected from among a CDRL2 having a sequence of amino acids set forth as DASNRAT (SEQ ID NO:871); STNTRSS (SEQ ID NO: 872); YYSDSSK (SEQ ID NO:873); GASTRAT (SEQ ID NO:874); AASSLQS (SEQ ID NO:875); GASSRAT (SEQ ID NO:876); DASSLGS (SEQ ID NO:877); TLSYRAS (SEQ ID NO:878); EVSNRPS (SEQ IDNO:879); HYSDSDK (SEQ ID NO:880); or a sequence of amino acids that exhibits at least 65% sequence identity to the sequence of amino acids set forth in any of SEQ ID NOS: 871-880. The antibody can contain a light chain CDR1 (CDRL1) that has a sequence of amino acids set forth as RASQSVSSYLA (SEQ ID NO: 861); GLSSGSVSTSYYPS (SEQ ID NO:862); TLRSGINLGSYRIF (SEQ ID NO:863); RASQSVSSNLA (SEQ ID NO:864); RASQGISSWLA (SEQ ID NO:865); RASQVSSSYLA (SEQ ID NO:866); RASQSISSWLA (SEQ ID NO:867); RSSQSLLDSDDGNTYLD (SEQ ID NO:868); TGTSSDVGGTNYVS (SEQ ID NO:869); TLSSDLSVGGKNMF (SEQ ID NO:870); or a sequence of amino acids that exhibits at least 65% sequence identity to the sequence of amino acids set foth in any of SEQ ID NOS: 861-870. The antibodies provided herein can contain 2, 3, 4, 5 or 6 different CDRs that is a CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 or CDRL3.

The antibodies provided herein includethose are are a full-length antibody or an antibody fragment. For example, the antibody fragment can be a Fab, Fab', F(ab')$_2$, single-chain Fvs (scFv), Fv, dsFv, diabody, Fd and Fd' fragments, Fab

fragments, Fd fragments, scFv fragments, or a scFab fragments. Generally, the antibody is a a Fab or is a full-length IgG.

The antibodies provided herein include antibodies where the CDR set forth in any of SEQ ID NOS:. 830-836 and 844-890 is modified by amino acid replacement, addition or deletion. In any of the antibodies provided herein, the CDR (e..g a CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, or CDRL3) exhibits 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence identity to the sequence of amino acids set forth in any of SEQ ID NOS:. 830-836 and 844-890.

In one example, an anti-DLL4 provided herein contains modification of a CDRH1 set forth in SEQ ID NO: 830 that has one or more amino acid replacement(s) at positions T28, F29, T30, S31 and Y33, based on kabat numbering. For example, the antibody can have one or more amino acid replacement(s) that is T28A, F29A, T30A, S31A and/or Y33A.

In another example, an anti-DLL4 antibody provided herein contains modification of a CDRH1 set forth in SEQ ID NO:831 that has one or more amino acid replacement(s) at positions S28, F29, T30, W33, I34 and G35, based on kabat numbering. For example, the antibody can have one or more amino acid replacement(s) that is S28A, S28R, S28K, S28N, F29A, T30A, W33A, I34A, G35T, G35A and/or G35V.

In an additional example, an anti-DLL4 antibody provided herein contains modification of a CDRH2 set forth in SEQ ID NO: 844 that has one or more amino acid replacement(s) at positions I50, I51, N52, P52a, S53, G54, G55, G56, T57 and S58, based on kabat numbering. For example, the one or more amino acid replacement(s) can be I50A, I50T, I51A, I51T, I51V, I51N, I51R, I51W, I51S, I51G, I51V, I51E, I51H, I51Y, N52A, N52V, N52G, N52T, N52P, N52L, N52W, N52Y, N52V, N52S, N52Q, N52K, P52aA, P52aM, P52aE, P52aH, P52aY, P52aT, P52aN, P52aR, P52aW, P52aS, P52aG, S53A, S53I, S53E, S53R, S53G, S53T, S53L, S53V, S53N, S53P, G54A, G54W, G54D, G55A, G55V, G55E, G55S, G55K, G55T, G55L, G55R, G55H, G55I, G55W, S58A, T57A and/or S58A. In particular, an antibody provided herein contains amino acid replacement(s) I51V/N52L/S53T/G55H, N52L/S53T/G55H, I51E/N52L/S53T/G55H or I51N/N52L/S53T/G55H.

In a further example, an anti-DLL4 antibody provided herein contains modification of a CDRH2 set forth in SEQ ID NO:845 that has one or more amino acid replacement(s) at positions I50, I51, Y52, P52a, D54, S55, D56 and/or T57, based on kabat numbering. The one or more amino acid replacement(s) can be I50A, I51A, Y52A, P52aA, D54A, S55G, D56A, T57D and/or T57A.

In another example, an anti-DLL4 antibody provided herein contains a modification of a CDRH3 set forth in SEQ ID NO:851 that has one or more amino acid replacement(s) at positions E96, Y97, S98, S99, S100, S100a, A100b, E100c, Q101 and/or H102, based on kabat numbering. The one or more amino acid replacement(s) can be E96A, Y97A, S98A, S98Q, S98V, S98I, S98G, S99P, S99A, S99L, S99W, S99F, S99N, S99H, S99C, S99G, S100F, S100A, S100G, S100C, S100H, S100L, S100R, S100aA, A100bE, E100cA, Q101A, H102A, H102S, H102F and/or H102Y. In particular, the amino acid replacement(s) is S98A/S99P/S100F, S98A/S99P/S100F/H102F or S98A/S99P/S100F/H102Y.

In an example of an anti-DLL4 antibody provided herein, the antibody contains a modification of a CDRH3 set forth in SEQ ID NO: 852 that has one or more amino acid replacement(s) at positions R95, G96, Y97, S98, Y99, G100, Y100a, D100b, and/or D101, based on kabat numbering. The one or more amino acid replacement(s) is selected from among R95A, G96K, G96R, G96L, G96D, G96T, Y97A, Y97H, S98A, Y99A, G100A, G100D, G100L, G100P, G100R, G100M, G100K, G100S, G100R, G100T, Y100aA, D100bA and/or D101A. In particular, the amino acid replacement(s) is G96K/G100T.

In another example, the antibody contains a modification of a CDRL1 set forth in SEQ ID NO:861 that has one or more amino acid replacement(s) at positions R24, Q27, S28, S30, S31 and/or Y32, based on kabat numbering. The one or more amino acid replacement(s) is selected from among R24G, Q27L, S28P, S28G, S28K, S28V, S28F, S28P, S28T, S28L, S28Q, S28A, S28N, S28H, S28I, S28R, S28W, S28M, S28E, S30N, S30W, S30R, S30L, S30C, S30D, S30L, S30T, S30P, S30Y, S30Q, S30A, S30G, S30V, S31K, S31T, S31N, S31K, S31L, S31M, S31F, S31I, S31V, S31H, S31A, S31P, S31D, S31R, S31Y, S31Q, S31E, S31G, Y32V and/or Y32S. In particular, the antibody has the amino acid replacement(s) is S28N/S30D/S31H.

In an additional example, an anti-DLL4 antibody provided herein contains a modification of a CDRL1 set forth in SEQ ID NO:862 that has one or more amino acid replacement(s) at positions G24, L25, S26, S27, G27a, S27b, V27c, S28, T29, S30, Y31, Y32, P33, based on kabat numbering. The one or more amino acid replacement(s) are selected from among G24A, G24R, G24L, L25A, S26A, S27A, G27aA, S27bA, V27cA, S28A, T29A, S30A, Y31A, Y32A and/or P33A.

In a further example, an anti-DLL4 antibody provided herein contains a modification of a CDRL2 set forth in SEQ ID NO:871 that has one or more amino acid replacement(s) at positions D50, A51, S52, N53, R54, A55 and/or T56, based on kabat numbering. The one or more amino acid replacement(s) are selected from among D50A, A51T, S52A, S52L, S52T, S52R, S52S, S52W, S52N, S52P, S52M, N53A, N53E, N53G, N53M, N53C, N53H, N53P, R54A, A55T, A55R, A55C, A55S, A55G and T56A. In particular, the amino acid replacement(s) are S52L/A55S or S52L/A55G.

In an example of an anti-DLL4 antibody provided herein, the antibody contains a modification of a CDRL2 set forth in SEQ ID NO:872 that has one or more amino acid replacement(s) at positions S50, T51, N52, T53, R54, S55 and/or S56, based on kabat numbering. The one or more amino acid replacement(s) are selected from among S50A, S50F, S50G, S50C, S50R, S50L, S50M, S50V, S50P, S50T, S50H, S50Q, S50N, S50K, S50D, S50E, S50W, T51A, T51F, T51L, T51I, T51M, T51V, T51S, T51P, T51Y, T51H, T51Q, T51N, T51K, T51D, T51E, T51W, T51R, T51G, N52A, T53A, R54A, R54I, R54Y, R54D, R54G, S55A, S55F, S55L, S55I, S55M, S55V, S55P, S55T, S55Y, S55H, S55Q, S55N, S55K, S55D, S55E, S55W, S55R, S55G and/or S56A.

In an additional example, an anti-DLL4 antibody provided herein contains a modification of a CDRL3 set forth in SEQ ID NO:881 that has one or more amino acid replacement(s) at positions R91, S92, N93 and/or W94, based on kabat numbering. The one or more amino acid replacements are selected from among R91P, R91L, R91G, S92P, S92A, S92Q, S92V, S92T, S92R, S92G, S92V, S92M, S92N, S92C, N93Y, N93S, N93H, N93Q, W94R, W94S, W94T, W94L, W94P and W94M.

In a further example, an anti-DLL4 antibody provided herein contains a modification of a CDRL3 set forth in SEQ ID NO:882 that has one or more amino acid replacement(s) at positions V89, L90, Y91, M92, G93, S94, G95, I95a and/or S95b, based on kabat numbering. The one or more amino acid replacement(s) are selected from among V89A, V89P, V89T, V89S, V89L, V89R, V89C, V89E, V89W, V89N, V89I, V89G, V89H, L90A, Y91A, M92A, M92E, M92S, M92G, M92L, M92P, M92V, M92D, M92R, M92N, M92T, M92F, G93A, S94A, S94W, S94G, S94P, S94R, S94L, S94M, S94E, S94V, G94A, I95aA and/or S95bA. In particular, the amino acid replacement(s) are M92R/S94M or V89L/S94P.

In any of the above antibodies provided herein, the antibody can contain at least two CDRs selected from among any of the CDRH3; a CDRH2; a CDRH1; a CDRL3; a CDRL2; and a CDRL1. For example, the antibody can contain a variable heavy chain containing at least one CDR that is any of the provided CDRH3; a CDRH2; a CDRH1; and a variable light chain containing at least one CDR that is any of the provided CDRL3; a CDRL2; and a CDRL1. In another example, antibodies provided herein can contain a variable heavy chain containing at least two CDRs that is any of the provided CDRH3; a CDRH2; a CDRH1; and a variable light chain containing at least one CDR that is a CDRL3; a CDRL2; and a CDRL1. In a further example, an anti-DLL4 antibody provided herein contains a variable heavy chain containing at least two CDRs that is any of the provide CDRH3; a CDRH2; a CDRH1; and contains a variable light chain containing at least two CDRs that is any of the provided CDRL3; a CDRL2; and a CDRL1.

Included among anti-DLL4 antibodies provided herein is an antibody that contains a CDRH2 set forth in SEQ ID NO: 844 that contains an amino acid replacement G55H; and a CDRH3 set forth in SEQ ID NO:851 that contains an amino acid replacement S98A/S99P/S100F/H102F. In another example, an anti-DLL4 antibody provided herein contains a CDRH3 set forth in SEQ ID NO:851 that contains an amino acid replacement S98A/S99P/S100F/H102F; and a CDRL1 set forth in SEQ ID NO: 861 that contains an amino acid replacement S28N/S30D/S31H. In a further example, an anti-DLL4 antibody provided herein contains a CDRH2 set forth in SEQ ID NO:844 that contains an amino acid replacement I51V/N52L/S53T/G55H; a CDRH3 set forth in SEQ ID NO:851 that contains an

amino acid replacement S98A/S99P/S100F/H102F; and a CDRL1 set forth in SEQ ID NO: 861 that contains an amino acid replacement S28N/S30D/S31H. In an additional example, an anti-DLL4 antibody provided herein contains a CDRH2 set forth in SEQ ID NO:844 that contains an amino acid replacement I51V/N52L/S53T/G55H; a CDRH3 set forth in SEQ ID NO:851 that contains an amino acid replacement S98A/S99P/S100F/H102F; a CDRL1 set forth in SEQ ID NO: 861 that contains an amino acid replacement S28N/S30D/S31H; and a CDRL2 set forth in SEQ ID NO:871 that contains an amino acid replacement S52L/A55S.

Further included among anti-DLL4 antibodies provided here is an antibody that contains a CDRH1 set forth in SEQ ID NO:831 that contains an amino acid replacement S28R/G35V; a CDRH3 set forth in SEQ ID NO:852 that contains an amino acid replacement G96K/G100T; and a CDRL3 set forth in SEQ ID NO:882 that contains an amino acid replacement M92R/S94M. In another example, an anti-DLL4 antibody provided herein contains a CDRH1 set forth in SEQ ID NO:831 that contains an amino acid replacement S28R/G35V; a CDRH3 set forth in SEQ ID NO:852 that contains an amino acid replacement G96K/G100T; and a CDRL3 set forth in SEQ ID NO:882 that contains an amino acid replacement V89L/S94P. In an additional example, an anti-DLL4 antibody provided herein contains a CDRH1 set forth in SEQ ID NO:831 that contains an amino acid replacement S28R/G35V; a CDRH3 set forth in SEQ ID NO:852 that contains an amino acid replacement G96K/G100T; a CDRL2 set forth in SEQ ID NO:872 that contains an amino aicd replacement S50G; and a CDRL3 set forth in SEQ ID NO:882 that contains an amino acid replacement V89L/S94P.

In any of the above anti-DLL4 antibodies provided herein, the antibody can further contain one or more amino acid replacements in a framework region of the antibody. For example, the antibody can have 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more amino acid replacements in a framework region of the antibody. In one example, the variable light chain an anti-DLL4 antibody provided herein includes one or more amino acid replacements and the amino acid replacement is at position 62 or 76, based on kabat numbering. The amino acid replacement(s) can be amino acid replacements F62L, S76E, S76Q, S76P, S76L, S76T, S76G, S76A, S76Y, S76N, T76S, T76E, T76Y and/or T76M. In another example, the variable heavy chain of an

anti-DLL4 antibody provided herein includes one or more amino acid replacements at amino acid position 24 and/ or 82a, based on kabat numbering. For example, the amino acid replacement(s) can be G24T, G24L G24A, and/or S82aT.

The anti-DLL4 antibodies provided herein exhibit at least a binding affinity that is 10^{-6} M, 10^{-7} M, 10^{-8} M, 10^{-9} M, 10^{-10} M, 10^{-11} M or 10^{-12} M or lower as measured by surface plasmon resonance (SPR).

The anti-DLL4 antibodies provided herein include antibodies that are germline-derived or a modified form thereof. For example, an antibody provided herein includes a VH chain encoded by a sequence of nucleotides compiled from a V_H, D_H and J_H germline segment or modified germline segments thereof where the V_H germline segment is an IGHV1, an IGHV4, an IGHV5 or an IGHV6 or genes and alleles thereof; the D_H germline segment is an IGHD6, an IGHD5, an IGHD4, an IGHD2, an IGHD3, or an IGHD7 or genes and alleles thereof; and the J_H germline segment is an IGHJ1, an IGHJ2, an IGHJ4, or an IGHJ6 or genes and alleles thereof. Antibodies provided herein also include those having a VL chain encoded by a sequence of nucleotides compiled from a V_κ and J_κ or V_λ and J_λ germline segments where the V_κ germline segment is an IGKV1, an IGKV2, or an IGKV3 and the Jκ is a IGKJ1 or genes and alleles thereof; or the V_λ germline segment is an IGLV2, an IGLV8, an IGLV11 or an IGLV5 and the J_λ germline segment is a IGLJ1 or a IGLJ4 or genes and alleles thereof, wherein the antibody binds DLL4 and/or modulates an activity of DLL4.

For example, anti-DLL4 antibodies provided herein include those that have a V_H germline segment that is an IGHV1-3*01, an IGHV1-3*02, an IGHV1-8*01, an IGHV1-46*01, an IGHV1-46*02, an IGHV1-46*03, an IGHV4-31*01, an IGHV4-31*02, an IGHV4-31*03, an IGHV4-31*04, an IGHV4-31*05, an IGHV4-31*06, an IGHV4-31*07, an IGHV4-31*08, an IGHV4-31*09, an IGHV4-31*10, an IGHV4-34*01, an IGHV4-34*02, an IGHV4-34*03, an IGHV4-34*04, an IGHV4-34*05, an IGHV4-34*06, an IGHV4-34*07, an IGHV4-34*08, an IGHV4-34*09, an IGHV4-34*10, an IGHV4-34*11, an IGHV4-34*12, an IGHV4-34*13, an IGHV5-51*01, an IGHV5-51*02, an IGHV5-51*03, an IGHV5-51*04, an IGHV5-51*05, an IGHV6-1*01, an IGHV6-1*02, or is a modified germline segment thereof; a D_H germline segment that is an IGHD2-2*01, an IGHD2-2*02, an IGHD2-15*01, an IGHD4-

23*01, an IGHD6-6*01, an IGHD6-13*01, IGHD5-18*01, IGHD3-3*01, an IGHD3-3*02, an IGHD3-10*01, an IGHD3-10*02, or an IGHD7-27*01, or is a modified germline segment thereof; a J_H germline segment that is an IGHJ1*01, an IGHJ2*01, an IGHJ4*01, an IGHJ4*02, an IGHJ4*03, an IGHJ6*01, an IGHJ6*02, an IGHJ6*03 or an IGHJ6*04 or is a modified germline segment thereof; a Vκ germline segment that is an IGKV1-5*01, an IGKV1-5*02, an IGKV1-5*03, an IGKV1-12*01, an IGKV1-12*02, an IGKV2-D-40*01, an IGKV3-11*01, an IGKV3-11*02, an IGKV3-15*01, an IGKV3-20*01 or an IGKV3-20*02 or is a modified germline segment thereof; a Jκ germline segment that is a IGKJ1*01 or is a modified germline segment thereof; a V_λ germline segment that is an IGLV2-14*01, an IGLV2-14*02, an IGLV2-14*03, an IGLV2-14*04, an IGLV8-61*01, an IGLV8-61*02, an IGLV8-61*03, an IGLV5-48*01, or an IGLV11-55*01 or is a modified germline segment thereof; and/or a J_λ germline segment that is a IGLJ1*01 or IGLJ4*01 or is a modified germline segment thereof.

The anti-DLL4 antibody provided herein includes an antibody or portion thereof containing: a) a VH chain encoded by a sequence of nucleotides compiled from an IGHV1-46*01, an IGHD6-6*01 and an IGHJ1*01 germline segments or modified forms thereof and a VL chain encoded by a sequence of nucleotides compiled from an IGKV3-11*01 and an IGKJ1*01 germline segments or modified forms thereof; b) a VH encoded by a sequence of nucleotides compiled from an IGHV5-51*03, an IGHD5-18*01 and an IGHJ4*01 germline segments or modified forms thereof and a VL chain encoded by a sequence of nucleotides compiled from an IGLV8-61*01 and an IGLJ1*01 germline segments or modified forms thereof; c) a VH chain encoded by a sequence of nucleotides compiled from an IGHV6-1*01, an IGHD3-3*01 and an IGHJ4*01 germline segments or modified forms thereof and a VL chain encoded by a sequence of nucleotides compiled from an IGLV5-48*01 and an IGLJ4*01 germline segments or a modified forms thereof; d) a VH chain encoded by a sequence of nucleotides compiled from an IGHV1-46*01, an IGHD6-13*01 and an IGHJ4*01 germline segments or modified forms thereof and a VL chain encoded by a sequence of nucleotides compiled from an IGKV3-15*01 and an IGKJ1*01 germline segments or modified forms thereof; e) a VH chain encoded by a sequence of nucleotides compiled from an IGHV4-34*01, an IGHD7-27*01 and an IGHJ4*01

germline segments or modified forms thereof and a VL chain encoded by a sequence of nucleotides compiled from an IGKV1-12*01 and an IGKJ1*01 germline segments or modified forms thereof; f) a VH chain encoded by a sequence of nucleotides compiled from an IGHV1-46*01, an IGHD6-13*01 and an IGHJ4*01 germline segments or modified forms thereof and a VL chain encoded by a sequence of nucleotides compiled from an IGKV3-20*01 and an IGKJ1*01 germline segments or modified forms thereof; g) a VH chain encoded by a sequence of nucleotides compiled from an IGHV1-3*02, an IGHD4-23*01 and an IGHJ4*01 germline segments or modified forms thereof and a VL chain encoded by a sequence of nucleotides compiled from an IGKV1-5*01 and an IGKJ1*01 germline segments or modified forms thereof; h) a VH chain encoded by a sequence of nucleotides compiled from an IGHV1-46*01, an IGHD2-15*01 and an IGHJ2*01 germline segments or modified forms thereof and a VL chain encoded by a sequence of nucleotides compiled from an IGKV1-5*01 and an IGKJ1*01 germline segments or modified forms thereof; i) a VH chain encoded by a sequence of nucleotides compiled from an IGHV1-46*01, an IGHD3-10*01 and an IGHJ4*01 germline segments or modified forms thereof and a VL chain encoded by a sequence of nucleotides compiled from an IGKV1-5*01 and an IGKJ1*01 germline segments or modified forms thereof; j) a VH chain encoded by a sequence of nucleotides compiled from an IGHV1-8*01, an IGHD2-2*01 and an IGHJ6*01 germline segments or modified forms thereof and a VL chain encoded by a sequence of nucleotides compiled from an IGKV1-5*01 and an IGKJ1*01 germline segments or modified forms thereof; k) a VH chain encoded by a sequence of nucleotides compiled from an IGHV1-46*01, an IGHD6-13*01 and an IGHJ4*01 germline segments or modified forms thereof and a VL chain encoded by a sequence of nucleotides compiled from an IGKV2D-40*01 and an IGKJ1*01 germline segments or modified forms thereof; l) a VH chain encoded by a sequence of nucleotides compiled from an IGHV4-34*01, an IGHD7-27*01 and an IGHJ4*01 germline segments or modified forms thereof and a VL chain encoded by a sequence of nucleotides compiled from an IGLV2-14*01 and an IGLJ4*01 germline segments or modified forms thereof; m) a VH chain encoded by a sequence of nucleotides compiled from an IGHV4-31*02, an IGHD2-15*01 and an IGHJ2*01 germlien

segments or modified forms thereof and a VL chain encoded by a sequence of nucleotides compiled from an IGLV2-14*01 and an IGLJ4*01 germline segments or modified forms thereof; and n) a VH chain encoded by a sequence of nucleotides compiled from an IGHV4-34*01, an IGHD7-27*01 and an IGHJ4*01 germline segments or modified forms thereof and a VL chain encoded by a sequence of nucleotides compiled from an IGLV11-55*01 and an IGLJ4*01 germline segments or a modified form thereof.

For example, exemplary of anti-DLL4 antibodies provided herein is an antibody containing a) a VH chain comprising a sequence of amino acids set forth in SEQ ID NO: 131 and a VL chain comprising a sequence of amino acids set forth in SEQ ID NO:141; b) a VH chain comprising a sequence of amino acids set forth in SEQ ID NO: 132 and a VL chain comprising a sequence of amino acids set forth in SEQ ID NO:142; c) a VH chain comprising a sequence of amino acids set forth in SEQ ID NO: 133 and a VL chain comprising a sequence of amino acids set forth in SEQ ID NO:143; d) a VH chain comprising a sequence of amino acids set forth in SEQ ID NO: 135 and a VL chain comprising a sequence of amino acids set forth in SEQ ID NO:145; e) a VH chain comprising a sequence of amino acids set forth in SEQ ID NO: 137 and a VL chain comprising a sequence of amino acids set forth in SEQ ID NO:146; f) a VH chain comprising a sequence of amino acids set forth in SEQ ID NO: 135 and a VL chain comprising a sequence of amino acids set forth in SEQ ID NO:144; g) a VH chain comprising a sequence of amino acids set forth in SEQ ID NO: 138 and a VL chain comprising a sequence of amino acids set forth in SEQ ID NO:147; h) a VH chain comprising a sequence of amino acids set forth in SEQ ID NO: 136 and a VL chain comprising a sequence of amino acids set forth in SEQ ID NO:147; i) a VH chain comprising a sequence of amino acids set forth in SEQ ID NO: 134 and a VL chain comprising a sequence of amino acids set forth in SEQ ID NO:147; j) a VH chain comprising a sequence of amino acids set forth in SEQ ID NO: 139 and a VL chain comprising a sequence of amino acids set forth in SEQ ID NO:147; k) a VH chain comprising a sequence of amino acids set forth in SEQ ID NO: 135 and a VL chain comprising a sequence of amino acids set forth in SEQ ID NO:148; l) a VH chain comprising a sequence of amino acids set forth in SEQ ID NO: 137 and a VL chain comprising a sequence of amino acids set forth in

SEQ ID NO:149; m) a VH chain comprising a sequence of amino acids set forth in SEQ ID NO: 140 and a VL chain comprising a sequence of amino acids set forth in SEQ ID NO:149; or n) a VH chain comprising a sequence of amino acids set forth in SEQ ID NO: 137 and a VL chain comprising a sequence of amino acids set forth in SEQ ID NO:150.

In particular, an anti-DLL4 antibody provided herein contains a) a VH chain comprising a sequence of amino acids set forth in SEQ ID NO: 155 and a VL chain comprising a sequence of amino acids set forth in SEQ ID NO:141; b) a VH chain comprising a sequence of amino acids set forth in SEQ ID NO: 156 and a VL chain comprising a sequence of amino acids set forth in SEQ ID NO:141; or c) a VH chain comprising a sequence of amino acids set forth in SEQ ID NO: 385 and a VL chain comprising a sequence of amino acids set forth in SEQ ID NO:142.

In one example, anti-DLL4 antibodies provided herein have a binding affinity that is at least 10^{-9} M or lower as measured by surface plasmon resonance (SPR). Such antibodies include an antibody that contains a) a VH chain comprising a sequence of amino acids set forth in SEQ ID NO: 384 and a VL chain comprising a sequence of amino acids set forth in SEQ ID NO:142; b) a VH chain comprising a sequence of amino acids set forth in SEQ ID NO: 414 and a VL chain comprising a sequence of amino acids set forth in SEQ ID NO:142; c) a VH chain comprising a sequence of amino acids set forth in SEQ ID NO: 433 and a VL chain comprising a sequence of amino acids set forth in SEQ ID NO:142; d) a VH chain comprising a sequence of amino acids set forth in SEQ ID NO: 433 and a VL chain comprising a sequence of amino acids set forth in SEQ ID NO:479; e) a VH chain comprising a sequence of amino acids set forth in SEQ ID NO: 433 and a VL chain comprising a sequence of amino acids set forth in SEQ ID NO:537; f) a VH chain comprising a sequence of amino acids set forth in SEQ ID NO: 433 and a VL chain comprising a sequence of amino acids set forth in SEQ ID NO:536; g) a VH chain comprising a sequence of amino acids set forth in SEQ ID NO: 131 and a VL chain comprising a sequence of amino acids set forth in SEQ ID NO:141; h) a VH chain comprising a sequence of amino acids set forth in SEQ ID NO: 151 and a VL chain comprising a sequence of amino acids set forth in SEQ ID NO:141; i) a VH chain comprising a sequence of amino acids set forth in SEQ ID NO: 155 and a VL chain comprising a

sequence of amino acids set forth in SEQ ID NO:141; j) a VH chain comprising a sequence of amino acids set forth in SEQ ID NO: 156 and a VL chain comprising a sequence of amino acids set forth in SEQ ID NO:141; k) a VH chain comprising a sequence of amino acids set forth in SEQ ID NO: 157 and a VL chain comprising a sequence of amino acids set forth in SEQ ID NO:141; l) a VH chain comprising a sequence of amino acids set forth in SEQ ID NO: 155 and a VL chain comprising a sequence of amino acids set forth in SEQ ID NO:266; m) a VH chain comprising a sequence of amino acids set forth in SEQ ID NO: 219 and a VL chain comprising a sequence of amino acids set forth in SEQ ID NO:141; n) a VH chain comprising a sequence of amino acids set forth in SEQ ID NO: 156 and a VL chain comprising a sequence of amino acids set forth in SEQ ID NO:343; o) a VH chain comprising a sequence of amino acids set forth in SEQ ID NO: 239 and a VL chain comprising a sequence of amino acids set forth in SEQ ID NO:343; p) a VH chain comprising a sequence of amino acids set forth in SEQ ID NO: 239 and a VL chain comprising a sequence of amino acids set forth in SEQ ID NO:370; or q) a VH chain comprising a sequence of amino acids set forth in SEQ ID NO: 134 and a VL chain comprising a sequence of amino acids set forth in SEQ ID NO:147.

In particular, included among anti-DLL4 antibodies provided herein is an antibody containing a VH chain comprising a sequence of amino acids set forth in SEQ ID NO: 433 and a VL chain comprising a sequence of amino acids set forth in SEQ ID NO:537. In another example, a DLL4 antibody provided herein contains a VH chain comprising a sequence of amino acids set forth in SEQ ID NO: 433 and a VL chain comprising a sequence of amino acids set forth in SEQ ID NO:536. In a further example, an anti-DLL4 antibody provided herein contains a VH chain comprising a sequence of amino acids set forth in SEQ ID NO:239 and a VL chain comprising a sequence of amino aicds set forth in SEQ ID NO:343. In an additional example, an anti-DLL4 antibody provided herein contains a VH chain comprising a sequence of amino acids set forth in SEQ ID NO:239 and a VL chain comprising a sequence of amino acids set forth in SEQ ID NO:370.

Among the anti-DLL4 antibodies provided herein are those that exhibit affinity for recombinant human DLL4. In some examples, the antibody exhibits

affinity for human DLL4 expressed on the surface of a cell. For example, anti-DLL4 antibodies can bind to DLL4 expressed on an endothelial cell.

Also included among anti-DLL4 antibodies provided herein are those that modulates an activity of DLL4. For example, anti-DLL4 antibodies provided herein can inhibits Notch activation. Anti-DLL4 antibodies include those that are agonists and those that are antagonist antibodies.

Futher included among anti-DLL4 antibodies provided herein are those that specifically binds to an epitope in the EGF2 domain of DLL4. In another examples, anti-DLL4 antibodies provided herein specifically binds to an epitope within the EGF2 to EGF4 domains of DLL4. In a further example, anti-DLL4 antibodies provided herein include those that specifically bind to an epitope within the EGF3 to EGF4 domain of DLL4.

Provided herein are anti-DLL4 antibodies that specifically binds to the same epitope as any of the antibodies set forth above.

Provided herein is an anti-DLL4 antibody that specifically binds to a human DLL4 epitope within amino acids 283 to 360 of human DLL4 set forth in SEQ ID NO:114. Such an anti-DLL4 antibody includes an antibody that contains a CDRH1 that is GYSFTSYWIG (SEQ ID NO:831), or that has at least 65% sequence identity to SEQ ID NO:831; a CDRH2 that is IIYPGDSDTRYSPSFQG (SEQ ID NO:845), or that has at least 65% sequence identity to SEQ ID NO:845; a CDRH3 that is RGYSYGYDYFDY(SEQ ID NO:852), or that has at least 65% sequence identity to SEQ ID NO:852; a CDRL1 that is GLSSGSVSTSYYPS(SEQ ID NO:862), or that has at least 65% sequence identity to SEQ ID NO:862; a CDRL2 that is STNTRSS (SEQ ID NO:872),or that has at least 65% sequence identity to SEQ ID NO:872; and a CDRL3 that is VLYMGSGISYV (SEQ ID NO:882), or that has at least 65% sequence identity to SEQ ID NO:882.

In one example, such an antibody can be a full-length antibody or an antibody fragment. For example, the antibody fragment can be a Fab, Fab', $F(ab')_2$, single-chain Fvs (scFv), Fv, dsFv, diabody, Fd and Fd' fragments, Fab fragments, Fd fragments, scFv fragments, or a scFab fragments Generally, the antibody is a Fab or is a full-length IgG.

In another example, an anti-DLL4 that specifically binds the epitope within amino acids 283 to 360 includes an antibody where a CDR exhibits 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence identity to the sequence of amino acids set forth in any of SEQ ID NOS: 831, 845, 852, 862, 872 and 882. For example, the anti-DLL4 antibody includes a CDRH1 that contains a modification of a CDRH1 set forth in SEQ ID NO:831 that has one or more amino acid replacement(s) at positions S28, F29, T30, W33, I34 and G35, based on kabat numbering. The one or more amino acid replacement(s) is selected from among S28A, S28R, S28K, S28N, F29A, T30A, W33A, I34A, G35T, G35A and/or G35V. The antibody also can contain a modification of a CDRH2 set forth in SEQ ID NO:845 that has one or more amino acid replacement(s) at positions I50, I51, Y52, P52a, D54, S55, D56 and/or T57, based on kabat numbering. The one or more amino acid replacement(s) is selected from among I50A, I51A, Y52A, P52aA, D54A, S55G, D56A, T57D and/or T57A. In a further example, the anti-DLL4 antibody can contains a modification of a CDRH3 set forth in SEQ ID NO: 852 that has one or more amino acid replacement(s) at positions R95, G96, Y97, S98, Y99, G100, Y100a, D100b, and/or D101, based on kabat numbering. The one or more amino acid replacement(s) is selected from among R95A, G96K, G96R, G96L, G96D, G96T, Y97A, Y97H, S98A, Y99A, G100A, G100D, G100L, G100P, G100R, G100M, G100K, G100S, G100R, G100T, Y100aA, D100bA and/or D101A. In particular, the amino acid replacement(s) is G96K/G100T. In an additional example, the anti-DLL4 contains a a modification of a CDRL1 set forth in SEQ ID NO:862 that has one or more amino acid replacement(s) at positions G24, L25, S26, S27, G27a, S27b, V27c, S28, T29, S30, Y31, Y32 and/orP33, based on kabat numbering. The one or more amino acid replacement(s) are selected from among G24A, G24R, G24L, L25A, S26A, S27A, G27aA, S27bA, V27cA, S28A, T29A, S30A, Y31A, Y32A and/or P33A. In another example, an anti-DLL4 antibody provided herein contains a modification of a CDRL2 set forth in SEQ ID NO:872 that has one or more amino acid replacement(s) at positions S50, T51, N52, T53, R54, S55 and/or S56, based on kabat numbering. The one or more amino acid replacement(s) are selected from among S50A, S50F, S50G, S50C, S50R, S50L, S50M, S50V, S50P, S50T, S50H, S50Q, S50N, S50K, S50D, S50E, S50W, T51A, T51F, T51L, T51I, T51M, T51V,

T51S, T51P, T51Y, T51H, T51Q, T51N, T51K, T51D, T51E, T51W, T51R, T51G, N52A, T53A, R54A, R54I, R54Y, R54D, R54G, S55A, S55F, S55L, S55I, S55M, S55V, S55P, S55T, S55Y, S55H, S55Q, S55N, S55K, S55D, S55E, S55W, S55R, S55G and/or S56A. In yet another example, the anti-DLL4 antibody can contain a modification of a CDRL3 set forth in SEQ ID NO:882 that has one or more amino acid replacement(s) at positions V89, L90, Y91, M92, G93, S94, G95, I95a and/or S95b, based on kabat numbering. The one or more amino acid replacement(s) are selected from among V89A, V89P, V89T, V89S, V89L, V89R, V89C, V89E, V89W, V89N, V89I, V89G, V89H, L90A, Y91A, M92A, M92E, M92S, M92G, M92L, M92P, M92V, M92D, M92R, M92N, M92T, M92F, G93A, S94A, S94W, S94G, S94P, S94R, S94L, S94M, S94E, S94V, G94A, I95aA and/or S95bA. In particular, the amino acid replacement(s) are M92R/S94M or V89L/S94P. Exemplary of such anti-DLL4 antibodies provided herein is an antibody that has a VH chain comprising a sequence of amino acids set forth in SEQ ID NO: 433 and a VL chain comprising a sequence of amino acids set forth in SEQ ID NO:537.

Any of the anti-DLL4 antibodies provided be an isolated antibody.

Also provided herein is a polypeptide that has a sequence of amino acids set forth in any of SEQ ID NOS: 830-836 and 844-890; or has at least 65% identical to a sequence of amino acids set forth in any of SEQ ID NOS: 831-836 and 844-890, with the proviso that the polypeptide does not comprise the sequence of amino acids GYTFTSYVIN (SEQ ID NO:904); or has at least 72% identical to a sequence of amino acids set forth in SEQ ID NO:830; whereby when contained in an antibody or antigen-binding fragment or antibody fragment thereof specifically binds to human DLL4.

Provided herein is a polynucleotide(s) encoding any of the above-anti-DLL4 antibodies. Also provided herein is a polynucleotide encoding the variable heavy chain of any of the above anti-DLL4 antibodies. Also provided herein is a polynucleotide encoding the variable light chain of any of the above anti-DLL4 antibodies.

Provided herein is a vector containing any of the above polynucleotides. Also provided is a host cell containing any of the provided vectors. The host cell can be prokaryotic or eukaryotic.

Provided herein is a method of making an anti-DLL4 antibody by expressing any of the provided vectors in a suitable host cells and recovering the antibody.

Provided herein is a combination containing any of the above anti-DLL4 antibodies and an anti-angiogenic agent. The anti-angiogenic agent is an antagonist of vascular endothelial growth factor (VEGF). In one example, the VEGF antagonist is an anti-VEGF antibody. For example, the anti-VEGF antibody is bevacizumab.

Provided herein is a pharmaceutical composition containing any of the provided anti-DLL4 antibodies, polypeptides or combinations. The pharmaceutical can further contain a carrier. The pharmaceutical composition can be formulated as a gel, ointment, cream, paste, suppository, flush, liquid, suspension, aerosol, tablet, pill or powder. The pharmaceutical composition can be formulated for systemic, parenteral, topical, oral, mucosal, intranasal, subcutaneous, aerosolized, intravenous, bronchial, pulmonary, vaginal, vulvovaginal or esophageal administration. In some examples, the pharmaceutical composition is formulated for single dosage administration. In other examples, the pharmaceutical composition is formulated a sustained release formulation.

Provided herein is a method of treatment by adminstering a therapeutically effective amount of any one of the anti-DLL4 antibodies provided herein or any of the pharmaceutical compositions provided herein for treating a disease or disorder associated with expression and/or activity of DLL4. The disease or disorder is can be a tumor, cancer or cell proliferative disorder. For example, the disease or disorder can be atherosclerosis, arthritis, ocular neovascularization, endometriosis, uterine fibroids, pre-eclampsia and cancer. In one example, the disease or disorder is cancer and the cancer is prostate cancer, pancreatic cancer, colon cancer, lung cancer or breast cancer.

In the methods of treatment herein, any of the anti-DLL4 antibodies can be further administered in combination with an effective amount of an anti-angiogenic agent. The anti-angiogenic agent can be an antagonist of vascular endothelial growth factor (VEGF). For example, the VEGF antagonist is an anti-VEGF antibody. In one example, the anti-VEGF antibody is bevacizumab. Further provided herein are methods of treatment by administering any of the anti-DLL4 antibodies provided herein in combination with an effective amount of a chemotherapeutic agent.

Also provided herein is use of any of the anti-DLL4 antibodies provided herein in the formulation of a medicament for the treatment of a disease or disorder associated with expression and/or activity of DLL4. Further provided herein is a pharmaceutical composition containing any of the anti-DLL4 antibodies provided herein for use in treating a disease or disorder associated with expression and/or activity of DLL4.

Provided herein is a method of inhibiting Notch activation by administering any of the provided anti-DLL4 antibody that inactivates Notch signaling. Also provided is use of any of the anti-DLL4 antibodies in the formulation of a medicament for use in inhibiting Notch activation. Further provided is a pharmaceutical composition containing any of the provided anti-DLL4 antibodies for use in inhibiting Notch activation.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1. Sequence of DLL4 antibody VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01. Figure 1 depicts the sequence of antibody VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01 (SEQ ID NOS:131 and141) (in boldface type). **Figure 1A** depicts the sequence of the variable heavy chain VH1-46_IGHD6-6*01_IGHJ1*01. **Figure 1B** depicts the sequence of the variable light chain L6_IGKJ1*01. The sequences are numbered in sequential amino acid order (1st row) and according to Kabat (3rd row)and Chothia numbering (4th row). Framework (FW) and complementarity determining regions (CDRs) are identified.

Figure 2. Sequence of DLL4 antibody VH5-51_IGHD5-18*01>3_IGHJ4*01 & V3-4_IGLJ1*01. Figure 2 depicts the sequence of antibody VH5-51_IGHD5-18*01>3_IGHJ4*01 & V3-4_IGLJ1*01 (SEQ ID NOS:132 and 142) (in boldface type). **Figure 2A** depicts the sequence of the variable heavy chain VH5-51_IGHD5-18*01>3_IGHJ4*01. **Figure 2B** depicts the sequence of the variable light chain V3-4_IGLJ1*01. The sequences are numbered in sequential amino acid order (1st row) and according to Kabat (3rd row)and Chothia numbering (4th row). Framework (FW) and complementarity determining regions (CDRs) are identified.

DETAILED DESCRIPTION

Outline

A. Definitions

B. DLL4
1. Structure
2. Expression
3. Function
C. Antibodies
1. Germline-Derived Anti-DLL4 antibodies
a. Exemplary Germline-derived anti-DLL4 antibodies
b. Germline-Derived Modified Antibodies
i. Variable heavy chain
ii. Variable light chain
iii. Exemplary Germline-Derived Modified Antibodies
2. Anti-DLL4: Complementary Determining Regions (CDRs)
D. Further Modifications
1. Modifications to reduce immunogenicity
2. Fc Modifications
3. Pegylation
4. Conjugation of a Detectable Moiety
5. Modifications to improve binding specificity
E. Methods of Generating or Identifying Anti-DLL4 Antibodies
1. Immunization and Hybridoma Screening
2. Screening Assays
a. Display Libraries
Phage Display Libraries
b. Addressable Libraries
Method of Generating a Combinatorial Addressable Antibody Library
3. Optimization and Affinity Maturation
F. Assessing Anti-DLL4 Antibody Properties And Activities
1. Binding
a. Binding Assays
b. Binding Affinity
2. Functional Activity
3. Animal Models
G. Methods of Production of Antibodies
1. Vectors
2. Cells and Expression Systems
a. Prokaryotic Expression
b. Yeast
c. Insects
d. Mammalian Cells
e. Plants
3. Purification
H. Formulations, Administration And Articles of Manufacture/Kits
1. Formulations
2. Articles of Manufacture and Kits
I. Methods and Uses of Antibodies
1. Methods of Treatment and Uses

Combination Therapy
2. Diagnosis and Detection
J. Examples

A. DEFINITIONS

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which the invention(s) belong. All patents, patent applications, published applications and publications, Genbank sequences, databases, websites and other published materials referred to throughout the entire disclosure herein, unless noted otherwise, are incorporated by reference in their entirety. In the event that there are a plurality of definitions for terms herein, those in this section prevail. Where reference is made to a URL or other such identifier or address, it understood that such identifiers can change and particular information on the internet can come and go, but equivalent information can be found by searching the internet. Reference thereto evidences the availability and public dissemination of such information.

As used herein, Delta-like 4 (DLL4) refers to a protein that is a ligand for Notch receptors 1 and 4. DLL4 includes any DLL4 polypeptide, including but not limited to, a recombinantly produced polypeptide, a synthentically produced polypeptide, a native DLL4 polypeptide, and a DLL4 polypeptide extracted from cells or tissues, including endothelial cells. DLL4 also includes related polypeptides from different species including, but not limited to animals of human and non-human origin. Human DLL4 includes DLL4, allelic variant isoforms, synthetic molecules from nucleic acids, protein isolated from human tissue and cells, and modified forms thereof. An exemplary DLL4 includes human DLL4 having a sequence of amino acids set forth in SEQ ID NO:114 and encoded by a sequence of nucleotides set forth in SEQ ID NO:113. For purposes herein, reference to DLL4 is typically with reference to human DLL4, unless stated otherwise.

As used herein, antibody refers to immunoglobulins and immunoglobulin portions, whether natural or partially or wholly synthetic, such as recombinantly, produced, including any portion thereof containing at least a portion of the variable region of the immunoglobulin molecule that is sufficient to form an antigen binding site. Hence, an antibody or portion thereof includes any protein having a binding

domain that is homologous or substantially homologous to an immunoglobulin antigen binding site. For example, an antibody refers to an antibody that contains two heavy chains (which can be denoted H and H') and two light chains (which can be denoted L and L'), where each heavy chain can be a full-length immunoglobulin heavy chain or a portion thereof sufficient to form an antigen binding site (e.g. heavy chains include, but are not limited to, VH chains, VH-CH1 chains and VH-CH1-CH2-CH3 chains), and each light chain can be a full-length light chain or a portion thereof sufficient to form an antigen binding site (e.g. light chains include, but are not limited to, VL chains and VL-CL chains). Each heavy chain (H and H') pairs with one light chain (L and L', respectively). Typically, antibodies minimally include all or at least a portion of the variable heavy (VH) chain and/or the variable light (VL) chain. The antibody also can include all or a portion of the constant region.

For purposes herein, the term antibody includes full-length antibodies and portions thereof including antibody fragments, such as, but not limited to, Fab, Fab', $F(ab')_2$, single-chain Fvs (scFv), Fv, dsFv, diabody, Fd and Fd' fragments, Fab fragments, Fd fragments and scFv fragments. Other known fragments include, but are not limited to, scFab fragments (Hust *et al.*, *BMC Biotechnology* (2007), 7:14). Antibodies include members of any immunoglobulin class, including IgG, IgM, IgA, IgD and IgE.

As used herein, a full-length antibody is an antibody having two full-length heavy chains (e.g. VH-CH1-CH2-CH3 or VH-CH1-CH2-CH3-CH4) and two full-length light chains (VL-CL) and hinge regions, such as human antibodies produced by antibody secreting B cells and antibodies with the same domains that are produced synthetically.

As used herein, antibody fragment or antibody portion refers to any portion of a full-length antibody that is less than full length but contains at least a portion of the variable region of the antibody sufficient to form an antigen binding site (e.g. one or more CDRs) and thus retains the a binding specificity and/or an activity of the full-length antibody; antibody fragments include antibody derivatives produced by enzymatic treatment of full-length antibodies, as well as synthetically, e.g. recombinantly produced derivatives. Examples of antibody fragments include, but are not limited to, Fab, Fab', $F(ab')_2$, single-chain Fvs (scFv), Fv, dsFv, diabody, Fd and

Fd' fragments (see, for example, *Methods in Molecular Biology*, Vol 207: *Recombinant Antibodies for Cancer Therapy Methods and Protocols* (2003); Chapter 1; p 3-25, Kipriyanov). The fragment can include multiple chains linked together, such as by disulfide bridges and/or by peptide linkers. An antibody fragment generally contains at least about 50 amino acids and typically at least 200 amino acids.

As used herein, an Fv antibody fragment is composed of one variable heavy domain (VH) and one variable light (VL) domain linked by noncovalent interactions.

As used herein, a dsFv refers to an Fv with an engineered intermolecular disulfide bond, which stabilizes the VH-VL pair.

As used herein, an Fd fragment is a fragment of an antibody containing a variable domain (VH) and one constant region domain (CH1) of an antibody heavy chain.

As used herein, Fab fragment is an antibody fragment that contains the portion of the full-length antibody that results from digestion of a full-length immunoglobulin with papain, or a fragment having the same structure that is produced synthetically, e.g. recombinantly. A Fab fragment contains a light chain (containing a VL and CL portion) and another chain containing a variable domain of a heavy chain (VH) and one constant region domain portion of the heavy chain (CH1); it can be recombinantly produced.

As used herein, a $F(ab')_2$ fragment is an antibody fragment that results from digestion of an immunoglobulin with pepsin at pH 4.0-4.5, or a synthetically, e.g. recombinantly, produced antibody having the same structure. The $F(ab')_2$ fragment contains two Fab fragments but where each heavy chain portion contains an additional few amino acids, including cysteine residues that form disulfide linkages joining the two fragments; it can be recombinantly produced.

As used herein, a Fab' fragment is a fragment containing one half (one heavy chain and one light chain) of the $F(ab')_2$ fragment.

As used herein, an Fd' fragment is a fragment of an antibody containing one heavy chain portion of a $F(ab')_2$ fragment.

As used herein, an Fv fragment is a fragment containing only the V_H and V_L domains of an antibody molecule.

As used herein, a scFv fragment refers to an antibody fragment that contains a variable light chain (VL) and variable heavy chain (VH), covalently connected by a polypeptide linker in any order. The linker is of a length such that the two variable domains are bridged without substantial interference. Exemplary linkers are (Gly-Ser)$_n$ residues with some Glu or Lys residues dispersed throughout to increase solubility.

As used herein, diabodies are dimeric scFv; diabodies typically have shorter peptide linkers than scFvs, and they preferentially dimerize.

As used herein, hsFv refers to antibody fragments in which the constant domains normally present in a Fab fragment have been substituted with a heterodimeric coiled-coil domain (see, e.g., Arndt *et al.* (2001) *J Mol Biol.* 7:312:221-228).

As used herein, a polypeptide domain is a part of a polypeptide (a sequence of three or more, generally 5 or 7 or more amino acids) that is a structurally and/or functionally distinguishable or definable. Exemplary of a polypeptide domain is a part of the polypeptide that can form an independently folded structure within a polypeptide made up of one or more structural motifs (e.g. combinations of alpha helices and/or beta strands connected by loop regions) and/or that is recognized by a particular functional activity, such as enzymatic activity or antigen binding. A polypeptide can have one, typically more than one, distinct domains. For example, the polypeptide can have one or more structural domains and one or more functional domains. A single polypeptide domain can be distinguished based on structure and function. A domain can encompass a contiguous linear sequence of amino acids. Alternatively, a domain can encompass a plurality of non-contiguous amino acid portions, which are non-contiguous along the linear sequence of amino acids of the polypeptide. Typically, a polypeptide contains a plurality of domains. For example, each heavy chain and each light chain of an antibody molecule contains a plurality of immunoglobulin (Ig) domains, each about 110 amino acids in length. Domains (*i.e.*, EGF, an Ig-like domain) often are identified by virtue of structural and/or sequence homology to domains in particular proteins. For exemplification herein, definitions are provided, but it is understood that it is well within the skill in the art to recognize particular domains by name. If needed appropriate software can be employed to

identify domains. Further, reference to the amino acids positions of a domain herein are for exemplification purposes only. Since interactions are dynamic, amino acid positions noted are for reference and exemplification. The noted positions reflects a range of loci that vary by 2, 3, 4, 5 or more amino acids. Variations also exist among allelic variants and species variants. Those of skill in the art can identify corresponding sequences by visual comparison or other comparisons including readily available algorithms and software.

As used herein, an Ig domain is a domain, recognized as such by those in the art, that is distinguished by a structure, called the Immunoglobulin (Ig) fold, which contains two beta-pleated sheets, each containing anti-parallel beta strands of amino acids connected by loops. The two beta sheets in the Ig fold are sandwiched together by hydrophobic interactions and a conserved intra-chain disulfide bond. Individual immunoglobulin domains within an antibody chain further can be distinguished based on function. For example, a light chain contains one variable region domain (VL) and one constant region domain (CL), while a heavy chain contains one variable region domain (VH) and three or four constant region domains (CH). Each VL, CL, VH, and CH domain is an example of an immunoglobulin domain.

As used herein, a variable domain with reference to an antibody is a specific Ig domain of an antibody heavy or light chain that contains a sequence of amino acids that varies among different antibodies. Each light chain and each heavy chain has one variable region domain (VL and VH). The variable domains provide antigen specificity, and thus are responsible for antigen recognition. Each variable region contains CDRs that are part of the antigen binding site domain and framework regions (FRs).

As used herein, "hypervariable region," "HV," "complementarity-determining region," "CDR" and "antibody CDR" are used interchangeably to refer to one of a plurality of portions within each variable region that together form an antigen binding site of an antibody. Each variable region domain contains three CDRs, named CDR1, CDR2, and CDR3. The three CDRs are non-contiguous along the linear amino acid sequence, but are proximate in the folded polypeptide. The CDRs are located within the loops that join the parallel strands of the beta sheets of the variable domain.

As used herein, framework regions (FRs) are the domains within the antibody variable region domains that are located within the beta sheets; the FR regions are comparatively more conserved, in terms of their amino acid sequences, than the hypervariable regions.

As used herein, a constant region domain is a domain in an antibody heavy or light chain that contains a sequence of amino acids that is comparatively more conserved among antibodies than the variable region domain. Each light chain has a single light chain constant region (CL) domain and each heavy chain contains one or more heavy chain constant region (CH) domains, which include, CH1, CH2, CH3 and CH4. Full-length IgA, IgD and IgG isotypes contain CH1, CH2, CH3 and a hinge region, while IgE and IgM contain CH1, CH2, CH3 and CH4. CH1 and CL domains extend the Fab arm of the antibody molecule, thus contributing to the interaction with antigen and rotation of the antibody arms. Antibody constant regions can serve effector functions, such as, but not limited to, clearance of antigens, pathogens and toxins to which the antibody specifically binds, e.g. through interactions with various cells, biomolecules and tissues.

As used herein, humanized antibodies refer to antibodies that are modified to include "human" sequences of amino acids so that administration to a human does not provoke an immune response. Methods for preparation of such antibodies are known. For example, the antibody in which the amino acid composition of the non-variable regions can be based on human antibodies. Computer programs have been designed to identify such regions.

As used herein, "antigen-binding site" refers to the interface formed by one or more complementary determining regions (CDRs; also called hypervariable region). Each antigen binding site contains three CDRs from the heavy chain variable region and three CDRs from the light chain variable region. An antibody molecule has two antigen combining sites, each containing portions of a heavy chain variable region and portions of a light chain variable region. The antigen combining sites can contain other portions of the variable region domains in addition to the CDRs.

As used herein, reference to an "antibody or portion thereof that is sufficient to form an antigen binding site" means that the antibody or portion thereof contains at least 1 or 2, typically 3, 4, 5 or all 6 CDRs of the VH and VL sufficient to retain at

least a portion of the binding specificity of the corresponding full-length antibody containing all 6 CDRs. Generally, a sufficient antigen binding site at least requires CDR3 of the heavy chain (CDRH3). It typically futher requires the CDR3 of the light chain (CDRL3). As described herein, one of skill in the art knows and can identify the CDRs based on Kabat or Chothia numbering (see e.g., Kabat, E.A. *et al.* (1991) *Sequences of Proteins of Immunological Interest*, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242, and Chothia, C. *et al.* (1987) *J. Mol. Biol.* 196:901-917). For example, based on Kabat numbering, CDR-LI corresponds to residues L24-L34; CDR-L2 corresponds to residues L50-L56; CDR-L3 corresponds to residues L89-L97; CDR-H1 corresponds to residues H31 – H35, 35a or 35b depending on the length; CDR-H2 corresponds to residues H50-H65; and CDR-H3 corresponds to residues H95-H102.

As used herein, a "target protein" refers to candidate proteins or peptides that are specifically recognized by an antibody or portion thereof and/or whose activity is modulated by an antibody or portion thereof. A target protein includes any peptide or protein that contains an epitope for antibody recognition. Target proteins include proteins involved in the etiology of a disease or disorder by virtue of expression or activity. An exemplary target protein is DLL4.

As used herein, activity towards a target protein (e.g. DLL4) refers to binding specificity and/or modulation of a functional activity of a target protein, or other measurements that reflects the activity of an antibody or portion thereof towards a target protein.

As used herein, the term assessing is intended to include quantitative and qualitative determination in the sense of obtaining an absolute value for the binding of an antibody or portion thereof with a target protein and/or modulation of an activity of a target protein by an antibody or portion thereof, and also of obtaining an index, ratio, percentage, visual or other value indicative of the level of the binding or activity. Assessment can be direct or indirect. For example, binding can be determined by directly labeling an antibody or portion thereof with a detectable label and/or by using a secondary antibody that itself is labeled. In addition, functional activities can be determined using any of a variety of assays known to one of skill in the art, for example, proliferation, cytotoxicity and others as described herein, and

comparing the activity of the target protein in the presence versus the absence of an antibody or portion thereof.

As used herein, "functional activity" refer to activities of a polypeptide (e.g. target protein) or portion thereof associated with a full-length (complete) protein. Functional activities include, but are not limited to, biological activity, catalytic or enzymatic activity, antigenicity (ability to bind to or compete with a polypeptide for binding to an anti-polypeptide antibody), immunogenicity, ability to form multimers, the ability to specifically bind to a receptor or ligand for the polypeptide and signaling and downstream effector functions. For purposes herein, modulation (i.e. activation or inhibition) of a functional activity of a polypeptide by an antibody or portion thereof means that a functional activity of the polypeptide is changed or altered in the presence of the antibody compared to the absence of the antibody or portion thereof.

As used herein, "modulate" or "modulation" and other various grammatical forms thereof with reference to the effect of an antibody or portion thereof on the functional activity of a target protein refers to increased activity such as induction or potentiation of activity, as well as inhibition of one or more activities of the target protein. Hence, modulation can include an increase in the activity (i.e., up-regulation or agonist activity), a decrease in activity (i.e., down-regulation or inhibition) or any other alteration in an activity (such as a change in periodicity, frequency, duration, kinetics or other parameter). Modulation can be context dependent and typically modulation is compared to a designated state, for example, the wildtype protein, the protein in a constitutive state, or the protein as expressed in a designated cell type or condition. The functional activity of a target protein by an antibody or portion thereof can be modulated by 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more compared to the activity of the target protein in the absence of the antibody or portion thereof.

As used herein, "agonist" refers to an antibody or portion thereof that modulates signal transduction or other functional activity of a receptor by potentiating, inducing or otherwise enhancing the signal transduction activity or other functional activity of a receptor. Agonists can modulate signal transduction or other functional activity when used alone or can alter signal transduction or other functional

activity in the presence of the natural ligand of the receptor or other receptor stimulator to enhance signaling by the receptor compared to the ligand alone.

As used herein, "antagonist" refers to an antibody or portion thereof that modulates signal transduction or other functional activity of a receptor by blocking or decreasing the signal transduction activity or other functional activity of a receptor

As used herein, a label is a detectable marker that can be attached or linked directly or indirectly to a molecule or associated therewith. The detection method can be any method known in the art.

As used herein, binding activity refer to characteristics of a molecule, e.g. a polypeptide, relating to whether or not, and how, it binds one or more binding partners. Binding activities include ability to bind the binding partner(s), the affinity with which it binds to the binding partner (e.g. high affinity), the avidity with which it binds to the binding partner, the strength of the bond with the binding partner and specificity for binding with the binding partner.

As used herein, "affinity" or "binding affinity" refers to the strength with which an antibody molecule or portion thereof binds to an epitope on a target protein or antigen. Affinity is often measured by equilibrium association constant (K_A) or equilibrium dissociation constant (K_D). Low-affinity antibody-antigen interaction is weak, and the molecules tend to dissociate rapidly, while high affinity antibody-antigen binding is strong and the molecules remain bound for a longer amount of time. A high antibody affinity means that the antibody specifically binds to a target protein with an equilibrium association constant (K_A) of greater than or equal to about $10^6\ M^{-1}$, greater than or equal to about $10^7\ M^{-1}$, greater than or equal to about $10^8\ M^{-1}$, or greater than or equal to about $10^9\ M^{-1}$, $10^{10}\ M^{-1}$, $10^{11}\ M^{-1}$ or $10^{12}\ M^{-1}$. Antibodies also can be characterized by an equilibrium dissociation constant (K_D), for example, 10^{-6} M, 10^{-7} M, 10^{-8} M, 10^{-9} M, 10^{-10} M, 10^{-11} M or 10^{-12} M or lower. Generally, antibodies having a nanomolar or sub-nanomolar dissociaton constant are deemed to be high affinity antibodies. Such affinities can be readily determined using conventional techniques, such as by equilibrium dialysis; by using surface plasmon resonance; by radioimmunoassay using radiolabeled target antigen; or by another method known to the skilled artisan. The affinity data can be analyzed, for example, by the method of Scatchard *et al.*, Ann N.Y. Acad. ScL, 51:660 (1949).

As used herein, "specifically bind" or "immunospecifically bind" with respect to an antibody or antigen-binding fragment thereof are used interchangeably herein and refer to the ability of the antibody or antigen-binding fragment to form one or more noncovalent bonds with a cognate antigen, by noncovalent interactions between the antibody combining site(s) of the antibody and the antigen (e.g. human DLL4). Typically, an antibody that immunospecifically binds (or that specifically binds) to an antigen is one that binds to the antigen with an affinity constant Ka of about or $1\times10^{7}M^{-1}$ or $1x\ 10^{8}M^{-1}$or greater (or a dissociation constant (K_d) of $1x\ 10^{-7}M$ or $1\times10^{-8}M$ or less). Affinity constants can be determined by standard kinetic methodology for antibody reactions, for example, immunoassays, surface plasmon resonance (SPR) (Rich and Myszka (2000) *Curr. Opin. Biotechnol* 11:54; Englebienne (1998) *Analyst.* 123:1599), isothermal titration calorimetry (ITC) or other kinetic interaction assays known in the art (see, *e.g.*, Paul, ed., Fundamental Immunology, 2nd ed., Raven Press, New York, pages 332-336 (1989); see also U.S. Pat. No. 7,229,619 for a description of exemplary SPR and ITC methods for calculating the binding affinity of anti-RSV antibodies). Instrumentation and methods for real time detection and monitoring of binding rates are known and are commercially available (*e.g.*, BiaCore 2000, Biacore AB, Upsala, Sweden and GE Healthcare Life Sciences; Malmqvist (2000) *Biochem. Soc. Trans.* 27:335).

As used herein, the term "bind selectively" or "selectively binds," in reference to a polypeptide or an antibody provided herein, means that the polypeptide or antibody binds with a selected epitope without substantially binding to another epitope. Typically, an antibody or fragment thereof that selectively binds to a selected epitope specifically binds to the epitope, such as with an affinity constant Ka of about or $1\times10^{7}M^{-1}$ or $1\ x\ 10^{8}M^{-1}$or greater.

As used herein, "epitope" refers to the localized region on the surface of an antigen or protein that is recognized by an antibody. An epitope can be a linear or conformational epitope, and can be continuous or discontinuous. Typically, linear epitopes are continuous, i.e. made up of one continuous stretch of amino acids. Conformational epitopes can be discontinuous i.e. made up of two or more discontinuous segments of amino acids that come together to form an epitope when the antigen is folded. Methods for determining whether antibodies binds to the same

epitope are known in the art. Epitopes can be defined or mapped by standard methods well known in art. For example, epitopes can be mapped using assays, such as ELISA assays, utilizing peptide libraries or site-directed mutagenesis of the antigen (such as alanine-scanning of the antigen).

As used herein, "binds to the same epitope" with reference to two or more antibodies means that the antibodies compete for binding to an antigen and bind to the same, overlapping or encompassing continuous or discontinuous segments of amino acids. Those of skill in the art understand that the phrase "binds to the same epitope" does not necessarily mean that the antibodies bind to exactly the same amino acids. The precise amino acids to which the antibodies bind can differ. For example, a first antibody can bind to a segment of amino acids that is completely encompassed by the segment of amino acids bound by a second antibody. In another example, a first antibody binds one or more segments of amino acids that significantly overlap the one or more segments bound by the second antibody. For the purposes herein, such antibodies are considered to "bind to the same epitope."

Antibody competition assays can be used to determine whether an antibody "binds to the same epitope" as another antibody. Such assays are well known on the art and are described herein (see.e.g. Example 9). Typically, competition of 70 % or more, such as 70%, 71%, 72%, 73%, 74%, 75%, 80%, 85%, 90%, 95% or more, of an antibody known to interact with the epitope by a second antibody under conditions in which the second antibody is in excess and the first saturates all sites, is indicative that the antibodies "bind to the same epitope." To assess the level of competition between two antibodies, for example, radioimmunoassays or assays using other labels for the antibodies, can be used. For example, a DLL4 antigen can be incubated with a a saturating amount of a first anti-DLL4 antibody or antigen-binding fragment thereof conjugated to a labeled compound (e.g., ^{3}H, ^{125}I, biotin, or rubidium) in the presence the same amount of a second unlabeled anti-DLL4 antibody. The amount of labeled antibody that is bound to the antigen in the presence of the unlabeled blocking antibody is then assessed and compared to binding in the absence of the unlabeled blocking antibody. Competition is determined by the percentage change in binding signals in the presence of the unlabeled blocking antibody compared to the absence of the blocking antibody. Thus, if there is a 70% inhibition of binding of the labeled

antibody in the presence of the blocking antibody compared to binding in the absence of the blocking antibody, then there is competition between the two antibodies of 70%. Thus, reference to competition between a first and second antibody of 70 % or more, such as 70%, 71%, 72%, 73%, 74%, 75%, 80%, 85%, 90%, 95% or more, means that the first antibody inhibits binding of the second antibody (or *vice versa*) to the antigen by 70%, 71%, 72%, 73%, 74%, 75%, 80%, 85%, 90%, 95% or more (compared to binding of the antigen by the second antibody in the absence of the first antibody). Thus, inhibition of binding of a first antibody to an antigen by a second antibody of 70%, 71%, 72%, 73%, 74%, 75%, 80%, 85%, 90%, 95% or more indicates that the two antibodies bind to the same epitope.

As used herein, the term "surface plasmon resonance" refers to an optical phenomenon that allows for the analysis of real-time interactions by detection of alterations in protein concentrations within a biosensor matrix, for example, using the BiaCore system (GE Healthcare Life Sciences).

As used herein, a "bispecific" antibody is a multispecific antibody that contains two or more antigen-binding sites and can immunospecifically bind to two different epitopes. A "trispecific" antibody is a multispecific antibody that contains three or more antigen-binding sites and can immunospecifically bind to three different epitopes, a "tetraspecific" antibody is a multispecific antibody that contains four or more antigen-binding sites and can immunospecifically bind to four different epitopes, and so on.

As used herein, "epitope mapping" is the process of identification of the molecular determinants for antibody-antigen recognition.

As used herein, Basic Local Alignment Search Tool (BLAST) is a search algorithm developed by Altschul *et al. J Mol Biol.* 215(3):403-10 (1990) to separately search protein or DNA databases, for example, based on sequence identity. For example, blastn is a program that compares a nucleotide query sequence against a nucleotide sequence database (e.g. GenBank). BlastP is a program that compares an amino acid query sequence against a protein sequence database.

As used herein, a BLAST bit score is a value calculated from the number of gaps and substitutions associated with each aligned sequence. The higher the score, the more significant the alignment.

As used herein, a human protein is one encoded by a nucleic acid molecule, such as DNA, present in the genome of a human, including all allelic variants and conservative variations thereof. A variant or modification of a protein is a human protein if the modification is based on the wildtype or prominent sequence of a human protein.

As used herein, "naturally occurring amino acids" refers to the 20 L-amino acids that occur in polypeptides. The residues are those 20 α-amino acids found in nature which are incorporated into protein by the specific recognition of the charged tRNA molecule with its cognate mRNA codon in humans.

As used herein, "non-naturally occurring amino acids" refers to amino acids that are not genetically encoded. For example, a non-natural amino acid is an organic compound that has a structure similar to a natural amino acid but has been modified structurally to mimic the structure and reactivity of a natural amino acid. Non-naturally occurring amino acids thus include, for example, amino acids or analogs of amino acids other than the 20 naturally-occurring amino acids and include, but are not limited to, the D-isostereomers of amino acids. Exemplary non-natural amino acids are known to those of skill in the art.

As used herein, nucleic acids include DNA, RNA and analogs thereof, including peptide nucleic acids (PNA) and mixtures thereof. Nucleic acids can be single or double-stranded. When referring to probes or primers, which are optionally labeled, such as with a detectable label, such as a fluorescent or radiolabel, single-stranded molecules are contemplated. Such molecules are typically of a length such that their target is statistically unique or of low copy number (typically less than 5, generally less than 3) for probing or priming a library. Generally a probe or primer contains at least 14, 16 or 30 contiguous nucleotides of sequence complementary to or identical to a gene of interest. Probes and primers can be 10, 20, 30, 50, 100 or more nucleic acids long.

As used herein, a peptide refers to a polypeptide that is from 2 to 40 amino acids in length.

As used herein, amino acids which occur in the various sequences of amino acids provided herein are identified according to their known, three-letter or one-letter abbreviations (Table 1). The nucleotides which occur in the various nucleic acid

fragments are designated with the standard single-letter designations used routinely in the art.

As used herein, an "amino acid" is an organic compound containing an amino group and a carboxylic acid group. A polypeptide contains two or more amino acids. For purposes herein, amino acids include the twenty naturally-occurring amino acids, non-natural amino acids and amino acid analogs (i.e., amino acids wherein the α-carbon has a side chain).

As used herein, "amino acid residue" refers to an amino acid formed upon chemical digestion (hydrolysis) of a polypeptide at its peptide linkages. The amino acid residues described herein are presumed to be in the "L" isomeric form. Residues in the "D" isomeric form, which are so designated, can be substituted for any L-amino acid residue as long as the desired functional property is retained by the polypeptide. NH_2 refers to the free amino group present at the amino terminus of a polypeptide. COOH refers to the free carboxy group present at the carboxyl terminus of a polypeptide. In keeping with standard polypeptide nomenclature described in *J. Biol. Chem.*, 243: 3557-3559 (1968), and adopted 37 C.F.R. §§ 1.821-1.822, abbreviations for amino acid residues are shown in Table 1:

Table 1 – Table of Correspondence

SYMBOL		
1-Letter	**3-Letter**	**AMINO ACID**
Y	Tyr	Tyrosine
G	Gly	Glycine
F	Phe	Phenylalanine
M	Met	Methionine
A	Ala	Alanine
S	Ser	Serine
I	Ile	Isoleucine
L	Leu	Leucine
T	Thr	Threonine
V	Val	Valine
P	Pro	Proline
K	Lys	Lysine
H	His	Histidine
Q	Gln	Glutamine
E	Glu	Glutamic acid
Z	Glx	Glu and/or Gln
W	Trp	Tryptophan
R	Arg	Arginine
D	Asp	Aspartic acid

SYMBOL		
1-Letter	**3-Letter**	**AMINO ACID**
N	Asn	Asparagine
B	Asx	Asn and/or Asp
C	Cys	Cysteine
X	Xaa	Unknown or other

It is noted that all amino acid residue sequences represented herein by formulae have a left to right orientation in the conventional direction of amino-terminus to carboxyl-terminus. In addition, the phrase "amino acid residue" is broadly defined to include the amino acids listed in the Table of Correspondence (Table 1) and modified and unusual amino acids, such as those referred to in 37 C.F.R. §§ 1.821-1.822, and incorporated herein by reference. Furthermore, it is noted that a dash at the beginning or end of an amino acid residue sequence indicates a peptide bond to a further sequence of one or more amino acid residues, to an amino-terminal group such as NH_2 or to a carboxyl-terminal group such as COOH. The abbreviations for any protective groups, amino acids and other compounds, are, unless indicated otherwise, in accord with their common usage, recognized abbreviations, or the IUPAC-IUB Commission on Biochemical Nomenclature (see, (1972) *Biochem.* 11:1726). Each naturally occurring L-amino acid is identified by the standard three letter code (or single letter code) or the standard three letter code (or single letter code) with the prefix "L-"; the prefix "D-" indicates that the stereoisomeric form of the amino acid is D.

As used herein, an isokinetic mixture is one in which the molar ratios of amino acids has been adjusted based on their reported reaction rates (see, e.g., Ostresh *et al.*, (1994) *Biopolymers* 34:1681).

As used herein, modification is in reference to modification of a sequence of amino acids of a polypeptide or a sequence of nucleotides in a nucleic acid molecule and includes deletions, insertions, and replacements of amino acids and nucleotides, respectively. Methods of modifying a polypeptide are routine to those of skill in the art, such as by using recombinant DNA methodologies.

As used herein, suitable conservative substitutions of amino acids are known to those of skill in this art and can be made generally without altering the biological

activity of the resulting molecule. Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity (see, e.g., Watson *et al.* Molecular Biology of the Gene, 4th Edition, 1987, The Benjamin/Cummings Pub. co., p.224). Such substitutions can be made in accordance with those set forth in TABLE 2 as follows:

TABLE 2

Original residue	Exemplary conservative substitution
Ala (A)	Gly; Ser
Arg (R)	Lys
Asn (N)	Gln; His
Cys (C)	Ser
Gln (Q)	Asn
Glu (E)	Asp
Gly (G)	Ala; Pro
His (H)	Asn; Gln
Ile (I)	Leu; Val
Leu (L)	Ile; Val
Lys (K)	Arg; Gln; Glu
Met (M)	Leu; Tyr; Ile
Phe (F)	Met; Leu; Tyr
Ser (S)	Thr
Thr (T)	Ser
Trp (W)	Tyr
Tyr (Y)	Trp; Phe
Val (V)	Ile; Leu

Other substitutions also are permissible and can be determined empirically or in accord with known conservative substitutions.

As used herein, a DNA construct is a single or double stranded, linear or circular DNA molecule that contains segments of DNA combined and juxtaposed in a manner not found in nature. DNA constructs exist as a result of human manipulation, and include clones and other copies of manipulated molecules.

As used herein, a DNA segment is a portion of a larger DNA molecule having specified attributes. For example, a DNA segment encoding a specified polypeptide is a portion of a longer DNA molecule, such as a plasmid or plasmid fragment, which, when read from the 5' to 3' direction , encodes the sequence of amino acids of the specified polypeptide.

As used herein, the term "nucleic acid" refers to single-stranded and/or double-stranded polynucleotides such as deoxyribonucleic acid (DNA), and ribonucleic acid (RNA) as well as analogs or derivatives of either RNA or DNA.

Also included in the term "nucleic acid" are analogs of nucleic acids such as peptide nucleic acid (PNA), phosphorothioate DNA, and other such analogs and derivatives or combinations thereof. Nucleic acid can refer to polynucleotides such as deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). The term also includes, as equivalents, derivatives, variants and analogs of either RNA or DNA made from nucleotide analogs, single (sense or antisense) and double-stranded polynucleotides. Deoxyribonucleotides include deoxyadenosine, deoxycytidine, deoxyguanosine and deoxythymidine. For RNA, the uracil base is uridine.

As used herein, "nucleic acid molecule encoding" refers to a nucleic acid molecule which directs the expression of a specific protein or peptide. The nucleic acid sequences include both the DNA strand sequence that is transcribed into RNA and the RNA sequence that is translated into protein or peptide. The nucleic acid molecule includes both the full length nucleic acid sequences as well as non-full length sequences derived from the full length mature polypeptide, such as for example a full length polypeptide lacking a precursor sequence. For purposes herein, a nucleic acid sequence also includes the degenerate codons of the native sequence or sequences that can be introduced to provide codon preference in a specific host.

As used herein, the term "polynucleotide" refers to an oligomer or polymer containing at least two linked nucleotides or nucleotide derivatives, including a deoxyribonucleic acid (DNA), a ribonucleic acid (RNA), and a DNA or RNA derivative containing, for example, a nucleotide analog or a "backbone" bond other than a phosphodiester bond, for example, a phosphotriester bond, a phosphoramidate bond, a phophorothioate bond, a thioester bond, or a peptide bond (peptide nucleic acid). The term "oligonucleotide" also is used herein essentially synonymously with "polynucleotide," although those in the art recognize that oligonucleotides, for example, PCR primers, generally are less than about fifty to one hundred nucleotides in length.

Polynucleotides can include nucleotide analogs, including, for example, mass modified nucleotides, which allow for mass differentiation of polynucleotides; nucleotides containing a detectable label such as a fluorescent, radioactive, luminescent or chemiluminescent label, which allow for detection of a polynucleotide; or nucleotides containing a reactive group such as biotin or a thiol

group, which facilitates immobilization of a polynucleotide to a solid support. A polynucleotide also can contain one or more backbone bonds that are selectively cleavable, for example, chemically, enzymatically or photolytically. For example, a polynucleotide can include one or more deoxyribonucleotides, followed by one or more ribonucleotides, which can be followed by one or more deoxyribonucleotides, such a sequence being cleavable at the ribonucleotide sequence by base hydrolysis. A polynucleotide also can contain one or more bonds that are relatively resistant to cleavage, for example, a chimeric oligonucleotide primer, which can include nucleotides linked by peptide nucleic acid bonds and at least one nucleotide at the 3' end, which is linked by a phosphodiester bond or other suitable bond, and is capable of being extended by a polymerase. Peptide nucleic acid sequences can be prepared using well-known methods (see, for example, Weiler *et al. Nucleic acids Res.* 25: 2792-2799 (1997)).

As used herein, "similarity" between two proteins or nucleic acids refers to the relatedness between the sequence of amino acids of the proteins or the nucleotide sequences of the nucleic acids. Similarity can be based on the degree of identity and/or homology of sequences of residues and the residues contained therein. Methods for assessing the degree of similarity between proteins or nucleic acids are known to those of skill in the art. For example, in one method of assessing sequence similarity, two amino acid or nucleotide sequences are aligned in a manner that yields a maximal level of identity between the sequences. "Identity" refers to the extent to which the amino acid or nucleotide sequences are invariant. Alignment of amino acid sequences, and to some extent nucleotide sequences, also can take into account conservative differences and/or frequent substitutions in amino acids (or nucleotides). Conservative differences are those that preserve the physico-chemical properties of the residues involved. Alignments can be global (alignment of the compared sequences over the entire length of the sequences and including all residues) or local (the alignment of a portion of the sequences that includes only the most similar region or regions).

"Identity" per se has an art-recognized meaning and can be calculated using published techniques. (See, e.g.: *Computational Molecular Biology*, Lesk, A.M., ed., Oxford University Press, New York, 1988; *Biocomputing: Informatics and Genome*

Projects, Smith, D.W., ed., Academic Press, New York, 1993; *Computer Analysis of Sequence Data*, Part I, Griffin, A.M., and Griffin, H.G., eds., Humana Press, New Jersey, 1994; *Sequence Analysis in Molecular Biology*, von Heinje, G., Academic Press, 1987; and Sequence Analysis Primer, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991). While there exists a number of methods to measure identity between two polynucleotide or polypeptides, the term "identity" is well known to skilled artisans (Carillo, H. & Lipton, D., *SIAM J Applied Math 48*:1073 (1988)).

As used herein, homologous (with respect to nucleic acid and/or amino acid sequences) means about greater than or equal to 25% sequence homology, typically greater than or equal to 25%, 40%, 50%, 60%, 70%, 80%, 85%, 90% or 95% sequence homology; the precise percentage can be specified if necessary. For purposes herein the terms "homology" and "identity" are often used interchangeably, unless otherwise indicated. In general, for determination of the percentage homology or identity, sequences are aligned so that the highest order match is obtained (see, e.g.: *Computational Molecular Biology*, Lesk, A.M., ed., Oxford University Press, New York, 1988; *Biocomputing: Informatics and Genome Projects*, Smith, D.W., ed., Academic Press, New York, 1993; *Computer Analysis of Sequence Data, Part I*, Griffin, A.M., and Griffin, H.G., eds., Humana Press, New Jersey, 1994; *Sequence Analysis in Molecular Biology*, von Heinje, G., Academic Press, 1987; and *Sequence Analysis Primer*, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991; Carillo *et al.* (1988) *SIAM J Applied Math 48*:1073). By sequence homology, the number of conserved amino acids is determined by standard alignment algorithms programs, and can be used with default gap penalties established by each supplier. Substantially homologous nucleic acid molecules hybridize typically at moderate stringency or at high stringency all along the length of the nucleic acid of interest. Also contemplated are nucleic acid molecules that contain degenerate codons in place of codons in the hybridizing nucleic acid molecule.

Whether any two molecules have nucleotide sequences or amino acid sequences that are at least 60%, 70%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% "identical" or "homologous" can be determined using known computer algorithms such as the "FASTA" program, using for example, the default parameters as in

Pearson *et al.* (1988) *Proc. Natl. Acad. Sci. USA 85*:2444 (other programs include the GCG program package (Devereux, J., *et al., Nucleic Acids Research 12(I)*:387 (1984)), BLASTP, BLASTN, FASTA (Atschul, S.F., *et al., J Molec Biol 215*:403 (1990)); Guide to Huge Computers, Martin J. Bishop, ed., Academic Press, San Diego, 1994, and Carillo *et al.* (1988) *SIAM J Applied Math 48*:1073). For example, the BLAST function of the National Center for Biotechnology Information database can be used to determine identity. Other commercially or publicly available programs include, DNAStar "MegAlign" program (Madison, WI) and the University of Wisconsin Genetics Computer Group (UWG) "Gap" program (Madison WI). Percent homology or identity of proteins and/or nucleic acid molecules can be determined, for example, by comparing sequence information using a GAP computer program (e.g., Needleman *et al.* (1970) *J. Mol. Biol.* 48:443, as revised by Smith and Waterman (1981) *Adv. Appl. Math.* 2:482). Briefly, the GAP program defines similarity as the number of aligned symbols (i.e., nucleotides or amino acids), which are similar, divided by the total number of symbols in the shorter of the two sequences. Default parameters for the GAP program can include: (1) a unary comparison matrix (containing a value of 1 for identities and 0 for non-identities) and the weighted comparison matrix of Gribskov *et al.* (1986) *Nucl. Acids Res.* 14:6745, as described by Schwartz and Dayhoff, eds., *ATLAS OF PROTEIN SEQUENCE AND STRUCTURE*, National Biomedical Research Foundation, pp. 353-358 (1979); (2) a penalty of 3.0 for each gap and an additional 0.10 penalty for each symbol in each gap; and (3) no penalty for end gaps.

Therefore, as used herein, the term "identity" or "homology" represents a comparison between a test and a reference polypeptide or polynucleotide. As used herein, the term at least "90% identical to" refers to percent identities from 90 to 99.99 relative to the reference nucleic acid or amino acid sequence of the polypeptide. Identity at a level of 90% or more is indicative of the fact that, assuming for exemplification purposes a test and reference polypeptide length of 100 amino acids are compared, no more than 10% (i.e., 10 out of 100) of the amino acids in the test polypeptide differs from that of the reference polypeptide. Similar comparisons can be made between test and reference polynucleotides. Such differences can be represented as point mutations randomly distributed over the entire length of a

polypeptide or they can be clustered in one or more locations of varying length up to the maximum allowable, e.g. 10/100 amino acid difference (approximately 90% identity). Differences are defined as nucleic acid or amino acid substitutions, insertions or deletions. At the level of homologies or identities above about 85-90%, the result can be independent of the program and gap parameters set; such high levels of identity can be assessed readily, often by manual alignment without relying on software.

As used herein, a polypeptide comprising a specified percentage of amino acids set forth in a reference polypeptide refers to the proportion of contiguous identical amino acids shared between a polypeptide and a reference polypeptide. For example, an isoform that comprises 70% of the amino acids set forth in a reference polypeptide having a sequence of amino acids set forth in SEQ ID NO:XX, which recites 147 amino acids, means that the reference polypeptide contains at least 103 contiguous amino acids set forth in the amino acid sequence of SEQ ID NO:XX.

As used herein, an aligned sequence refers to the use of homology (similarity and/or identity) to align corresponding positions in a sequence of nucleotides or amino acids. Typically, two or more sequences that are related by 50% or more identity are aligned. An aligned set of sequences refers to 2 or more sequences that are aligned at corresponding positions and can include aligning sequences derived from RNAs, such as ESTs and other cDNAs, aligned with genomic DNA sequence.

As used herein, "primer" refers to a nucleic acid molecule that can act as a point of initiation of template-directed DNA synthesis under appropriate conditions (e.g., in the presence of four different nucleoside triphosphates and a polymerization agent, such as DNA polymerase, RNA polymerase or reverse transcriptase) in an appropriate buffer and at a suitable temperature. It will be appreciated that a certain nucleic acid molecules can serve as a "probe" and as a "primer." A primer, however, has a 3' hydroxyl group for extension. A primer can be used in a variety of methods, including, for example, polymerase chain reaction (PCR), reverse-transcriptase (RT)-PCR, RNA PCR, LCR, multiplex PCR, panhandle PCR, capture PCR, expression PCR, 3' and 5' RACE, in situ PCR, ligation-mediated PCR and other amplification protocols.

As used herein, "primer pair" refers to a set of primers that includes a 5' (upstream) primer that hybridizes with the 5' end of a sequence to be amplified (e.g. by PCR) and a 3' (downstream) primer that hybridizes with the complement of the 3' end of the sequence to be amplified.

As used herein, "specifically hybridizes" refers to annealing, by complementary base-pairing, of a nucleic acid molecule (e.g. an oligonucleotide) to a target nucleic acid molecule. Those of skill in the art are familiar with *in vitro* and *in vivo* parameters that affect specific hybridization, such as length and composition of the particular molecule. Parameters particularly relevant to *in vitro* hybridization further include annealing and washing temperature, buffer composition and salt concentration. Exemplary washing conditions for removing non-specifically bound nucleic acid molecules at high stringency are 0.1 x SSPE, 0.1% SDS, 65°C, and at medium stringency are 0.2 x SSPE, 0.1% SDS, 50°C. Equivalent stringency conditions are known in the art. The skilled person can readily adjust these parameters to achieve specific hybridization of a nucleic acid molecule to a target nucleic acid molecule appropriate for a particular application.

As used herein, substantially identical to a product means sufficiently similar so that the property of interest is sufficiently unchanged so that the substantially identical product can be used in place of the product.

As used herein, it also is understood that the terms "substantially identical" or "similar" varies with the context as understood by those skilled in the relevant art.

As used herein, an allelic variant or allelic variation references any of two or more alternative forms of a gene occupying the same chromosomal locus. Allelic variation arises naturally through mutation, and can result in phenotypic polymorphism within populations. Gene mutations can be silent (no change in the encoded polypeptide) or can encode polypeptides having altered amino acid sequence. The term "allelic variant" also is used herein to denote a protein encoded by an allelic variant of a gene. Typically the reference form of the gene encodes a wildtype form and/or predominant form of a polypeptide from a population or single reference member of a species. Typically, allelic variants, which include variants between and among species typically have at least 80%, 90% or greater amino acid identity with a wildtype and/or predominant form from the same species; the degree of identity

depends upon the gene and whether comparison is interspecies or intraspecies. Generally, intraspecies allelic variants have at least about 80%, 85%, 90% or 95% identity or greater with a wildtype and/or predominant form, including 96%, 97%, 98%, 99% or greater identity with a wildtype and/or predominant form of a polypeptide. Reference to an allelic variant herein generally refers to variations n proteins among members of the same species.

As used herein, "allele," which is used interchangeably herein with "allelic variant" refers to alternative forms of a gene or portions thereof. Alleles occupy the same locus or position on homologous chromosomes. When a subject has two identical alleles of a gene, the subject is said to be homozygous for that gene or allele. When a subject has two different alleles of a gene, the subject is said to be heterozygous for the gene. Alleles of a specific gene can differ from each other in a single nucleotide or several nucleotides, and can include substitutions, deletions and insertions of nucleotides. An allele of a gene also can be a form of a gene containing a mutation.

As used herein, species variants refer to variants in polypeptides among different species, including different mammalian species, such as mouse and human.

As used herein, a splice variant refers to a variant produced by differential processing of a primary transcript of genomic DNA that results in more than one type of mRNA.

As used herein, the term promoter means a portion of a gene containing DNA sequences that provide for the binding of RNA polymerase and initiation of transcription. Promoter sequences are commonly, but not always, found in the 5' non-coding region of genes.

As used herein, isolated or purified polypeptide or protein or biologically-active portion thereof is substantially free of cellular material or other contaminating proteins from the cell or tissue from which the protein is derived, or substantially free from chemical precursors or other chemicals when chemically synthesized. Preparations can be determined to be substantially free if they appear free of readily detectable impurities as determined by standard methods of analysis, such as thin layer chromatography (TLC), gel electrophoresis and high performance liquid chromatography (HPLC), used by those of skill in the art to assess such purity, or

sufficiently pure such that further purification does not detectably alter the physical and chemical properties, such as enzymatic and biological activities, of the substance. Methods for purification of the compounds to produce substantially chemically pure compounds are known to those of skill in the art. A substantially chemically pure compound, however, can be a mixture of stereoisomers. In such instances, further purification might increase the specific activity of the compound.

The term substantially free of cellular material includes preparations of proteins in which the protein is separated from cellular components of the cells from which it is isolated or recombinantly-produced. In one embodiment, the term substantially free of cellular material includes preparations of protease proteins having less that about 30% (by dry weight) of non-protease proteins (also referred to herein as a contaminating protein), generally less than about 20% of non-protease proteins or 10% of non-protease proteins or less that about 5% of non-protease proteins. When the protease protein or active portion thereof is recombinantly produced, it also is substantially free of culture medium, i.e., culture medium represents less than about or at 20%, 10% or 5% of the volume of the protease protein preparation.

As used herein, the term substantially free of chemical precursors or other chemicals includes preparations of protease proteins in which the protein is separated from chemical precursors or other chemicals that are involved in the synthesis of the protein. The term includes preparations of protease proteins having less than about 30% (by dry weight), 20%, 10%, 5% or less of chemical precursors or non-protease chemicals or components.

As used herein, synthetic, with reference to, for example, a synthetic nucleic acid molecule or a synthetic gene or a synthetic peptide refers to a nucleic acid molecule or polypeptide molecule that is produced by recombinant methods and/or by chemical synthesis methods.

As used herein, production by recombinant means by using recombinant DNA methods means the use of the well known methods of molecular biology for expressing proteins encoded by cloned DNA.

As used herein, vector (or plasmid) refers to discrete elements that are used to introduce a heterologous nucleic acid into cells for either expression or replication thereof. The vectors typically remain episomal, but can be designed to effect

integration of a gene or portion thereof into a chromosome of the genome. Also contemplated are vectors that are artificial chromosomes, such as yeast artificial chromosomes and mammalian artificial chromosomes. Selection and use of such vehicles are well known to those of skill in the art.

As used herein, an expression vector includes vectors capable of expressing DNA that is operatively linked with regulatory sequences, such as promoter regions, that are capable of effecting expression of such DNA fragments. Such additional segments can include promoter and terminator sequences, and optionally can include one or more origins of replication, one or more selectable markers, an enhancer, a polyadenylation signal, and the like. Expression vectors are generally derived from plasmid or viral DNA, or can contain elements of both. Thus, an expression vector refers to a recombinant DNA or RNA construct, such as a plasmid, a phage, recombinant virus or other vector that, upon introduction into an appropriate host cell, results in expression of the cloned DNA. Appropriate expression vectors are well known to those of skill in the art and include those that are replicable in eukaryotic cells and/or prokaryotic cells and those that remain episomal or those which integrate into the host cell genome.

As used herein, vector also includes "virus vectors" or "viral vectors." Viral vectors are engineered viruses that are operatively linked to exogenous genes to transfer (as vehicles or shuttles) the exogenous genes into cells.

As used herein, operably or operatively linked when referring to DNA segments means that the segments are arranged so that they function in concert for their intended purposes, e.g., transcription initiates in the promoter and proceeds through the coding segment to the terminator.

As used herein, biological sample refers to any sample obtained from a living or viral source and includes any cell type or tissue of a subject from which nucleic acid or protein or other macromolecule can be obtained. Biological samples include, but are not limited to, body fluids, such as blood, plasma, serum, cerebrospinal fluid, synovial fluid, urine and sweat, tissue and organ samples from animals and plants. Also included are soil and water samples and other environmental samples, viruses, bacteria, fungi, algae, protozoa and components thereof. Hence bacterial and viral and other contamination of food products and environments can be assessed. The

methods herein are practiced using biological samples and in some embodiments, such as for profiling, also can be used for testing any sample.

As used herein, macromolecule refers to any molecule having a molecular weight from the hundreds up to the millions. Macromolecules include peptides, proteins, nucleotides, nucleic acids, and other such molecules that are generally synthesized by biological organisms, but can be prepared synthetically or using recombinant molecular biology methods.

As used herein, the term "biopolymer" is a biological molecule, including macromolecules, composed of two or more monomeric subunits, or derivatives thereof, which are linked by a bond or a macromolecule. A biopolymer can be, for example, a polynucleotide, a polypeptide, a carbohydrate, or a lipid, or derivatives or combinations thereof, for example, a nucleic acid molecule containing a peptide nucleic acid portion or a glycoprotein, respectively. Biopolymers include, but are not limited to, nucleic acids, proteins, polysaccharides, lipids and other macromolecules. Nucleic acids include DNA, RNA, and fragments thereof. Nucleic acids can be derived from genomic DNA, RNA, mitochondrial nucleic acid, chloroplast nucleic acid and other organelles with separate genetic material.

As used herein, a biomolecule is any compound found in nature, or derivatives thereof. Biomolecules include, but are not limited to: oligonucleotides, oligonucleosides, proteins, peptides, amino acids, peptide nucleic acids (PNAs), oligosaccharides and monosaccharides.

As used herein, a biological particle refers to a virus, such as a viral vector or viral capsid with or without packaged nucleic acid, phage, including a phage vector or phage capsid, with or without encapsulated nucleic acid, a single cell, including eukaryotic and prokaryotic cells or fragments thereof, a liposome or micellar agent or other packaging particle, and other such biological materials.

As used herein, a composition refers to any mixture. It can be a solution, a suspension, liquid, powder, a paste, aqueous, non-aqueous or any combination thereof.

As used herein, a combination refers to any association between or among two or more items. The combination can be two or more separate items, such as two

compositions or two collections, can be a mixture thereof, such as a single mixture of the two or more items, or any variation thereof.

As used herein, kit refers to a packaged combination, optionally including instructions and/or reagents for their use.

As used herein, fluid refers to any composition that can flow. Fluids thus encompass compositions that are in the form of semi-solids, pastes, solutions, aqueous mixtures, gels, lotions, creams and other such compositions.

As used herein, antigenic means that a polypeptide induce an immune response. Highly antigenic polypeptides are those that reproducibly and predictably induce an immune response.

As used herein, a pharmaceutical effect or therapeutic effect refers to an effect observed upon administration of an agent intended for treatment of a disease or disorder or for amelioration of the symptoms thereof.

As used herein, "disease or disorder" refers to a pathological condition in an organism resulting from cause or condition including, but not limited to, infections, acquired conditions, genetic conditions, and characterized by identifiable symptoms. Diseases and disorders of interest herein are those involving a specific target protein including those mediated by a target protein and those in which a target protein plays a role in the etiology or pathology. Exemplary target proteins and associated diseases and disorders are described elsewhere herein.

As used herein, "treating" a subject with a disease or condition means that the subject's symptoms are partially or totally alleviated, or remain static following treatment. Hence treatment encompasses prophylaxis, therapy and/or cure. Prophylaxis refers to prevention of a potential disease and/or a prevention of worsening of symptoms or progression of a disease. Treatment also encompasses any pharmaceutical use of a modified interferon and compositions provided herein.

As used herein, a therapeutic agent, therapeutic regimen, radioprotectant, or chemotherapeutic mean conventional drugs and drug therapies, including vaccines, which are known to those skilled in the art. Radiotherapeutic agents are well known in the art.

As used herein, treatment means any manner in which the symptoms of a condition, disorder or disease or other indication, are ameliorated or otherwise beneficially altered.

As used herein therapeutic effect means an effect resulting from treatment of a subject that alters, typically improves or ameliorates the symptoms of a disease or condition or that cures a disease or condition. A therapeutically effective amount refers to the amount of a composition, molecule or compound which results in a therapeutic effect following administration to a subject.

As used herein, the term "subject" refers to an animal, including a mammal, such as a human being.

As used herein, a patient refers to a human subject.

As used herein, amelioration of the symptoms of a particular disease or disorder by a treatment, such as by administration of a pharmaceutical composition or other therapeutic, refers to any lessening, whether permanent or temporary, lasting or transient, of the symptoms that can be attributed to or associated with administration of the composition or therapeutic.

As used herein, prevention or prophylaxis refers to methods in which the risk of developing disease or condition is reduced.

As used herein, an effective amount is the quantity of a therapeutic agent necessary for preventing, curing, ameliorating, arresting or partially arresting a symptom of a disease or disorder.

As used herein, administration refers to any method in which an antibody or protion thereof is contacted with its target protein. Adminstration can be effected *in vivo* or *ex vivo* or *in vitro*. For example, for *ex vivo* administration a body fluid, such as blood, is removed from a subject and contacted outside the body with the antibody or portion thereof. For *in vivo* administration, the antibody or portion thereof can be introduced into the body, such as by local, topical, systemic and/or other route of introduction. *In vitro* administration encompasses methods, such as cell culture methods.

As used herein, unit dose form refers to physically discrete units suitable for human and animal subjects and packaged individually as is known in the art.

As used herein, a single dosage formulation refers to a formulation for direct administration.

As used herein, an "article of manufacture" is a product that is made and sold. As used throughout this application, the term is intended to encompass compiled germline antibodies or antibodies obtained therefrom contained in articles of packaging.

As used herein, fluid refers to any composition that can flow. Fluids thus encompass compositions that are in the form of semi-solids, pastes, solutions, aqueous mixtures, gels, lotions, creams and other such compositions.

As used herein, animal includes any animal, such as, but are not limited to primates including humans, gorillas and monkeys; rodents, such as mice and rats; fowl, such as chickens; ruminants, such as goats, cows, deer, sheep; mammals, such as pigs and other animals. Non-human animals exclude humans as the contemplated animal. The germline segments, and resulting antibodies, provided herein are from any source, animal, plant, prokaryotic and fungal. Most germline segments, and resulting antibodies, are of animal origin, including mammalian origin.

As used herein, a control refers to a sample that is substantially identical to the test sample, except that it is not treated with a test parameter, or, if it is a sample plasma sample, it can be from a normal volunteer not affected with the condition of interest. A control also can be an internal control.

As used herein, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to compound, comprising "an extracellular domain" includes compounds with one or a plurality of extracellular domains.

As used herein, ranges and amounts can be expressed as "about" a particular value or range. About also includes the exact amount. Hence "about 5 bases" means "about 5 bases" and also "5 bases."

As used herein, "optional" or "optionally" means that the subsequently described event or circumstance does or does not occur, and that the description includes instances where said event or circumstance occurs and instances where it does not. For example, an optionally substituted group means that the group is unsubstituted or is substituted.

As used herein, the abbreviations for any protective groups, amino acids and other compounds, are, unless indicated otherwise, in accord with their common usage, recognized abbreviations, or the IUPAC-IUB Commission on Biochemical Nomenclature (see, (1972) *Biochem.* 11:1726).

B. DLL4

Provided herein are antibodies or antigen-binding antibody fragments that specifically bind to human Delta-like ligand 4 (DLL4).

1. Structure

DLL4 (set forth in SEQ ID NO:114; and encoded by a sequence of nucleotides set forth in SEQ ID NO:113) is a transmembrane protein ligand for Notch transmembrane receptors. The extracellular region contains 8 EGF-like repeats, as well as a DSL domain that is conserved among all Notch ligands and is necessary for receptor binding. The protein also contains a transmembrane region, and a cytoplasmic tail lacking any catalytic motifs. Human DLL4 is a 685 amino acid protein and contains the following domains corresponding to amino acids set forth in SEQ ID NO:114: signal peptide (amino acids 1-25); MNNL (amino acids 26-92); DSL (amino acids 155-217); EGF-Like 1 (EGF1; amino acids 221-251); EGF-Like 2 (EGF2; amino acids 252-282); EGF-Like 3 (EGF3; amino acids 284-322); EGF-Like 4 (EGF4; amino acids 324-360); EGF-Like 5 (EGF5; amino acids 366-400); EGF-Like 6 (EGF6; amino acids 402-438); EGF-Like 7 (EGF7; amino acids 440-476); EGF-Like 8 (EGF8; amino acids 480-518); transmembrane (amino acids 529-551); and cytoplasmic domain (amino acids 553-685).

2. Expression

DLL4 is expressed widely in a variety of tissues, but its expression is predominantly localized to the vasculature. It is required for normal vascular development and is expressed on tumor vessels. It is upregulated in blood vessels during tumor angiogenesis and expression is dependent on VEGF signaling. DLL4 also is expressed on activated macrophages exposed to proinflammatory stimuli such as lipopolysaccharide, interleukin-1β, Toll-like receptor 4 ligands and other proinflammatory stimuli and it's signaling through the Notch pathway plays a role in inflammatory states characterized by macrophage activation (Fung *et al.* (2007) *Circulation*, 115: 2948-2956).

3. Function

DLL4 binds to Notch receptors. The evolutionary conserved Notch pathway is a key regulator of many developmental processes as well as postnatal self-renewing organ systems. From invertebrates to mammals, Notch signaling guides cells through a myriad of cell fate decisions and incluences proliferation, differentiation and apoptosis (Miele and Osborne (1999) *J Cell Physiol.*, 181:393-409). The Notch family is made up of structurally conserved cell surface receptors that are activated by membrane bound ligands of the DSL gene family (named for Delta and Serrate from Drosophila and Lag-2 from *C. elegans*). Mammals have four receptors (Notch 1, Notch 2, Notch 3 and Notch 4) and five ligands (Jag 1, Jag 2, DLL1, DLL3, and DLL4). Upon activation by ligands presented on neighboring cells, Notch receptors undergo successive proteolytic cleavages; an extracellular cleavage mediated by an ADAM protease and a cleavage within the trnamembrane domain mediated by gamma secretase. This leads to the release of the Notch Intra-Cellular Domain (NICD), which translocates into the nucleus and forms a transcriptional complex with the DNA binding protein, RBP-Jk (also known as CSL for CBF1/Su(H)/Lag-1) and other transcriptional cofactors. The primary target genes of Notch activation include the HES (Hairy/Enhance of Split) gene family and HES-related genes (Hey, CHF, HRT, HESR), which in turn regulate the downstream transcriptional effectors in a tissue and cell-type specific manner (Iso et al. (2003) *J Cell Physiol.*, 194:237-255; Li and Harris (2005) *Cancer Cell*, 8:1-3).

Signaling by Notch receptors implicate a variety of cellular processes including, but not limited to, the normal maintenance and leukemic transformation of hematopoietic stem cells (HSCs; Kopper & Hajdu (2004) *Pathol. Oncol. Res.*, 10:69-73); maintenance of neural stem cells including in their normal maintenance as well as in brain cancers (Kopper & Hajdu (2004) *Pathol. Oncol. Res.*, 10:69-73; Purow et al. (2005) *Cancer Res.* 65:2353-63; Hallahan et al., (2004) *Cancer Res.* 64:7794-800); generation of a number of human cancers including in lymphoblastic leukemia/lymphoma (Ellisen et al. (1991) *Cell*, 66:649-61; Robey et al. (1996) *Cell*, 87:483-92; Pear et al. (1996) *J. Exp. Med.* 183:2283-91; Yan et al. (2001) *Blood* 98:3793-9; Bellavia et al. (2000) *EMBO J.* 19:3337-48; Pear & Aster (2004) *Curr. Opin. Hematol.*, 11:416-33); breast cancer (Gallahan & Callahan (1987) *J. Virol.*,

61:66-74; Brennan & Brown (2003) *Breast Cancer Res.*, 5:69; Politi et al. (2004) *Semin. Cancer Biol.*, 14:341-7; Weijzen et al. (2002) *Nat. Med.*, 8:979-86; Parr et al. (2004) *Int. J. Mol. Med.*, 14:779-86); cervical cancer (Zagouras et al. (1995) *PNAS*, 92:6414-8); renal cell carcinomas (Rae et al (2000) *Int. J. Cancer*, 88:726-32); head and neck squamous cell carcinomas (Leethanakul et al (2000) *Oncogene*, 19:3220-4); endometrial cancers (Suzuki *et al.* (2000) *Int. J. Oncol.*, 17:1131-9); and neuroblastomas (van Limpt *et al.* (2000) *Med. Pediatr. Oncol.*, 35:554-8).

The Notch pathway also is involved in multiple aspects of vascular development including proliferation, migration, smooth muscle differentiation, angiogenesis and arterial-venous differentiation (Iso *et al.* (2003) *Arterioscler. Thromb. Vasc. Biol.* 23: 543).

Specifically, DLL4 activiates Notch-1 (Uniprot accession No. P46531; SEQ ID NO:899) and Notch-4 receptors (Uniprot accession No. Q99466; SEQ ID NO:900). DLL4 is involved in stem cell self-renewal and in stem cell growth and differentiation in many lineages and tumor types (Wilson and Radtke (2006), *FEBS Lett.*, 580:2860-8). DLL4 also is involved in vascular development. Deletion of a single allele of DLL4 results in embryonic lethality caused by defects in development of the vasculature (Duarte et al. (2004) *Genes Dev.*, 18:2474-8; Gale et al. (2004) *PNAS*, 101:15949-54; Krebs et al. (2004), *Genes Dev.*, 18:2469-73).

DLL4-mediated Notch signaling is involved in embryonic vascular development. For example, DLL4 expression in growing endothelial cells in the neonatal retina indicates a role for DLL4 in retinal vascular development. DLL4 also is involved in tumor angiogenesis. Down-regulation of DLL4 expression inhibits VEGF-mediated endotheilial cell proliferation, migration, and network formation (Patel et al. (2005) *Cancer Res.* 65:8690-7). Yet, DLL4 expression on angiogenic endothelial cells acts as a negative regulator of tumor angiogenesis and vascular growth. (Ridgway *et al.* (2006) *Nature*, 444:1083; Noguera-Troise *et al.* (2006) *Nature*, 444:1032). Although blockage of DLL4 is associated with increased angiogenesis characterized by sprouting and branching of blood vessels, it also is associated with a decrease in vessel function, thereby resulting in decreased tumor growth (Ridgway *et al.* (2006) *Nature*, 444:1083; Noguera-Troise *et al.* (2006) *Nature*, 444:1032). Accordingly, DLL4 function is associated with deregulated

angiogenesis by uncoupling of tumor growth from tumor vascular density. Thus, blocking DLL4 signaling effectively reduces tumor growth by disrupting productive angiogenesis. The inhibitory effect of DLL4 on angiogenesis is distinct from traditional antiangiogenic therapies by causing hyperproliferation of tumor vessels that leads to a reduction in tumor growth (Sainson and Harris (2007) *Trend Mol. Med.*, 13:389-395; Thurston et al. (2007), *Nat Rev. Cancer*, 7:327-331). Blocking DLL4 also inhibits tumor growth and tumorigenic cell frequency independent of an angiogenic mechanism by decreasing tumor growth, delaying tumor recurrence after chemotherapeutic treatment and decreasing the percentage of tumorogenic cells (Hoey et al. (2009) *Cell Stem Cell*, 5:168-177). Blocking DLL4 activity is associated with decreased gene expression of *HES1* (Hoey et al. (2009) *Cell Stem Cell*, 5:168-177).

C. ANTIBODIES

Provided herein are antibodies that modulate the activity of DLL4 and therefore can be used in the treatment of diseases or conditions associated with expression or activity of DLL4. Such antibodies include those that have a VH chain and a VL chain sufficient to form an antigen binding site. The antibodies further can contain a constant region. Anti-DLL4 antibodies include full-length antibodies and antigen binding antibody fragments, whereby the fragment or portion of the antibody is sufficient to form an antigen binding site. Included among fragments or portions of antibody members in the libraries provided herein are a Fab, Fab', $F(ab')_2$, single-chain Fvs (scFv), Fv, dsFv, diabody, Fd and Fd' fragments, Fab fragments, Fd fragments, scFv fragments, or a scFab fragments. Exemplary of such antibodies are Fab antibodies. Antibodies provided herein include isolated antibodies.

Antibodies or fragments thereof provided herein bind DLL4. The antibodies include those that have a binding affinity for DLL4 that is or is about 10^{-6} M, 10^{-7} M, 10^{-8} M, 10^{-9} M, 10^{-10} M, 10^{-11} M, 10^{-12} M or lower, in particular any that have a nanomolar or sub-nanomolar binding affinity, for example, that is or is about 1×10^{-9} M, 2×10^{-9} M, 3×10^{-9} M, 4×10^{-9} M, 5×10^{-9} M, 6×10^{-9} M, 7×10^{-9} M, 8×10^{-9} M, 9×10^{-9} M, 1×10^{-10} M, 2×10^{-10} M, 3×10^{-10} M, 4×10^{-10} M, 5×10^{-10} M, 10^{-11} M, 10^{-12} M or lower.

In some embodiments, the antibody specifically binds to DLL4. In other examples, the antibody has dual- or multi-specificity for DLL4 and one or more other target proteins. Hence, anti-DLL4 antibodies provided herein are bispecific or multispecific having binding specificity for at least two different antigens. For example, an anti-DLL4 antibody can exhibit binding specificity for DLL4 and at least one other target protein that is a a cytokine receptor, a receptor kinase, a receptor phosphatase, a receptor involved in cell-cell interactions or a cellular adhesion molecule. For example, an anti-DLL4 antibody also can exhibit binding specificity for a target protein including, but not limited to, a VEGFR-1, VEGFR-2, VEGFR-3, a epidermal growth factor receptor (EGFR), ErbB-2, ErbB-3, IGF-R1, C-Met, TNF-R1, TNF-R2, BTLA, HVEM, LT-βR, CD20, CD3, CD25, NOTCH, DLL4, DDR1 (discoidin domain receptor), KIT (receptor for c-kit), FGFR1, FGFR2, FGFR4 (fibroblast growth factor receptors 1, 2 and 4), RON (recepteur d'origine nantais; also known as macrophage stimulating 1 receptor), TEK (endothelial-specific receptor tyrosine kinase), TIE (tyrosine kinase with immunoglobulin and epimermal growth factor homology domains receptor), CSF1R (colngly stimulating factor 1 receptor), PDGFRB (platelet-derived growth factor receptor B), EPHA1, EPHA2, EPHB1 (erythropoietin-producing hepatocellular receptor A1, A2 and B1), (recepteur d'origine nantais; also known as macrophage stimulating 1 receptor), G-CSF-R, GM-CSF-R, EPO-R, a cadherin (e.g. p-cadherin), an integrin, CD52 and CD44, a VEGF-A, VEGF-B, VEGF-C, VEGF-D, PIGF, EGF, HGF, TNF-α, LIGHT, lymphotoxin (LT), IgE, G-CSF, GM-CSF and EPO. Generally, when exhibiting dual- or multi-specific binding an antibody provided herein has a binding affinity for each of the target antigens that is or is about 10^{-6} M, 10^{-7} M, 10^{-8} M, 10^{-9} M, 10^{-10} M, 10^{-11} M, 10^{-12} M or lower.

In some embodiments, the antibody specifically binds to the DLL4 extracellular domain (ECD). For example, an anti-DLL4 antibody provided herein binds to an epitope in any one or more of the domains within the ECD, including, but not limited an epitope within the MNNL, DSL, EGF1, EGF2, EGF3, EGF4, EGF5, EGF6, EGF7 or EGF8 domain. In particular, an anti-DLL4 antibody provided herein binds to an epitope within the ECD that is between the EGF2 to EGF8 region, for example, within amino acid residues 252 to 524 of DLL4 set forth in SEQ ID

NO:114. In one examples, anti-DLL4 antibodies provided herein bind to an epitope within the ECD that is within EGF2 corresponding to an epitope within or between amino acids 252 to 280 of DLL4 set forth in SEQ ID NO:114. In another example, anti-DLL4 antibodies provided herein bind to an epitope within or between amino acid residues 283 to 360 of DLL4 set forth in SEQ ID NO:114 in the EGF3 to EGF4 region.

Anti-DLL4 antibody provided herein includes those that are agonists, mimicking the normal effects of receptor binding, or antagonists, inhibiting the normal effects of receptor binding. Of particular interest are antibodies which bind to the target protein and modulate intracellular signalling. In some embodiments, an antibody reduces, inhibits, and/or blocks DLL4 activity *in vivo* and/or *in vitro*. In some embodiments, the antibody competes for binding with DLL4-ligand (reduces and/or blocks Notch receptor binding to DLL4). In some embodiments, the antibodies can modulate one or more aspects of DLL4-associated effects, including but not limited to any one or more of reduction or blocking of Notch receptor activation, reduction or blocking of Notch receptor downstream molecular signaling, disruption or blocking of Notch receptor binding to DLL4, and/or promotion of endothelial cell proliferation, and/or inhibition of endothelial cell differentiation, and/or inhibition of arterial differentiation, and/or inhibition of tumor vascular perfusion, and/or treatment and/or prevention of a tumor, cell proliferative disorder or a cancer; and/or treatment or prevention of a disorder associated with DLL4 expression and/or activity and/or treatment or prevention of a disorder associated with Notch receptor expression and/or activity. Exemplary of activities modulated by anti-DLL4 antibodies include inhibiting angiogenesis, tumor growth and/or tumorigenic cell frequency.

Anti-DLL4 antibodies provided herein include germline-derived anti-DLL4 antibodies, or modified antibodies thereof. Anti-DLL4 antibodies provided herein also include those that contain one or more complementary determining regions (CDRs) involved in binding to DLL4.

1. Germline-Derived Anti-DLL4 Antibodies

Anti-DLL4 antibodies provided herein include those that are derived from germline segments of human origin. Exemplary antibody germline sources include

but are not limited to databases at the National Center for Biotechnology Information (NCBI), the international ImMunoGeneTics information system® (IMGT), the Kabat database and the Tomlinson's VBase database (Lefranc (2003) *Nucleic Acids Res.*, 31:307-310; Martin *et al.*, Bioinformatics Tools for Antibody Engineering in Handbook of Therapeutic Antibodies, Wiley-VCH (2007), pp. 104-107). Variable gene segments include V_H, D_H, J_H, V_κ, J_κ, V_λ and J_λ. Hence, the heavy chain of an anti-DLL4 antibody provided herein includes amino acids encoded by a V_H, D_H, and J_H germline segment. Table 3 lists exemplary human heavy chain germline gene segments. The light chain of an anti-DLL4 antibody provided herein includes amino acids encoded by a V_κ, J_κ, V_λ and J_λ germline segment. Tables 4 and 5 list exemplary human light chain germline gene segments.

For purposes herein, germline segments are listed using IMGT gene names and definitions previously approved by the Human Genome Organization (HUGO) nomenclature committee. The segments are named using IMGT nomenclature, whereby the first three letters indicate the locus (IGH, IGK or IGL), the fourth letter represents the gene (e.g., V for V-gene, D for D-gene, J for J-gene), the fifth position indicates the number of the subgroup, followed by a hyphen indicating the gene number classification. For alleles, the IMGT name is followed by an asterisk and a two figure number. Any desired naming convention can be used to identify antibody germline segments. For purposes herein when describing the variable heavy or light chain nucleic acid sequence derived from germline segments (see e.g., Tables 3-5), VH germline segments are named using IMGT nomenclature without any allele identified; VK germline segments are named using Zachau nomenclature; and VL germline segments are identified using Kawasaki nomenclature. DH, JH, JK and JL germline segments are named using IMGT nomenclature.

Table 3: Human Heavy Chain Germline V Genes

V Segments			D Segments		J Segments	
SEQ ID NO	**IMGT with alleles**	**IMGT**	**SEQ ID NO**	**IMGT with alleles**	**SEQ ID NO**	**IMGT with alleles**
574	IGHV1-18*01	VH1-18	690	IGHD2-15*01	719	IGHJ1*01
575	IGHV1-18*02		691	IGHD2-2*01	720	IGHJ2*01
576	IGHV1-2*01		692	IGHD2-2*02	721	IGHJ3*01

Table 3: Human Heavy Chain Germline V Genes

V Segments			D Segments		J Segments	
SEQ ID NO	IMGT with alleles	IMGT	SEQ ID NO	IMGT with alleles	SEQ ID NO	IMGT with alleles
577	IGHV1-2*02	VH1-2	693	IGHD2-2*03	722	IGHJ4*01
578	IGHV1-2*03		694	IGHD2-21*01	723	IGHJ4*02
579	IGHV1-2*04		695	IGHD2-21*02	724	IGHJ4*03
580	IGHV1-24*01	VH1-24	696	IGHD2-8*01	725	IGHJ6*01
581	IGHV1-3*01		697	IGHD2-8*02	726	IGHJ6*02
582	IGHV1-3*02	VH1-3	698	IGHD3-10*01	727	IGHJ6*03
583	IGHV1-45*01		699	IGHD3-10*02	728	IGHJ6*04
584	IGHV1-45*02	VH1-45	700	IGHD3-16*01		
585	IGHV1-45*03		701	IGHD3-16*02		
586	IGHV1-46*01	VH1-46	702	IGHD3-22*01		
587	IGHV1-46*02		703	IGHD3-3*01		
588	IGHV1-46*03		704	IGHD3-3*02		
589	IGHV1-58*01		705	IGHD3-9*01		
590	IGHV1-58*02	VH1-58	706	IGHD4-11*01		
591	IGHV1-69*01		707	IGHD4-17*01		
592	IGHV1-69*02		708	IGHD4-23*01		
593	IGHV1-69*03		709	IGHD4-4*01		
594	IGHV1-69*04		710	IGHD5-12*01		
595	IGHV1-69*05		711	IGHD5-18*01		
596	IGHV1-69*06	VH1-69	712	IGHD5-24*01		
597	IGHV1-69*07		713	IGHD5-5*01		
598	IGHV1-69*08		714	IGHD6-13*01		
599	IGHV1-69*09		715	IGHD6-19*01		
600	IGHV1-69*10		716	IGHD6-25*01		
601	IGHV1-69*11		717	IGHD6-6*01		
602	IGHV1-69*12		718	IGHD7-27*01		
603	IGHV1-69*13					
604	IGHV1-8*01	VH1-8				
605	IGHV1-c*01					
606	IGHV1-f*01					
607	IGHV1-f*02					
608	IGHV4-28*01	VH4-28				
609	IGHV4-28*02					
610	IGHV4-28*03					
611	IGHV4-28*04					
612	IGHV4-28*05					
613	IGHV4-30-2*01					
614	IGHV4-30-2*02					

Table 3: Human Heavy Chain Germline V Genes						
V Segments			D Segments		J Segments	
SEQ ID NO	IMGT with alleles	IMGT	SEQ ID NO	IMGT with alleles	SEQ ID NO	IMGT with alleles
615	IGHV4-30-2*03					
616	IGHV4-30-2*04					
617	IGHV4-30-4*01					
618	IGHV4-30-4*02					
619	IGHV4-30-4*03					
620	IGHV4-30-4*04					
621	IGHV4-30-4*05					
622	IGHV4-30-4*06					
623	IGHV4-31*01					
624	IGHV4-31*02	VH4-31				
625	IGHV4-31*03					
626	IGHV4-31*04					
627	IGHV4-31*05					
628	IGHV4-31*06					
629	IGHV4-31*07					
630	IGHV4-31*08					
631	IGHV4-31*09					
632	IGHV4-31*10					
633	IGHV4-34*01	V4-34				
634	IGHV4-34*02					
635	IGHV4-34*03					
636	IGHV4-34*04					
637	IGHV4-34*05					
638	IGHV4-34*06					
639	IGHV4-34*07					
640	IGHV4-34*08					
641	IGHV4-34*09					
642	IGHV4-34*10					
643	IGHV4-34*11					
644	IGHV4-34*12					
645	IGHV4-34*13					
646	IGHV4-39*01	VH4-39				
647	IGHV4-39*02					

Table 3: Human Heavy Chain Germline V Genes

V Segments			D Segments		J Segments	
SEQ ID NO	IMGT with alleles	IMGT	SEQ ID NO	IMGT with alleles	SEQ ID NO	IMGT with alleles
648	IGHV4-39*03					
649	IGHV4-39*04					
650	IGHV4-39*05					
651	IGHV4-39*06					
652	IGHV4-39*07					
653	IGHV4-4*01					
654	IGHV4-4*02					
655	IGHV4-4*03					
656	IGHV4-4*04					
657	IGHV4-4*05					
658	IGHV4-4*06					
659	IGHV4-4*07	VH4-4				
660	IGHV4-59*01	VH4-59				
661	IGHV4-59*02					
662	IGHV4-59*03					
663	IGHV4-59*04					
664	IGHV4-59*05					
665	IGHV4-59*06					
666	IGHV4-59*07					
667	IGHV4-59*08					
668	IGHV4-59*09					
669	IGHV4-59*10					
670	IGHV4-61*01					
671	IGHV4-61*02					
672	IGHV4-61*03					
673	IGHV4-61*04					
674	IGHV4-61*05					
675	IGHV4-61*06					
676	IGHV4-61*07					
677	IGHV4-61*08	VH4-61				
678	IGHV4-b*01					
679	IGHV4-b*02					
680	IGHV5-51*01					
681	IGHV5-51*02					
682	IGHV5-51*03	VH5-51				
683	IGHV5-51*04					
684	IGHV5-51*05					
685	IGHV5-a*01					
686	IGHV5-a*03					
687	IGHV5-a*04					

Table 3: Human Heavy Chain Germline V Genes						
V Segments			D Segments		J Segments	
SEQ ID NO	IMGT with alleles	IMGT	SEQ ID NO	IMGT with alleles	SEQ ID NO	IMGT with alleles
688	IGHV6-1*01	VH6-1				
689	IGHV6-1*02					

Table 4: Human Light Chain Germline Kappa V Genes				
SEQ ID NO	IMGT with alleles	Zachau	SEQ ID NO	J SEGMENTS
729	IGKV1-12*01	L5	795	IGKJ1*01
730	IGKV1-12*02			
731	IGKV1-13*02	L4/18a		
732	IGKV1-16*01	L1		
733	IGKV1-17*01	A30		
734	IGKV1-17*02			
735	IGKV1-27*01	A20		
736	IGKV1-33*01	O18		
737	IGKV1-37*01	O14		
738	IGKV1-39*01	O12		
739	IGKV1-39*02	O12a		
740	IGKV1-5*01	L12		
741	IGKV1-5*02			
742	IGKV1-5*03	L12a		
743	IGKV1-6*01	L11		
744	IGKV1-8*01	L9		
745	IGKV1-9*01	L8		
746	IGKV1-NL1*01			
747	IGKV1/OR2-0*01	Z0		
748	IGKV1/OR2-108*01			
749	IGKV1D-12*01	L19		
750	IGKV1D-12*02			
751	IGKV1D-13*01	L18		
752	IGKV1D-16*01	L15		
753	IGKV1D-16*02	L15a		
754	IGKV1D-17*01	L14		
755	IGKV1D-33*01	08		
756	IGKV1D-37*01	O4		
757	IGKV1D-39*01	O2		
758	IGKV1D-42*01	L22		

759	IGKV1D-43*01	L23		
760	IGKV1D-8*01	L24		
761	IGKV2-24*01	A23		
762	IGKV2-28*01	A19		
763	IGKV2-29*02	A18b		
764	IGKV2-29*03			
765	IGKV2-30*01	A17		
766	IGKV2-40*01	O11		
767	IGKV2-40*02	O11a		
768	IGKV2D-24*01	A7		
769	IGKV2D-26*01	A5		
770	IGKV2D-26*02			
771	IGKV2D-28*01	A3		
772	IGKV2D-29*01	A2		
773	IGKV2D-29*02			
774	IGKV2D-30*01	A1		
775	IGKV2D-40*01	O1		
776	IGKV3-11*01	L6		
777	IGKV3-11*02			
778	IGKV3-15*01	L2		
779	IGKV3-20*01	A27		
780	IGKV3-20*02			
781	IGKV3-7*01	L10		
782	IGKV3-7*02	L10a		
783	IGKV3-7*03			
784	IGKV3-NL1*01			
785	IGKV3-NL2*01			
786	IGKV3-NL3*01			
787	IGKV3-NL4*01			
788	IGKV3-NL5*01			
789	IGKV3/OR2-268*01			
790	IGKV3/OR2-268*02			
791	IGKV3D-11*01	L20		
792	IGKV3D-15*01	L16		
793	IGKV3D-20*01	A11		
794	IGKV3D-7*01	L25		

Table 5: Human Light Chain Germline Lambda V Genes

SEQ ID NO	V Segments	Kawasaki	SEQ ID NO	J SEGMENTS
796	IGLV2-11*01	V1-3	828	IGLJ1*01
797	IGLV2-11*02		829	IGLJ4*01
798	IGLV2-11*03			

799	IGLV2-14*01	V1-4		
800	IGLV2-14*02			
801	IGLV2-14*03			
802	IGLV2-14*04			
803	IGLV2-18*01	V1-5		
804	IGLV2-18*02			
805	IGLV2-18*03			
806	IGLV2-18*04			
807	IGLV2-23*01			
808	IGLV2-23*02			
809	IGLV2-23*03	V1-7		
810	IGLV2-33*01	V1-9		
811	IGLV2-33*02			
812	IGLV2-33*03			
813	IGLV2-8*01	V1-2		
814	IGLV2-8*02			
815	IGLV2-8*03			
816	IGLV5-37*01	V4-1		
817	IGLV5-39*01			
818	IGLV5-39*02			
819	IGLV5-45*01			
820	IGLV5-45*02			
821	IGLV5-45*03	V4-2		
822	IGLV5-48*01	V4-3		
823	IGLV5-52*01	V4-4		
824	IGLV8-61*01	V3-4		
825	IGLV8-61*02			
826	IGLV8-61*03			
827	IGLV11-55*01	V4-6		

In particular, provided herein are antibodies or antigen-binding antibody fragments that specifically bind and/or modulate an activity of DLL4. For example, antibodies that specifically bind and/or modulate an activity of DLL4 include any that contain a VH chain encoded by a sequence of nucleotides containing germline components compiled from a V_H germline segment that is an IGHV1 (e.g. any set forth in any of SEQ ID NOS:574-607), an IGHV4 (e.g. any set forth in SEQ ID NOS: 608-679), an IGHV5 (e.g. any set forth in SEQ ID NOS: 680-687) or an IGHV6 (e.g., any set forth in any of SEQ ID NOS: 688 or 689); a D_{H} germline segment that is an IGHD6 (e.g. any set forth in SEQ ID NOS: 714-717), an IGHD5 (e.g. any set forth in any of SEQ ID NOS: 710-713), an IGHD4 (e.g. any set forth in SEQ ID NOS: 706-709), an IGHD2 (e.g. any set forth in SEQ ID NOS: 690-697), an IGHD3 (e.g. any set

forth in any of SEQ ID NOS: 698-705), or an IGHD7 (e.g. set forth in SEQ ID NO:718); and a J_H germline segment that is an IGHJ1 (e.g., set forth in SEQ ID NO:719), an IGHJ2 (set forth in SEQ ID NO:720), an IGHJ4 (e.g. any set forth in any of SEQ ID NOS: 722-274), or an IGHJ6 (e.g. any set forth in SEQ ID NOS: 725-728). Such antibodies also include any that contain a VL chain encoded by a sequence of nucleotides containing germline components compiled from a Vκ germline segment that is an IGKV1 (e.g. any set forth in any of SEQ ID NOS: 729-760), an IGKV2 (e.g. any set forth in SEQ ID NOS: 761-775), or an IGKV3 (e.g. any set forth in any of SEQ ID NOS:776-794) and a Jκ germline segment that is an IGKJ1 (e.g. set forth in SEQ ID NO: 795); or from a V_λ germline segment that is an IGLV2 (e.g. any set forth in any of SEQ ID NOS:796-815), IGLV8 (e.g. any set forth in any of SEQ ID NOS: 824-826), IGLV11 (e.g. any set forth in any of SEQ ID NO: 827), or a IGLV5 (e.g. any set forth in any of SEQ ID NOS: 816-823) and a J_λ germline segment that is a IGLJ1 (e.g. set forth in SEQ ID NO:828) or an IGLJ4 (e.g. set forth in SEQ ID NO:829). Such antibodies also include any that are encoded by a sequence of nucleotides containing germline segments that are variants of any of the above germline segments, for example due to conservative mutations or other nucleotide mutations, so long as the resulting antibody is a functional and productive antibody and binds to DLL4 and/or modulates a functional activity.

Exemplary of antibodies against DLL4 include an antibody where the VH chain is encoded by a sequence of nucleotides compiled from a V_H germline segment that is an IGHV1-3 (e.g. IGHV1-3*01 or IGHV1-3*02), an IGHV1-8*01, an IGHV1-46 (e.g. an IGHV1-46*01, IGHV1-46*02 or IGHV1-46*03), an IGHV4-31 (e.g. IGHV4-31*01, IGHV4-31*02, IGHV4-31*03, IGHV4-31*04, IGHV4-31*05, IGHV4-31*06, IGHV4-31*07, IGHV4-31*08, IGHV4-31*09 or IGHV4-31*10), an IGHV4-34 (e.g. IGHV4-34*01, IGHV4-34*02, IGHV4-34*03, IGHV4-34*04, IGHV4-34*05, IGHV4-34*06, IGHV4-34*07, IGHV4-34*08, IGHV4-34*09, IGHV4-34*10, IGHV4-34*11, IGHV4-34*12 or IGHV4-34*13), an IGHV5-51 (e.g., IGHV5-51*01, IGHV5-51*02, IGHV5-51*03, IGHV5-51*04 or IGHV5-51*05) or is an IGHV6-1 (e.g. IGHV6-1*01 or IGHV6-1*02); a D_H germline segment that is an IGHD2-2 (e.g. IGHD2-2*01 or IGHD2-2*02), an IGHD2-15*01, an IGHD4-23*01, an IGHD6-6*01, an IGHD6-13*01, an IGHD5-18*01, an IGHD3-3 (e.g. IGHD3-

3*01 or IGHD3-3*02), an IGHD3-10 (e.g. IGHD3-10*01 or IGHD3-10*02), or is an IGHD7-27*01; and a J_H germline segment that is a IGHJ1*01, IGHJ2*01, an IGHJ4 (e.g. IGHJ4*01, IGHJ4*02 or IGHJ4*03), or is an IGHJ6 (e.g. IGHJ6*01, IGHJ6*02, IGHJ6*03, IGHJ6*04). The VL chain is encoded by a sequence of nucleotides compiled from a Vκ germline segment that is an IGKV1-5 (e.g. IGKV1-5*01, IGKV1-5*02 or IGKV1-5*03), an IGKV1-12 (e.g IGKV1-12*01 or IGKV1-12*02), an IGKV2-D-40*01, an IGKV3-11 (e.g. IGKV3-11*01 or IGKV3-11*02), an IGKV3-15*01, or is an IGKV3-20 (e.g. IGKV3-20*01, IGKV3-20*02) and a Jκ germline segment that is an IGKJ1*01; or is compiled from a V_λ germline segment that is an IGLV2-14 (e.g. IGLV2-14*01, IGLV2-14*02, IGLV2-14*03 or IGLV2-14*04), an IGLV8-61 (e.g. IGLV8-61*01, IGLV8-61*02 or IGLV8-61*03), an IGLV5-48*01, or an IGLV11-55*01 and a J_λ germline segment that is an IGLJ1*01 or an IGLJ4*01.

a. Exemplary Germline-derived anti-DLL4 antibodies

Exemplary antibodies provided herein that specifically bind and/or modulate an activity of DLL4 are set forth in Table 6.

TABLE 6: Anti-DLL4 Antibodies

Heavy Chain Germline Segments	SEQ ID NO		Light Chain Germline Segments	SEQ ID NO	
	nucleotide	Amino acid		nucleotide	Amino acid
IGHV1-46*01; IGHD6-6*01; IGHJ1*01	88	131	IGKV3-11*01; IGKJ1*01	98	141
IGHV5-51*03; IGHD5-18*01; IGHJ4*01	89	132	IGLV8-61*01; IGLJ1*01	99	142
IGHV6-1*01; IGHD3-3*01; IGHJ4*01	90	133	IGLV5-48*01; IGLJ4*01	100	143
IGHV1-46*01; IGHD6-13*01; IGHJ4*01	92	135	IGKV3-15*01; IGKJ1*01	102	145
IGHV4-34*01; IGHD7-27*01; IGHJ4*01	94	137	IGKV1-12*01; IGKJ1*01	103	146
IGHV1-46*01; IGHD6-13*01;	92	135	IGKV3-20*01; IGKJ1*01	101	144

IGHJ4*01					
IGHV1-3*02; IGHD4-23*01; IGHJ4*01	95	138	IGKV1-5*01; IGKJ1*01	104	147
IGHV1-46*01; IGHD2-15*01; IGHJ2*01	93	136	IGKV1-5*01; IGKJ1*01	104	147
IGHV1-46*01; IGHD3-10*01; IGHJ4*01	91	134	IGKV1-5*01; IGKJ1*01	104	147
IGHV1-8*01; IGHD2-2*01; IGHJ6*01	96	139	IGKV1-5*01; IGKJ1*01	104	147
IGHV1-46*01; IGHD6-13*01; IGHJ4*01	92	135	IGKV2D-40*01; IGKJ1*01	105	148
IGHV4-34*01; IGHD7-27*01; IGHJ4*01	94	137	IGLV2-14*01; IGLJ4*01	106	149
IGHV4-31*02; IGHD2-15*01; IGHJ2*01	97	140	IGLV2-14*01; IGLJ4*01	106	149
IGHV4-34*01; IGHD7-27*01; IGHJ4*01	94	137	IGLV11-55*01; IGLJ4*01	107	150

b. Germline-Derived Modified Antibodies

Anti-DLL4 antibodies provided herein include antibodies that are optimized compared to an anti-DLL4 germline-derived antibody or antigen-binding antibody fragment. Germline-derived modified antibodies include one or more mutations in the VH chain and/or one or more mutations in the VL chain compared to a germline-derived antibody. For example, the antibodies can contain 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more amino acid replacements in the VH chain and/or VL chain compared to the corresponding germline-derived antibody. The mutations can be in the VH chain, for example, in any one or more of the amino acid residues of a V_H, D_H or J_H region. Alternatively, or in addition, the mutations can be in the VL chain, for example, in any one or more of the amino acid residues of the V_L or J_L region.

Optimized antibodies containing one or more mutations exhibit improved activity compared to the parent antibody (e.g. germline-derived antibody not

containing the modification(s)). The antibodies exhibit an improved functional activity, either agonistic or antagonistic, against the DLL4 target protein. In other examples, the antibodies exhibit an improved binding affinity for DLL4. Generally, an activity or binding affinity is increased by at or about 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, 10-fold, 20-fold, 30-fold, 40-fold, 50-fold, 60-fold, 70-fold, 80-fold, 90-fold, 100-fold, 200-fold, 300-fold, 400-fold, 500-fold, 600-fold, 700-fold, 800-fold, 900-fold, 1000-fold or more compared to an activity or binding affinity of the parent antibody (e.g. germline-derived antibody not containing the modification(s)). For example, as described in the Examples, optimized anti-DLL4 antibodies provided herein exhibit a binding affinity that is improved by at least 100-fold to 1000-fold compared to the parent antibody. Such antibodies exhibit a nanomolar binding affinity. Typically, germline-derived modified anti-DLL4 antibodies provided herein exhibit a binding affinity that is at least 10^{-9} M, for example, that is or is about 1 x 10^{-9} M, 2 x 10^{-9} M, 3 x 10^{-9} M, 4 x 10^{-9} M, 5 x 10^{-9} M, 6 x 10^{-9} M, 7 x 10^{-9} M, 8 x 10^{-9} M, 9 x 10^{-9} M, 1 x 10^{-10} M, 2 x 10^{-10} M, 3 x 10^{-10} M, 4 x 10^{-10} M, 5 x 10^{-10} M, 10^{-11} M, 10^{-12} M or lower.

i. Variable heavy chain

For example, provided herein are germline-derived modified anti-DLL4 antibodies that contain one or more mutations in the VH chain of an anti-DLL4 Hit, for example, any set forth in any of SEQ ID NOS: 131-140.

In one example, a germline-derived modified anti-DLL4 antibody includes one or more mutations in a VH chain set forth in SEQ ID NO:132. The mutation(s) include one or more mutations at positions G24, Y27, S28, F29, T30, S31, Y32, W33, I34, G35, I50, I51, Y52, P52a, G53, D54, S55, D56, T57, S82a, R95, G96, Y97, S98, Y99, G100, Y100a, D100b, Y100c, F100d, D101 and/or Y102 set forth in the VH chain set forth in SEQ ID NO: 132, based on kabat numbering. The mutation can be to any other amino acid residue, in particular, the mutation is an alanine (A), phenyalanine (F), proline (P), tyrosine (Y), glutamine (Q), valine (V), isoleucine (I), glycine (G), leucine (L), tryptophan (W), lysine (K), asparagine (N), histidine (H), cysteine (C), glutamic acid (E), serine (S), Arginine (R) or threonine (T). Exemplary of such mutations are amino acid replacements G24A, G24L, G24S, G24R, G24T, S28A, S28R, S28K, S28N, F29A, T30A, W33A, I34A, G35T, G35A, G35V, I50A,

I51A, Y52A, P52aA, D54A, S55G, D56A, T57D, T57A, S82aV, S82aL, R95A, G96K, G96R, G96L, G96D, G96T, Y97A, Y97H, S98A, Y99A, G100A, G100D, G100L, G100P, G100R, G100M, G100K, G100S, G100R, G100T, Y100aA, D100bA, and/or D101A in the VH chain set forth in SEQ ID NO:132. In particular, exemplary of such mutations are amino acid replacements G24A, G24T, G24L, S28A, S28R, S28K, G35A, G25V, T57A, T57D, G96A, G96K, G96L, G96R, G100A, G100T and/or G100D. For example, exemplary of such mutations are amino acid replacements G24A, G24T, G24L, S28R, G35V, G96K, and/or G100T.

In another example, a germline-derived modified anti-DLL4 antibody provided herein includes one or more mutations in a VH chain set forth in SEQ ID NO:131. The mutation(s) include one or more mutations at positions T28, F29, T30, S31, Y33, I50, I51, N52, P52a, S53, G54, G55, S56, T57, S58, S82a, E96, Y97, S98, S99, S100, S100a, A100b, E100c, F100e, Q101 and/or H102 in the VH chain set forth in SEQ ID NO: 131, based on kabat numbering. The mutation can be to any other amino acid residue, in particular, the mutation is alanine (A), phenyalanine (F), proline (P), tyrosine (Y), glutamine (Q), valine (V), isoleucine (I), glycine (G), leucine (L), tryptophan (W), lysine (K), asparagine (N), aspartic acid (D), histidine (H), cysteine (C), glutamic acid (E), serine (S), Arginine (R) or threonine (T). Exemplary of such mutations are amino acid replacements T28A, F29A, T30A, S31A, Y33A, I50A, I50T, I51A, I51T, I51V, I51N, I51R, I51W, I51S, I51G, I51V, I51E, I51H, I51Y, N52A, N52V, N52G, N52T, N52P, N52L, N52W, N52Y, N52V, N52S, N52Q, N52K, P52aA, P52aM, P52aE, P52aH, P52aY, P52aT, P52aN, P52aR, P52aW, P52aS, P52aG, S53A, S53I, S53E, S53R, S53G, S53T, S53L, S53V, S53N, S53P, G54A, G54W, G54D, G55A, G55V, G55E, G55S, G55K, G55T, G55L, G55R, G55H, G55I, G55W, S58A, T57A, S58A, S82aG, S82aQ, S82aN, S82aH, S82aR, S82aK, S82aT, E96A, Y97A, S98A, S98Q, S98V, S98I, S98G, S99P, S99A, S99L, S99W, S99F, S99N, S99H, S99C, S99G, S100F, S100A, S100G, S100C, S100H, S100L, S100R, S100aA, A100bE, E100cA, Q101A, H102A, H102S, H102F and/or H102Y in the VH chain set forth in SEQ ID NO:131. In particular, exemplary of such mutations are amino acid replacements T28A, T30A, S31A, I51A, I51T, I51V, I51E, N52A, N52V, N52L, N52W, N52G, N52T, N52S, N52Q, N52K, P52Aa, S53A, S53G, S53T, G55A, G55V, G55E, G55N, G55S, G55K, G55D, G55T, G55L,

G55H, G55R, G55I, G55W, S56A, S82aT, S98A, S98Q, S98V, S98I, S99A, S99L, S99W, S99C, S99P, S100A, S100H, S100F, S100L, S100R, S100G, H102A, H102Y, H102F, and/or H102S. For example, exemplary of such mutations are amino acid replacements I51A, I51V, N52L, S53A, S53T, G55H, S98A, S99P, S100F, H102Y, and/or H102F.

ii. Variable Light Chain

Optimized anti-DLL4 antibodies provided herein also can contain one or more amino acid mutations in the VL chain. For example, provided herein are germline-derived modified anti-DLL4 antibodies that contain one or more mutations in the VH chain of an anti-DLL4 Hit, for example, any set forth in any of SEQ ID NOS: 141-150.

In one example, a germline-derived modified anti-DLL4 antibody includes one or more mutations in a VL chain set forth in SEQ ID NO: 141. The mutations(s) include one or more mutations at positions R24, Q27, S28, S30, S31, Y32, D50, A51, S52, N53, R54, A55, T56, F62, S76, R91, S92, N93 and/or W94 set forth in the VL chain set forth in SEQ ID NO:141, based on kabat numbering. The mutation can be to any other amino acid residue, in particular, the mutation is an alanine (A), phenyalanine (F), proline (P), tyrosine (Y), glutamine (Q), valine (V), isoleucine (I), glycine (G), leucine (L), tryptophan (W), lysine (K), asparagine (N), histidine (H), cysteine (C), glutamic acid (E), serine (S), aspartic acid (D), methionine (M), Arginine (R) or threonine (T). Exemplary of such mutations are amino acid replacements R24G, Q27L, S28P, S28G, S28K, S28V, S28F, S28P, S28T, S28L, S28Q, S28A, S28N, S28H, S28I, S28R, S28W, S28M, S28E, S30N, S30W, S30R, S30L, S30C, S30D, S30L, S30T, S30P, S30Y, S30Q, S30A, S30G, S30V, S31K, S31T, S31N, S31K, S31L, S31M, S31F, S31I, S31V, S31H, S31A, S31P, S31D, S31R, S31Y, S31Q, S31E, S31G, Y32V, Y32S, D50A, A51T, S52A, S52L, S52T, S52R, S52S, S52W, S52N, S52P, S52M, N53A, N53E, N53G, N53M, N53C, N53H, N53P, R54A, A55T, A55R, A55C, A55S, A55G, T56A, F62L, S76E, S76Q, S76P, S76L, S76T, S76G, S76A, S76Y, S76N, R91P, R91L, R91G, S92P, S92A, S92Q, S92V, S92T, S92R, S92G, S92V, S92M, S92N, S92C, N93Y, N93S, N93H, N93Q, W94R, W94S, W94T, W94L, W94P and/or W94M. In particular, exemplary of such mutations are amino acid replacements S28N, S28G, S28H, S28T, S30A, S30D,

S30Q, S30G, S30W, S30R, S31A, S31T, S31N, S31H, S31K, S31Y, S31R, S52A, S52L, S52T, S52R, S52M, N53A, N53H, N53G, A55T, A55S, A55G, S76T and/or S76Y. For example, exemplary of such mutations are amino acid replacements S28N, S30D, S31H, S31K, S52L, A55S and/or A55G.

In one example, a germline-derived modified anti-DLL4 antibody includes one or more mutations in a VL chain set forth in SEQ ID NO: 142. The mutations(s) include one or more mutations at positions G24, L25, S26, S27, G27a, S27b, V27c, S28, T29, S30, Y31, Y32, P33, S34, S50, T51, N52, T53, R54, S55, S56, T76, V89, L90, Y91, M92, G93, S94, G95, I95a and/or S95b, set forth in the VL chain set forth in SEQ ID NO:142, based on kabat numbering. The mutation can be to any other amino acid residue, in particular, the mutation is an alanine (A), phenyalanine (F), proline (P), tyrosine (Y), glutamine (Q), valine (V), isoleucine (I), glycine (G), leucine (L), tryptophan (W), lysine (K), asparagine (N), histidine (H), cysteine (C), glutamic acid (E), serine (S), aspartic acid (D), methionine (M), Arginine (R) or threonine (T). Exemplary of such mutations are amino acid replacements G24A, G24R, G24L, L25A, S26A, S27A, G27aA, S27bA, V27cA, S28A, T29A, S30A, Y31A, Y32A, P33A, S34A, S50A, S50F, S50G, S50C, S50R, S50L, S50M, S50V, S50P, S50T, S50H, S50Q, S50N, S50K, S50D, S50E, S50W, T51A, T51F, T51L, T51I, T51M, T51V, T51S, T51P, T51Y, T51H, T51Q, T51N, T51K, T51D, T51E, T51W, T51R, T51G, N52A, T53A, R54A, R54I, R54Y, R54D, R54G, S55A, S55F, S55L, S55I, S55M, S55V, S55P, S55T, S55Y, S55H, S55Q, S55N, S55K, S55D, S55E, S55W, S55R, S55G, S56A, T76S, T76E, T76Y, T76M, T76L, T76K, T76V, V89A, V89P, V89T, V89S, V89L, V89R, V89C, V89E, V89W, V89N, V89I, V89G, V89H, L90A, Y91A, M92A, M92E, M92S, M92G, M92L, M92P, M92V, M92D, M92R, M92N, M92T, M92F, G93A, S94A, S94W, S94G, S94P, S94R, S94L, S94M, S94E, S94V, G94A, I95aA and/or S95bA. In particular, exemplary of amino acid replacements are G24A, S26A, S27A, G27aA, S27bA, S28A, T29A, S30A, S50A, S50G, S50M, S50H, S50N, S50V, S50K, S50L, T51A, N52A, T53A, R54A, R54G, R54Y, R54S, S55A, S56A, T76E, T76M, T76Y, V89A, V89L, M92A, M92R, S94A, S94M, S94G and/pr S94P. For example, exemplary of such mutations are S50G, S50M, R54A, R54Y, V89L, M92R, S94M and/or S94P.

iii. Exemplary Germline-Derived Modified Antibodies

Provided herein are anti-DLL4 antibodies containing a variable heavy chain variant, for example, any set forth in SEQ ID NO:151-263, 381-438, and 894-898. In particular, among the exemplary anti-DLL4 antibodies provided herein, anti-DLL4 antibodies contain a variable heavy chain sequence having a sequence of amino acids set forth in SEQ ID NOS:155-157, 195, 219, 233, 238-239, 244, 263, 384, 414, 420 and 433-434.

Exemplary variable light chain variants include any set forth in SEQ ID NOS: 264-380, 439-571. In particular, among the exemplary anti-DLL4 antibodies provided herein, anti-DLL4 antibodies contain a variable heavy chain sequence having a sequence of amino acids set forth in SEQ ID NOS:343, 351, 367-370, 479, and 536-537.

In the anti-DLL4 antibodies provided herein, any of the exemplary variable heavy chains can be paired with any of the exemplary variable light chains. Exemplary anti-DLL4 antibodies include any of the heavy and light chain paired antibodies set forth in Example 5 herein (e.g. Tables 30 and 31).

2. Anti-DLL4: Complementary Determining Regions (CDRs)

Provided herein are anti-DLL4 antibodies that have a variable heavy (VH) chain and/or a variable light (VL) chain that contains CDR residues involved in binding to DLL4. The DLL4 antibodies provided herein can contain 1, 2, 3, 4, 5, or 6 of the provided CDRs (CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and/or CDRL3), or modified forms therof. The anti-DLL4 antibodies provided herein further can contain additional modification in other regions of the antibody as described elsewhere herein. For example, anti-DLL4 antibodies can contain one or more modifications in the framework region.

For example, provided herein are anti-DLL4 antibodies that have a VH chain that contains:

a CDRH1 (corresponding to amino acid positions 26-35 based on kabat numbering) that has a sequence of amino acids of GYTFTSYYMH (SEQ ID NO: 830), GYSFTSYWIG (SEQ ID NO:831), GDSVSSNSAA (SEQ ID NO:832), GGSFSGYYWS (SEQ ID NO:833), GYTFTSYAMH (SEQ ID NO:834), GYTFTSYAIN (SEQ ID NO:835), or GGSISSGGYY (SEQ ID NO:836), or a

sequence of amino acids that is a subset of any of SEQ ID NOS: 830-836, or has a sequence of amino acids of modified form of any of SEQ ID NOS:830-836; and/or

a CDRH2 (corresponding to amino acid positions 50-65 based on kabat numbering) that has a sequence of amino acids of IINPSGGSTSYAQKFQG (SEQ ID NO:844), IIYPGDSDTRYSPSFQG (SEQ ID NO:845), RTYYRSKWYNDYAVSVKS (SEQ ID NO:846), EINHSGSTNYNPSLKS (SEQ ID NO:847), INSNAGNGNTKYSQEFQG (SEQ ID NO: 848), WMNPNSGNTGYAQKFQG (SEQ ID NO:849); or YIYYSGSTYYNPSLKS (SEQ ID NO:850) or has a sequence of amino acids of modified form of any of SEQ ID NOS: 844-850; and/or

a CDRH3 (corresponding to amino acid positions 95-102) that has a sequence of amino acids of EEYSSSSAEYKQH (SEQ ID NO:851), RGYSYGYDYFDY (SEQ ID NO:852), EYYDFWSGYYTDYFDY (SEQ ID NO:853), EGYSSSWYDYFDY (SEQ ID NO:854), ANWGDYFDY (SEQ ID NO:855), DDYGGNSDYFDY (SEQ ID NO:856), EGYCSGGSCYS (SEQ ID NO:857), EYYYGSGSYYNDYFDY (SEQ ID NO:858), GCYCSSTSCYADYYYYYGMDV (SEQ ID NO:859), or GSCYSYWYFDL (SEQ ID NO:860), or has a sequence of amino acids of modified form any of SEQ ID NOS: 851-860.

Also provided herein are anti-DLL4 antibodies that have a variable light (VL) chain that contains:

a CDRL1 (corresponding to amino acid positions 24 to 33 or 34 based on kabat numbering) that has a sequence of amino acids of RASQSVSSYLA (SEQ ID NO: 861), GLSSGSVSTSYYPS (SEQ ID NO:862), TLRSGINLGSYRIF (SEQ ID NO:863), RASQSVSSNLA (SEQ ID NO:864); RASQGISSWLA (SEQ ID NO:865); RASQVSSSYLA (SEQ ID NO:866), RASQSISSWLA (SEQ ID NO:867), RSSQSLLDSDDGNTYLD (SEQ ID NO:868), TGTSSDVGGTNYVS (SEQ ID NO:869), or TLSSDLSVGGKNMF (SEQ ID NO:870), or has a sequence of amino acids of modified form of any of SEQ ID NOS: 861-870;

a CDRL2 (corresponding to amino acid positions 50-56 based on kabat numbering) that has a sequence of amino acids of amino acids of DASNRAT (SEQ ID NO:871), STNTRSS (SEQ ID NO: 872), YYSDSSK (SEQ ID NO:873), GASTRAT (SEQ ID NO:874), AASSLQS (SEQ ID NO:875), GASSRAT (SEQ ID

NO:876), DASSLGS (SEQ ID NO:877), TLSYRAS (SEQ ID NO:878), EVSNRPS (SEQ IDNO:879), or HYSDSDK (SEQ ID NO:880), or has a sequence of amino acids of modified form of any of SEQ ID NOS: 871-880); and/or

a CDRL3 (corresponding to amino acid positions 89-97 based on kabat numbering) that has a sequence of amino acids of QQRSNWPPWT (SEQ ID NO:881), VLYMGSGISYV (SEQ ID NO:882), MIWHSSASFV (SEQ ID NO: 883), QQYNNWPPWT (SEQ ID NO: 884) QANSFPPWT (SEQ ID NO:885), QQYGSSPPWT (SEQ ID NO: 886), QQYNSYSPWT (SEQ ID NO:887), MQRIEFPSWT (SEQ ID NO: 888), SSYTSSSTLFV (SEQ ID NO: 889), or QVYESSANFV (SEQ ID NO: 890), or has a sequence of amino acids of modified form any of SEQ ID NOS: 881-890.

Exemplary of anti-DLL4 antibodies are any that contain a variable heavy chain or a variable light chain set forth in Tables 7-8. The CDRs, including the SEQ ID NOS thereof, are indicated in the Tables.

Table 7. DLL4 Antibody Heavy Chains

Heavy Chain	CDR1	CDR2	CDR3
VH1-46_IGHD6-6*01_IGHJ1*01	GYTFTSYYMH (SEQ ID NO:830)	IINPSGGSTSYAQKFQG (SEQ ID NO:844)	EEYSSSSAEYKQH (SEQ ID NO:851)
	SYYMH (SEQ ID NO:837)		
VH5-51_IGHD5-18*01_IGHJ4*01	GYSFTSYWIG (SEQ ID NO:831)	IIYPGDSDTRYSPSFQG (SEQ ID NO:845)	RGYSYGYDYFDY (SEQ ID NO:852)
	SYWIG (SEQ ID NO:838)		
VH6-1_IGHD3-3*01_IGHJ4*01	GDSVSSNSAA (SEQ ID NO:832)	RTYYRSKWYNDYAVSV KS (SEQ ID NO:846)	EYYDFWSGYYTDYFDY (SEQ ID NO:853)
	SNSAA (SEQ ID NO:839)		
VH1-46_IGHD6-13*01_IGHJ4*01	GYTFTSYYMH (SEQ ID NO:830)	IINPSGGSTSYAQKFQG (SEQ ID NO:844)	EGYSSSWYDYFDY (SEQ ID NO:854)
	SYYMH (SEQ ID NO:837)		
VH4-34_IGHD7-27*01_IGHJ4*01	GGSFSGYYWS (SEQ ID NO:833)	EINHSGSTNYNPSLKS (SEQ ID NO:847)	ANWGDYFDY (SEQ ID NO:855)
	GYYWS (SEQ ID NO:840)		
VH1-3_IGHD4-23*01_IGHJ4*01	GYTFTSYAMH (SEQ ID NO:834)	INSNAGNGNTKYSQEFQG (SEQ ID NO:848)	DDYGGNSDYFDY (SEQ ID NO:856)
	SYAMH (SEQ ID NO:841)		
VH1-46_IGHD2-15*01_IGHJ2*01	GYGFTSYYMH (SEQ ID NO:830)	IINPSGGSTSYAQKFQG (SEQ ID NO:844)	EGYCSGGSCYS (SEQ ID NO:857)
	SYYMH (SEQ ID NO:837)		
VH1-46_IGHD3-	GYTFTSYYMH	IINPSGGSTSYAQKFQG	EYYYGSGSYYNDYFDY

10*01_IGHJ4*01	(SEQ ID NO:830)	(SEQ ID NO:844)	(SEQ ID NO:858)
	SYYMH (SEQ ID NO:837)		
VH1-8_IGHD2-2*01_IGHJ6*01	GYTFTSYAIN (SEQ ID NO:835)	WMNPNSGNTGYAQKFQG (SEQ ID NO:849)	GCYCSSTSCYADYYYYY GMDV (SEQ ID NO:859)
	SYAIN (SEQ ID NO:842)		
VH4-31_IGHD2-15*01_IGHJ2*01	GGSISSGGYY (SEQ ID NO:836)	YIYYSGSTYYNPSLKS (SEQ ID NO:850)	GSCYSYWYFDL (SEQ ID NO:860)
	SGGYY (SEQ ID NO:843)		

Table 8. DLL4 Antibody Light Chains

Light Chain	CDR1	CDR2	CDR3
L6_IGKJ1*01	RASQSVSSYLA (SEQ ID NO:861)	DASNRAT (SEQ ID NO:871)	QQRSNWPPWT (SEQ ID NO:881)
V3-4_IGLJ1*01	GLSSGSVSTSYYPS (SEQ ID NO:862)	STNTRSS (SEQ ID NO:872)	VLYMGSGISYV (SEQ ID NO:882)
V4-3_IGLJ4*01	TLRSGINLGSYRIF (SEQ ID NO:863)	YYSDSSK (SEQ ID NO:873)	MIWHSSASFV (SEQ ID NO:883)
L2_IGKJ1*01	RASQSVSSNLA (SEQ ID NO:864)	GASTRAT (SEQ ID NO:874)	QQYNNWPPWT (SEQ ID NO:884)
L5_IGKJ1*01	RASQGISSWLA (SEQ ID NO:865)	AASSLQS (SEQ ID NO:875)	QANSFPPWT (SEQ ID NO:885)
A27_IGKJ1*01	RASQVSSSYLA (SEQ ID NO:866)	GASSRAT (SEQ ID NO:876)	QQYGSSPPWT (SEQ ID NO:886)
L12_IGKJ1*01	RASQSISSWLA (SEQ ID NO:867)	DASSLGS (SEQ ID NO:877)	QQYNSYSPWT (SEQ ID NO:887)
O1_IGKJ1*01	RSSQSLLDSDDGNTYLD (SEQ ID NO:868)	TLSYRAS (SEQ ID NO:878)	MQRIEFPSWT (SEQ ID NO:888)
V1-4_IGLJ4*01	TGTSSDVGGTNYV (SEQ ID NO:869)	EVSNRPS (SEQ ID NO:879)	SSYTSSSTLFV (SEQ ID NO:889)
V4-6_IGLJ4*01	TLSSDLSVGGKNMF (SEQ ID NO:870)	HYSDSDK (SEQ ID NO:880)	QVYESSANFV (SEQ ID NO:890)

Also provided herein are anti-DLL4 antibodies that contain one or more, such as 1, 2, 3, 4, 5 or 6, CDRs that is(are) modified compared to a CDRH1 set forth in any of SEQ ID NOS: 830-836, a CDRH2 set forth in any of SEQ ID NOS: 844-850, a CDRH3 set forth in any of SEQ ID NOS: 851-860, a CDRL1 set forth in any of SEQ ID NOS: 861-870, a CDRL2 set forth in any of SEQ ID NOS: 871-880 and/or a CDRL3 set forth in any of SEQ ID NOS: 881-890. Such modified forms include those that exhibit at leat 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% sequence identity to a CDR set forth in any of SEQ ID NOS: 830-836, 844-890.

For example, provided herein are anti-DLL4 antibodies that contain a modified CDRH1 that is modified compared to the CDRH1 set forth in SEQ ID NO: 830 or SEQ ID NO:831. Amino acid replacements can be to any other amino acid

residue, in particular, the mutation is alanine (A), phenyalanine (F), proline (P), tyrosine (Y), glutamine (Q), valine (V), isoleucine (I), glycine (G), leucine (L), tryptophan (W), lysine (K), asparagine (N), aspartic acid (D), histidine (H), cysteine (C), glutamic acid (E), serine (S), Arginine (R) or threonine (T). In one example, a CDRH1 set forth in SEQ ID NO:830 is modified to contain one or more mutations at positions T28, F29, T30, S31 and/or Y33, based on kabat numbering. For example, exemplary of such amino acid replacements include T28A, F29A, T30A, S31A, Y33A. In another example, a CDRH1 set forth in SEQ ID NO:831 is modified to contain one or more mutations at positions S28, F29, T30, W33, I34 or G35, based on kabat numbering. For example, exemplary of such amino acid replacements include S28A, S28R, S28K, S28N, F29A, T30A, W33A, I34A, G35T, G35A and/or G35V. The CDRH1 can contain 1, 2, 3, 4, 5, 6 or more amino acid modifications. An exemplary combination mutant is S28R/G35V.

In another example, provided herein are anti-DLL4 antibodies that contain a modified CDRH2 that is modified compared to the CDRH2 set forth in SEQ ID NO: 844 or SEQ ID NO:845. Amino acid replacements can be to any other amino acid residue, in particular, the mutation is alanine (A), phenyalanine (F), proline (P), tyrosine (Y), glutamine (Q), valine (V), isoleucine (I), glycine (G), leucine (L), tryptophan (W), lysine (K), asparagine (N), aspartic acid (D), histidine (H), cysteine (C), glutamic acid (E), serine (S), Arginine (R) or threonine (T). In one example, a CDRH2 set forth in SEQ ID NO:844 is modified to contain one or more mutations at positions I50, I51, N52, P52a, S53, G54, G55, G56, T57 and/or S58, based on kabat numbering. For example, exemplary of such amino acid replacements include I50A, I50T, I51A, I51T, I51V, I51N, I51R, I51W, I51S, I51G, I51V, I51E, I51H, I51Y, N52A, N52V, N52G, N52T, N52P, N52L, N52W, N52Y, N52V, N52S, N52Q, N52K, P52aA, P52aM, P52aE, P52aH, P52aY, P52aT, P52aN, P52aR, P52aW, P52aS, P52aG, S53A, S53I, S53E, S53R, S53G, S53T, S53L, S53V, S53N, S53P, G54A, G54W, G54D, G55A, G55V, G55E, G55S, G55K, G55T, G55L, G55R, G55H, G55I, G55W, S58A, T57A and/or S58A. In another example, CDRH2 set forth in SEQ ID NO:845 is modified to contain one or more mutations at positions I50, I51, Y52, P52a, D54, S55, D56 and/or T57, based on kabat numbering. For example, exemplary of such amino acid replacements include I50A, I51A, Y52A,

P52aA, D54A, S55G, D56A, T57D and/or T57A. The CDRH2 can contain 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more amino acid modifications. Exemplary combination modifications in CDRH2 set frorth in SEQ ID NO:844 include, for example, I51V/N52L/S53T/G55H, N52L/S53T/G55H, I51E/N52L/S53T/G55H and/or I51N/N52L/S53T/G55H.

In a further example, provided herein are anti-DLL4 antibodies that contain a modified CDRH3 that is modified compared to the CDRH3 set forth in SEQ ID NO: 851 or SEQ ID NO:852. Amino acid replacements can be to any other amino acid residue, in particular, the mutation is alanine (A), phenyalanine (F), proline (P), tyrosine (Y), glutamine (Q), valine (V), isoleucine (I), glycine (G), leucine (L), tryptophan (W), lysine (K), asparagine (N), aspartic acid (D), histidine (H), cysteine (C), glutamic acid (E), serine (S), Arginine (R) or threonine (T). In one example, a CDRH3 set forth in SEQ ID NO:851 is modified to contain one or more mutations at positions E96, Y97, S98, S99, S100, S100a, A100b, E100c, Q101 and/or H102, based on kabat numbering. For example, exemplary of such amino acid replacements include E96A, Y97A, S98A, S98Q, S98V, S98I, S98G, S99P, S99A, S99L, S99W, S99F, S99N, S99H, S99C, S99G, S100F, S100A, S100G, S100C, S100H, S100L, S100R, S100aA, A100bE, E100cA, Q101A, H102A, H102S, H102F and/or H102Y. In another example, CDRH3 set forth in SEQ ID NO:852 is modified to contain one or more mutations at positions R95, G96, Y97, S98, Y99, G100, Y100a, D100b, and/or D101, based on kabat numbering. For example, exemplary of such amino acid replacements include R95A, G96K, G96R, G96L, G96D, G96T, Y97A, Y97H, S98A, Y99A, G100A, G100D, G100L, G100P, G100R, G100M, G100K, G100S, G100R, G100T, Y100aA, D100bA and/or D101A. The CDRH3 can contain 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more amino acid modifications. Exemplary combination modifications in CDRH3 set frorth in SEQ ID NO:851 include, for example, S98A/S99P/S100F, S98A/S99P/S100F/H102F and/or S98A/S99P/S100F/H102Y. Exemplary combination modification in CDRH3 set forth in SEQ ID NO:852 include, for example, G96K/G100T.

Also provided herein are anti-DLL4 antibodies that contain a modified CDRL1 that is modified compared to the CDRL1 set forth in SEQ ID NO: 861 or SEQ ID NO:862. Amino acid replacements can be to any other amino acid residue, in

particular, the mutation is alanine (A), phenyalanine (F), proline (P), tyrosine (Y), glutamine (Q), valine (V), isoleucine (I), glycine (G), leucine (L), tryptophan (W), lysine (K), asparagine (N), histidine (H), cysteine (C), glutamic acid (E), serine (S), aspartic acid (D), methionine (M), Arginine (R) or threonine (T). In one example, a CDRL1 set forth in SEQ ID NO:861 is modified to contain one or more mutations at positions R24, Q27, S28, S30, S31 and/or Y32, based on kabat numbering. For example, exemplary of such amino acid replacements include R24G, Q27L, S28P, S28G, S28K, S28V, S28F, S28P, S28T, S28L, S28Q, S28A, S28N, S28H, S28I, S28R, S28W, S28M, S28E, S30N, S30W, S30R, S30L, S30C, S30D, S30L, S30T, S30P, S30Y, S30Q, S30A, S30G, S30V, S31K, S31T, S31N, S31K, S31L, S31M, S31F, S31I, S31V, S31H, S31A, S31P, S31D, S31R, S31Y, S31Q, S31E, S31G, Y32V and/or Y32S. In another example, CDRL1 set forth in SEQ ID NO:862 is modified to contain one or more mutations at positions G24, L25, S26, S27, G27a, S27b, V27c, S28, T29, S30, Y31, Y32, P33, based on kabat numbering. For example, exemplary of such amino acid replacements include G24A, G24R, G24L, L25A, S26A, S27A, G27aA, S27bA, V27cA, S28A, T29A, S30A, Y31A, Y32A and/or P33A. The CDRL1 can contain 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or more amino acid modifications. Exemplary combination modifications in CDRL1 set forth in SEQ ID NO:861 include, for example, S28N/S30D/S31H.

In an additional example, provided herein are anti-DLL4 antibodies that contain a modified CDRL2 that is modified compared to the CDRL2 set forth in SEQ ID NO: 871 or SEQ ID NO:872. Amino acid replacements can be to any other amino acid residue, in particular, the mutation is alanine (A), phenyalanine (F), proline (P), tyrosine (Y), glutamine (Q), valine (V), isoleucine (I), glycine (G), leucine (L), tryptophan (W), lysine (K), asparagine (N), histidine (H), cysteine (C), glutamic acid (E), serine (S), aspartic acid (D), methionine (M), Arginine (R) or threonine (T). In one example, a CDRL2 set forth in SEQ ID NO:871 is modified to contain one or more mutations at positions D50, A51, S52, N53, R54, A55 and/or T56, based on kabat numbering. For example, exemplary of such amino acid replacements include D50A, A51T, S52A, S52L, S52T, S52R, S52S, S52W, S52N, S52P, S52M, N53A, N53E, N53G, N53M, N53C, N53H, N53P, R54A, A55T, A55R, A55C, A55S, A55G and/or T56A. In another example, CDRL2 set forth in SEQ ID NO:872 is modified to

contain one or more mutations at positions S50, T51, N52, T53, R54, S55 and/or S56, based on kabat numbering. For example, exemplary of such amino acid replacements include S50A, S50F, S50G, S50C, S50R, S50L, S50M, S50V, S50P, S50T, S50H, S50Q, S50N, S50K, S50D, S50E, S50W, T51A, T51F, T51L, T51I, T51M, T51V, T51S, T51P, T51Y, T51H, T51Q, T51N, T51K, T51D, T51E, T51W, T51R, T51G, N52A, T53A, R54A, R54I, R54Y, R54D, R54G, S55A, S55F, S55L, S55I, S55M, S55V, S55P, S55T, S55Y, S55H, S55Q, S55N, S55K, S55D, S55E, S55W, S55R, S55G and/or S56A. The CDRL2 can contain 1, 2, 3, 4, 5, 6, 7 or more amino acid modifications. Exemplary combination modifications in CDRL2 set forth in SEQ ID NO:871 include, for example, S52L/A55S and/or S52L/A55G.

In a further example, provided herein are anti-DLL4 antibodies that contain a modified CDRL3 that is modified compared to the CDRL3 set forth in SEQ ID NO: 881 or SEQ ID NO:882. Amino acid replacements can be to any other amino acid residue, in particular, the mutation is alanine (A), phenyalanine (F), proline (P), tyrosine (Y), glutamine (Q), valine (V), isoleucine (I), glycine (G), leucine (L), tryptophan (W), lysine (K), asparagine (N), histidine (H), cysteine (C), glutamic acid (E), serine (S), aspartic acid (D), methionine (M), Arginine (R) or threonine (T). In one example, a CDRL3 set forth in SEQ ID NO:881 is modified to contain one or more mutations at positions R91, S92, N93 and/or W94, based on kabat numbering. For example, exemplary of such amino acid replacements include R91P, R91L, R91G, S92P, S92A, S92Q, S92V, S92T, S92R, S92G, S92V, S92M, S92N, S92C, N93Y, N93S, N93H, N93Q, W94R, W94S, W94T, W94L, W94P and/or W94M. In another example, CDRL3 set forth in SEQ ID NO:882 is modified to contain one or more mutations at positions V89, L90, Y91, M92, G93, S94, G95, I95a and/or S95b, based on kabat numbering. For example, exemplary of such amino acid replacements include V89A, V89P, V89T, V89S, V89L, V89R, V89C, V89E, V89W, V89N, V89I, V89G, V89H, L90A, Y91A, M92A, M92E, M92S, M92G, M92L, M92P, M92V, M92D, M92R, M92N, M92T, M92F, G93A, S94A, S94W, S94G, S94P, S94R, S94L, S94M, S94E, S94V, G94A, I95aA, S95bA. The CDRL3 can contain 1, 2, 3, 4, 5, 6, 7, 8. 9 or more amino acid modifications. Exemplary modifications in CDRL3 set forth in SEQ ID NO:882 include, for example, M92R/S94M and/or V89L/S94P.

Exemplary of anti-DLL4 antibodies provided herein are antibodies set forth in Table 8a (e.g. 1-17) that contain a variable heavy chain containing the specified amino acid replacement in CDRH1, CDRH2 and/or CDRH3 and a variable light chain containing the specified amino acid replacement in CDRL1, CDRL2 and/or CDRL3. Where no amino acid modification is indicated, the antibody contains the CDR sequence of the reference antibody. In the Table, the modifications are exemplified with respect to kabat numbering corresponding to a reference CDR sequence having a sequence of amino acids indicated by a SEQ ID NO. In parenthesis, the modifications are exemplified based on their amino acid position in the respective SEQ ID NO.

TABLE 8A						
	CDRH1	CDRH2	CDRH3	CDRL1	CDRL2	CDRL3
	GYTFTSYYMH (SEQ ID NO:830)	IINPSGGSTSYAQKFQG (SEQ ID NO:844)	EEYSSSSAEYFQH SEQ ID NO:851)	RASQSVSSYLA (SEQ ID NO:861)	DASNRAT (SEQ ID NO:871)	QQRSNWPPWT (SEQ ID NO:881)
1			S100F (S104F)			
2			S99P (S103P)			
3			S98F (S102A)			
4			S98A/S99P/S100F (S102A/S103P/S104F)			
5			S98A/S99P/S100F/H102Y (S102A/S103P/S104F/H111Y)			
6			S98A/S99P/S100F/H102F (S102A/S103P/S104F/H111F)			
7			S98A/S99P/S100F/H102F (S102A/S103P/S104F/H111F)	S31K (S31K)		
8			S98A/S99P/S100F/H102F (S102A/S103P/S104F/H111F)	S28N/S30D/S31H (S28N/S30D/S31H)		
9		G55H (G56H)	S98A/S99P/S100F/H102F (S102A/S103P/S104F/H111F)			
10		I51V/N52L/S535/G55H (I51V/N52L/S54T/G56H)	S98A/S99P/S100F/H102F (S102A/S103P/S104F/H111F)	S28N/S30D/S31H (S28N/S30D/S31H)		
11		I51V/N52L/S535/G55H (I51V/N52L/S54T/G56H)	S98A/S99P/S100F/H102F (S102A/S103P/S104F/H111F)	S28N/S30D/S31H (S28N/S30D/S31H)	S52L/A55S (S52L/A55S)	
	CDRH1	CDRH2	CDRH3	CDRL1	CDRL2	CDRL3
	GYSFTSYWIG (SEQ ID NO:831)	IIYPGDSDTRYSPSFQG (SEQ ID NO:845)	RGYSYGYDYFDY (SEQ ID NO:852)	GLSSGSVSTSYYP (SEQ ID NO:862)	STNTRSS (SEQ ID NO:872)	VLYMGSGISYV (SEQ ID NO:882)
12			G96K/G100T (G100K/G104T)			
13	S28R (S28R)		G96K/G100T (G100K/G104T)			
14	S28R/G35V (S28R/G35V)		G96K/G100T (G100K/G104T)			
15	S28R/G35V (S28R/G35V)		G96K/G100T (G100K/G104T)			M92R/S94M (M94R/S96M)
16	S28R/G35V (S28R/G35V)		G96K/G100T (G100K/G104T)			V89L/S94P (V91L/S96P)
17	S28R/G35V (S28R/G35V)		G96K/G100T (G100K/G104T)		S50G (S52G)	V89L/S94P (V91L/S96P)

In any of the above anti-DLL4 antibodies provided herein that contain one or more CDRs, the antibody further can contain one or more amino acid modifications to a framework region of the variable heavy or light chain. The mutations can be any amino acid addition, deletion or substitution. Generally, as described in Section D below, any further modification is one that is identified as contributing to an improved property to the antibody. Exemplary of a modification in a variable heavy chain is amino acid replacement at position 24 and/or 82a based on kabat numbering. For example, exemplary modifications include amino acid replacement of G24A, G24L, G24S, G24R, G24T, S82aV, S82aL, S82aG, S82aQ, S82aN, S82aH, S82aR, S82aK and/or S82aT, based on kabat numbering. For example, exemplary modifications include G24T, G24L G24A, and/or S82aT. Exemplary of a modification in a variable light chain is amino acid replacement at position 62, 76 based on kabat numbering. For example, exemplary modifications include amino acid replacement of F62L, S76E, S76Q, S76P, S76L, S76T, S76G, S76A, S76Y, S76N, T76S, T76E, T76Y and/or T76M. For example, exemplary modifications include T76E, T76Y or T76M. An exemplary combination modification includes amino acid replacement of S28R/G35V in CDRH1 set forth in SEQ ID NO:831, and additionally a modifification of G24T, G24A or G24L.

In some examples, any of the above anti-DLL4 antibodies that contain one or more CDRs, or modified forms thereof, can be in a germline-derived antibody or a modified germline-derived antibody as described in Section.C.1 above. For example, exemplary anti-DLL4 antibodies that contain one or more CDRs, or modified forms thereof, provided herein include any that have a variable heavy chain set forth in SEQ ID NOS: 151-263, 381-438, and 894-898 and/or a variable light chain set forth in SEQ ID NOS: 264-380, 439-571.

In particular, provided herein are antibodies with nanomolar binding affinity for DLL4. These include, but are not limited to, anti-DLL4 antibodies set forth in Table 32. Exemplary antibodies include antibodies that have a variable heavy and light chain sequence set forth in SEQ ID NOS: 384 and 142; 414 and 142; 433 and 142; 433 and 479; 433 and 537; 433 and 536; 131 and 141; 151 and 141; 155 and 141; 156 and 141; 157 and 141; 155 and 266; 219 and 141; 156 and 343; 239 and 343; 239 and 370; and 134 and 147.

D. FURTHER MODIFICATIONS

The anti-DLL4 antibodies provided herein can be further modified. Modification of an anti-DLL4 antibody can improve one or more properties of the antibody, including, but not limited to, decreasing the immunogenicity of the antibody; improving the half-life of the antibody, such as as reducing the susceptibility to proteolysis and/or reducing susceptibility to oxidation; altering or improving of the binding properties of the antibody; and/or modulating the effector functions of the antibody. Exemplary modifications include modification of the primary sequence of the antibody and/or alteration of the post-translational modification of an antibody. Exemplary post-translational modifications include, for example, glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization with protecting/blocking group, proteolytic cleavage, and linkage to a cellular ligand or other protein. Other exemplary modifications include attachment of one or more heterologous peptides to the antibody to alter or improve one or more properties of the antibody.

Generally, the modifications do not result in increased immunogenicity of the antibody or antigen-binding fragment thereof or significantly negatively affect the binding of the antibody to DLL4. Methods of assessing the binding of the modified antibodies to DLL4 are provided herein and are known in the art. For example, modified antibodies can be assayed for binding to DLL4 by methods such as, but not limited to, ELISA or FACS binding assays.

Modification of the anti-DLL4 antibodies produced herein can include one or more amino acid substitutions, deletions or additions, either from natural mutation or human manipulation from the parent antibody from which it was derived. Methods for modification of polypeptides, such as antibodies, are known in the art and can be employed for the modification of any antibody or antigen-binding fragment provided herein. In some examples, the pharmacokinetic properties of the anti-DLL4 antibodies provided can be enhanced through Fc modifications by techniques known to those skilled in the art. Standard techniques known to those of skill in the art can be used to introduce mutations in the nucleotide molecule encoding an antibody or an antigen-binding fragment provided herein in order to produce a polypeptide with one or more amino acid substitutions. Exemplary techniques for introducing mutations

include, but are not limited to, site-directed mutagenesis and PCR-mediated mutagenesis.

The anti-DLL4 antibodies provided herein can be modified by either N-linked or O-linked glycosylation. N-linked glycosylation includes the the attachment of a carbohydrate moiety to the side chain of an asparagine residue within the tripeptide sequences asparagine-X-serine and asparagine-X-threonine, where X is any amino acid except proline.. O-linked glycosylation includes the attachment of one of the sugars N-aceylgalactosamine, galactose, or xylose to a hydroxyamino acid, most commonly serine or threonine, although 5-hydroxyproline or 5-hydroxylysine can also be used. The anti-DLL4 antibodies can be further modified to incorporate additional glycosylation sites by altering the amino acid sequence such that it contains one or more of the above-described tripeptide sequences (for N-linked glycosylation sites). The alteration can also be made by the addition of, or substitution by, one or more serine or threonine residues to the sequence of the original antibody (for O-linked glycosylation sites). Where the antibody comprises an Fc region, the carbohydrate attached thereto can be altered (see, e.g., U.S. Patent Pub. Nos. 2003/0157108, 2005/0123546 and US 2004/0093621; International Patent Pub. Nos. WO 2003/011878, WO 1997/30087, WO 1998/58964, WO 1999/22764; and U.S. Pat. No. 6,602,684).

For example, a glycosylation variantion is in the Fc region of the antibody, wherein a carbohydrate structure attached to the Fc region lacks fucose. Such variants have improved ADCC function. Optionally, the Fc region further contains one or more amino acid substitutions therein which further improve ADCC, for example, substitutions at positions 298, 333, and/or 334 of the Fc region (Eu numbering of residues) (see, e.g., US 2003/0157108; WO 2000/61739; WO 2001/29246; US 2003/0115614; US 2002/0164328; US 2004/0093621; US 2004/0132140; US 2004/0110704; US 2004/0110282; US 2004/0109865; WO 2003/085119; WO 2003/084570; WO 2005/035586; WO 2005/035778; WO2005/053742; Okazaki et al. *J. Mol. Biol.* 336:1239-1249 (2004); Yamane-Ohnuki et al. *Biotech. Bioeng.* 87: 614 (2004)). Examples of cell lines producing defucosylated antibodies include Lec13 CHO cells deficient in protein fucosylation (Ripka et al. *Arch. Biochem. Biophys.* 249:533-545 (1986); US Pat Appl No US 2003/0157108 A1, Presta, L; and WO

2004/056312 A1, Adams et al., especially at Example 11), and knockout cell lines, such as alpha-1,6-fucosyltransferase gene, FUT8, knockout CHO cells (Yamane-Ohnuki et al. *Biotech. Bioeng.* 87: 614 (2004)).

The anti-DLL4 antibodies provided herein can be modified by the attachment of a heterologous peptide to facilitate purification. Generally such peptides are expressed as a fusion protein containing the antibody fused to the peptide at the C- or N- terminus of the antibody. Exemplary peptides commonly used for purification include, but are not limited to, hexa-histidine peptides, hemagglutinin (HA) peptides, and flag tag peptides (see *e.g.*, Wilson *et al.* (1984) *Cell* 37:767; Witzgall *et al.* (1994) *Anal Biochem* 223:2, 291-8). The fusion does not necessarily need to be direct, but can occur through a linker peptide. In some examples, the linker peptide contains a protease cleavage site which allows for removal of the purification peptide following purification by cleavage with a protease that specifically recognizes the protease cleavage site.

The anti-DLL4 antibodies and fragments thereof provided herein also can be modified by the attachment of a heterologous polypeptide that targets the antibody or antigen-binding fragment to a particular cell type, either *in vitro* or *in vivo*. In some examples an anti-DLL4 antibody provided herein can be targeted to a particular cell type by fusing or conjugating the antibody to an antibody specific for a particular cell surface receptors or other polypeptide that interacts with a specific cell receptor. Various other heterologous polypeptides can be attached to an anti-DLL4 antibody or fragment thereof, including those which increase the serum half-life of the antibody and/or enzymes (e.g., for ADEPT).

The anti-DLL4 antibodies provided herein can be modified by the attachment of diagnostic and/or therapeutic moiety to the antibody. The anti-DLL4 antibodies provided herein can be modified by the covalent attachment of any type of molecule, such as a diagnostic or therapeutic molecule, to the antibody such that covalent attachment does not prevent the antibody from binding to its corresponding epitope. For example, an anti-DLL4 antibody provided herein can be further modified by covalent attachment of a molecule such that the covalent attachment does not prevent the antibody from binding to DLL4. In some examples, the antibodies can be recombinantly fused to a heterologous polypeptide at the N-terminus or C-terminus or

chemically conjugated, including covalent and non-covalent conjugation, to a heterologous polypeptide or other composition. For example, the heterologous polypeptide or composition can be a diagnostic polypeptide or other diagnostic moiety or a therapeutic polypeptide or other therapeutic moiety. Exemplary diagnostic and therapeutic moieties include, but are not limited to, drugs, radionucleotides, toxins, fluorescent molecules (see, *e.g.* International PCT Publication Nos. WO 92/08495; WO 91/14438; WO 89/12624; U.S. Pat. No. 5,314,995; and EP 396,387). Diagnostic polypeptides or diagnostic moieties can be used, for example, as labels for *in vivo* or *in vitro* detection.

Additional fusion proteins of the anti-DLL4 antibodies provided herein can be generated through the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"). DNA shuffling can be employed to alter the activities of anti-DLL4 antibodies provided herein, for example, to produce antibodies with higher affinities and lower dissociation rates (see, generally, U.S. Pat. Nos. 5,605,793; 5,811,238; 5,830,721; 5,834,252; and 5,837,458, and Patten *et al.* (1997) *Curr. Opinion Biotechnol.* 8:724-33; Harayama (1998) *Trends Biotechnol.* 16(2):76-82; Hansson *et al.*, (1999) *J. Mol. Biol.* 287:265-76; and Lorenzo and Blasco (1998) *Biotechniques* 24(2):308-13).

1. Modifications to reduce immunogenicity

In some examples, the antibodies provided herein can be further modified to reduce the immunogenicity in a subject, such as a human subject. For example, one or more amino acids in the antibody can be modified to alter potential epitopes for human T-cells in order to eliminate or reduce the immunogenicity of the antibody when exposed to the immune system of the subject. Exemplary modifications include substitutions, deletions and insertion of one or more amino acids, which eliminate or reduce the immunogenicity of the antibody. Generally, such modifications do not alter the binding specificity of the antibody for its respective antigen. Reducing the immunogenicity of the antibody can improve one or more properties of the antibody, such as, for example, improving the therapeutic efficacy of the antibody and/or increasing the half-life of the antibody *in vivo*.

2. Fc Modifications

The anti-DLL4 antibodies provided herein can contain wild-type or modified Fc region. In some examples, the Fc region can be modified to alter one or more properties of the Fc polypeptide. For example, the Fc region can be modified to alter (*i.e.* increase or decrease) effector functions compared to the effector function of an Fc region of a wild-type immunoglobulin heavy chain. The Fc region of an antibody interacts with a number of Fc receptors, and ligands, imparting an array of important functional capabilities referred to as effector functions. Fc effector functions include, for example, Fc receptor binding, complement fixation, and T cell depleting activity (see e.g., U.S. Patent No. 6,136,310). Methods of assaying T cell depleting activity, Fc effector function, and antibody stability are known in the art. For example, the Fc region of an IgG molecule interacts with the FcγRs. These receptors are expressed in a variety of immune cells, including for example, monocytes, macrophages, neutrophils, dendritic cells, eosinophils, mast cells, platelets, B cells, large granular lymphocytes, Langerhans' cells, natural killer (NK) cells, and γδ T cells. Formation of the Fc/FcγR complex recruits these effector cells to sites of bound antigen, typically resulting in signaling events within the cells and important subsequent immune responses such as release of inflammation mediators, B cell activation, endocytosis, phagocytosis, and cytotoxic attack. The ability to mediate cytotoxic and phagocytic effector functions is a potential mechanism by which antibodies destroy targeted cells. Recognition of and lysis of bound antibody on target cells by cytotoxic cells that express FcγRs is referred to as antibody dependent cell-mediated cytotoxicity (ADCC). Other Fc receptors for various antibody isotypes include FcεRs (IgE), FcαRs (IgA), and FcμRs (IgM).

Thus, a modified Fc domain can have altered affinity, including but not limited to, increased or low or no affinity for the Fc receptor. For example, the different IgG subclasses have different affinities for the FcγRs, with IgG1 and IgG3 typically binding substantially better to the receptors than IgG2 and IgG4. In addition, different FcγRs mediate different effector functions. FcγR1, FcγRIIa/c, and FcγRIIIa are positive regulators of immune complex triggered activation, characterized by having an intracellular domain that has an immunoreceptor tyrosine-based activation motif (ITAM). FcγRIIb, however, has an immunoreceptor tyrosine-

based inhibition motif (ITIM) and is therefore inhibitory. Thus, altering the affinity of an Fc region for a receptor can modulate the effector functions induced by the Fc domain.

In one example, an Fc region is used that is modified for optimized binding to certain FcγRs to better mediate effector functions, such as for example, antibody-dependent cellular cytotoxicity, ADCC. Such modified Fc regions can contain modifications at one or more of amino acid residues (according to the Kabat numbering scheme, Kabat *et al.* (1991) Sequences of Proteins of Immunological Interest, U.S. Department of Health and Human Services), including, but not limited to, amino acid positions 249, 252, 259, 262, 268, 271, 273, 277, 280, 281, 285, 287, 296, 300, 317, 323, 343, 345, 346, 349, 351, 352, 353, and 424. For example, modifications in an Fc region can be made corresponding to any one or more of G119S, G119A, S122D, S122E, S122N, S122Q, S122T, K129H, K129Y, D132Y, R138Y, E141Y, T143H, V147I, S150E, H151D, E155Y, E155I, E155H, K157E, G164D, E166L, E166H, S181A, S181D, S187T, S207G, S207I, K209T, K209E, K209D, A210D, A213Y, A213L, A213I, I215D, I215E, I215N, I215Q, E216Y, E216A, K217T, K217F, K217A, and P279L of the exemplary Fc sequence set forth in SEQ ID NO:891, or combinations thereof. A modified Fc containing these mutations can have enhanced binding to an FcR such as, for example, the activating receptor FcγIIIa and/or can have reduced binding to the inhibitory receptor FcγRIIb (see e.g., US 2006/0024298). Fc regions modified to have increased binding to FcRs can be more effective in facilitating the destruction of the fungal cells in patients.

In some examples, the antibodies or antigen-binding fragments provided herein can be further modified to improve the interaction of the antibody with the FcRn receptor in order to increase the *in vivo* half-life and pharmacokinetics of the antibody (see, *e.g.* U.S. Patent No. 7,217,797; and U.S Pat. Pub. Nos. 2006/0198840 and 2008/0287657). FcRn is the neonatal FcR, the binding of which recycles endocytosed antibody from the endosomes back to the bloodstream. This process, coupled with preclusion of kidney filtration due to the large size of the full length molecule, results in favorable antibody serum half-lives ranging from one to three weeks. Binding of Fc to FcRn also plays a role in antibody transport.

Exemplary modifications of the Fc region include but are not limited to, mutation of the Fc described in U.S. Patent No. 7,217,797; U.S Pat. Pub. Nos. 2006/0198840, 2006/0024298 and 2008/0287657; and International Patent Pub. No. WO 2005/063816, such as mutations at one or more of amino acid residues (Kabat numbering, Kabat *et al.* (1991)) 251-256, 285-90, 308-314, in the C_H2 domain and/or amino acids residues 385-389, and 428-436 in the C_H3 domain of the Fc heavy chain constant region, where the modification alters Fc receptor binding affinity and/or serum half-life relative to unmodified antibody. In some examples, the Fc region is modified at one or more of amino acid positions 250, 251, 252, 254, 255, 256, 263, 308, 309, 311, 312 and 314 in the C_H2 domain and/or amino acid positions 385, 386, 387, 389, 428, 433, 434, 436, and 459 in the C_H3 domain of the Fc heavy chain constant region. Such modifications correspond to amino acids Gly120, Pro121, Ser122, Phe124 Leu125, Phe126, Thr133, Pro174, Arg175, Glu177, Gln178, and Asn180 in the C_H2 domain and amino acids Gln245, Val246, Ser247, Thr249, Ser283, Gly285, Ser286, Phe288, and Met311 in the C_H3 domain in an exemplary Fc sequence set forth in SEQ ID NO:891 In some examples, the modification is at one or more surface-exposed residues, and the modification is a substitution with a residue of similar charge, polarity or hydrophobicity to the residue being substituted.

In particular examples, a Fc heavy chain constant region is modified at one or more of amino acid positions 251, 252, 254, 255, and 256 (Kabat numbering), where position 251 is substituted with Leu or Arg, position 252 is substituted with Tyr, Phe, Ser, Trp or Thr, position 254 is substituted with Thr or Ser, position 255 is substituted with Leu, Gly, Ile or Arg, and/or position 256 is substituted with Ser, Arg, Gln, Glu, Asp, Ala, Asp or Thr. In some examples, a Fc heavy chain constant region is modified at one or more of amino acid positions 308, 309, 311, 312, and 314 (Kabat numbering), where position 308 is substituted with Thr or Ile, position 309 is substituted with Pro, position 311 is substituted with serine or Glu, position 312 is substituted with Asp, and/or position 314 is substituted with Leu. In some examples, a Fc heavy chain constant region is modified at one or more of amino acid positions 428, 433, 434, and 436 (Kabat numbering), where position 428 is substituted with Met, Thr, Leu, Phe, or Ser, position 433 is substituted with Lys, Arg, Ser, Ile, Pro, Gln, or His, position 434 is substituted with Phe, Tyr, or His, and/or position 436 is

substituted with His, Asn, Asp, Thr, Lys, Met, or Thr. In some examples, a Fc heavy chain constant region is modified at one or more of amino acid positions 263 and 459 (Kabat numbering), where position 263 is substituted with Gln or Glu and/or position 459 is substituted with Leu or Phe.

In some examples, a Fc heavy chain constant region can be modified to enhance binding to the complement protein C1q. In addition to interacting with FcRs, Fc also interact with the complement protein C1q to mediate complement dependent cytotoxicity (CDC). C1q forms a complex with the serine proteases C1r and C1s to form the C1 complex. C1q is capable of binding six antibodies, although binding to two IgGs is sufficient to activate the complement cascade. Similar to Fc interaction with FcRs, different IgG subclasses have different affinity for C1q, with IgG1 and IgG3 typically binding substantially better than IgG2 and IgG4. Thus, a modified Fc having increased binding to C1q can mediate enhanced CDC, and can enhance destruction of fungal cells. Exemplary modifications in an Fc region that increase binding to C1q include, but are not limited to, amino acid modifications at positions 345 and 253 (Kabat numbering). Exemplary modifications are include those corresponding to K209W, K209Y, and E216S in an exemplary Fc sequence set forth in SEQ ID NO:891.

In another example, a variety of Fc mutants with substitutions to reduce or ablate binding with FcγRs also are known. Such muteins are useful in instances where there is a need for reduced or eliminated effector function mediated by Fc. This is often the case where antagonism, but not killing of the cells bearing a target antigen is desired. Exemplary of such an Fc is an Fc mutein described in U.S. Patent No. 5,457,035, which is modified at amino acid positions 248, 249 and 251 (Kabat numbering). In an exemplary Fc sequence set forth in amino acids 100-330 of SEQ ID NO:891, amino acid 118 is modified from Leu to Ala, amino acid 119 is modified from Leu to Glu, and amino acid 121 is modified from Gly to Ala. Similar mutations can be made in any Fc sequence such as, for example, the exemplary Fc sequence. This mutein exhibits reduced affinity for Fc receptors.

The antibodies provided herein can be engineered to contain modified Fc regions. For example, methods for fusing or conjugating polypeptides to the constant regions of antibodies (*i.e.* making Fc fusion proteins) are known in the art and

described in, for example, U.S. Pat. Nos. 5,336,603, 5,622,929, 5,359,046, 5,349,053, 5,447,851, 5,723,125, 5,783,181, 5,908,626, 5,844,095, and 5,112,946; EP 307,434; EP 367,166; EP 394,827; PCT publications WO 91/06570, WO 96/04388, WO 96/22024, WO 97/34631, and WO 99/04813; Ashkenazi *et al.* (1991) *Proc. Natl. Acad. Sci. USA* 88:10535-10539; Traunecker *et al.* (1988) Nature 331:84-86; Zheng *et al.* (1995) *J. Immunol.* 154:5590-5600; and Vil *et al.* (1992) *Proc. Natl. Acad. Sci. USA* 89:11337-11341 (1992) and described elsewhere herein. In some examples, a modified Fc region having one or more modifications that increases the FcRn binding affinity and/or improves half-life can be fused to an anti-DLL4 antibody provided herein.

3. Pegylation

The anti-DLL4 antibodies provided herein can be conjugated to polymer molecules, or water soluble polymers, such as high molecular weight polyethylene glycol (PEG) to increase half-life and/or improve their pharmacokinetic profiles. Water soluble polymers include, but are not limited to, polyethylene glycol (PEG), copolymers of ethylene glycol/propylene glycol, carboxymethylcellulose, dextran, polyvinyl alcohol, polyvinyl pyrrolidone, poly-1,3-dioxolane, poly-1,3,6-trioxane, ethylene/maleic anhydride copolymer, polyaminoacids (either homopolymers or random copolymers), and dextran or poly(n-vinyl pyrrolidone)polyethylene glycol, propropylene glycol homopolymers, prolypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols (e.g., glycerol), polyvinyl alcohol, and mixtures thereof. Polyethylene glycol propionaldehyde can have advantages in manufacturing due to its stability in water. The polymer can be of any molecular weight, and can be branched or unbranched. The number of polymers attached to the antibody can vary, and if more than one polymers are attached, they can be the same or different molecules. In general, the number and/or type of polymers used for derivatization can be determined based on considerations including, but not limited to, the particular properties or functions of the antibody to be improved, and whether the antibody derivative will be used in a therapy under defined conditions.

Conjugation can be carried out by techniques known to those skilled in the art. Conjugation of therapeutic antibodies with PEG has been shown to enhance pharmacodynamics while not interfering with function (see, *e.g.*, Deckert *et al.*, *Int. J.*

Cancer 87: 382-390, 2000; Knight *et al.*, *Platelets* 15: 409-418, 2004; Leong *et al.*, *Cytokine* 16: 106-119, 2001; and Yang *et al.*, *Protein Eng.* 16: 761-770, 2003). PEG can be attached to the antibodies or antigen-binding fragments with or without a multifunctional linker either through site-specific conjugation of the PEG to the N- or C-terminus of the antibodies or antigen-binding fragments or via epsilon-amino groups present on lysine residues. Linear or branched polymer derivatization that results in minimal loss of biological activity can be used. The degree of conjugation can be monitored by SDS-PAGE and mass spectrometry to ensure proper conjugation of PEG molecules to the antibodies. Unreacted PEG can be separated from antibody-PEG conjugates by, *e.g.*, size exclusion or ion-exchange chromatography. PEG-derivatized antibodies can be tested for binding activity to DLL4 as well as for *in vivo* efficacy using methods known to those skilled in the art, for example, by functional assays described herein.

4. Conjugation of a Detectable Moiety

In some examples, the anti-DLL4 antibodies and antibody fragments provided herein can be further modified by conjugation to a detectable moiety. The detectable moieties can be detected directly or indirectly. Depending on the detectable moiety selected, the detectable moiety can be detected *in vivo* and/or *in vitro*. The detectable moieties can be employed, for example, in binding assays for determining the binding affinity of the anti-DLL4 antibody for DLL4. The detectable moieties also can be employed in methods of preparation of the anti-DLL4 antibodies, such as, for example, purification of the antibody. Typically, detectable moieties are selected such that conjugation of the detectable moiety does not interfere with the binding of the antibody to the target epitope. Generally, the choice of the detectable moiety depends on sensitivity required, ease of conjugation with the compound, stability requirements, available instrumentation, and disposal provisions. One of skill in the art is familiar with labels and can identify a detectable label suitable for and compatible with the assay employed. Methods of labeling antibodies with detectable moieties are known in the art and include, for example, recombinant and chemical methods.

The detectable moiety can be any material having a detectable physical or chemical property. Such detectable labels have been well-developed in the field of

immunoassays and, in general, most any label useful in such methods can be applied in the methods provided. Thus, a label is any composition detectable by spectroscopic, photochemical, biochemical, immunochemical, electrical, optical or chemical means. Useful labels include, but are not limited to, fluorescent dyes (*e.g.*, fluorescein isothiocyanate, Texas red, rhodamine, and the like), radiolabels (*e.g.*, ^{3}H, ^{125}I, ^{35}S, ^{14}C, or ^{32}P), in particular, gamma and positron emitting radioisotopes (*e.g.*, ^{157}Gd, ^{55}Mn, ^{162}Dy, ^{52}Cr, and ^{56}Fe), metallic ions (*e.g.*, ^{111}In, ^{97}Ru, ^{67}Ga, ^{68}Ga, ^{72}As, ^{89}Zr, and ^{201}Ti), enzymes (e.g., horse radish peroxidase, alkaline phosphatase and others commonly used in an ELISA), electron transfer agents (e.g., including metal binding proteins and compounds); luminescent and chemiluminescent labels (*e.g.*, luciferin and 2,3-dihydrophtahlazinediones, e.g., luminol), magnetic beads (*e.g.*, DYNABEADS™), and colorimetric labels such as colloidal gold or colored glass or plastic beads (*e.g.*, polystyrene, polypropylene, latex, etc.). For a review of various labeling or signal producing systems that can be used, see *e.g.* United States Patent No. 4,391,904.

5. Modifications to improve binding specificity

The binding specificity of the anti-DLL4 antibodies and antibody fragments provided can be altered or improved by techniques, such as phage display, which are described in further detail elsewhere herein. Methods for phage display generally involve the use of a filamentous phage (phagemid) surface expression vector system for cloning and expressing antibody species of the library. Various phagemid cloning systems to produce combinatorial libraries have been described by others. See, for example the preparation of combinatorial antibody libraries on phagemids as described by Kang, *et al.*, *Proc. Natl. Acad. Sci., USA*, 88:4363-4366 (1991); Barbas, *et al.*, *Proc. Natl. Acad. Sci., USA*, 88:7978-7982 (1991); Zebedee, *et al.*, *Proc. Natl. Acad. Sci., USA*, 89:3175-3179 (1992); Kang, *et al.*, *Proc. Natl. Acad. Sci., USA*, 88:11120-11123 (1991); Barbas, *et al.*, *Proc. Natl. Acad. Sci.*, USA, 89:4457-4461 (1992); and Gram, *et al.*, *Proc. Natl. Acad. Sci., USA*, 89:3576-3580 (1992), which references are hereby incorporated by reference.

In particular examples, DNA sequences encoding V_H and V_L domains are amplified from animal cDNA libraries (*e.g.*, human or murine cDNA libraries of lymphoid tissues). The DNA encoding the V_H and V_L domains are recombined

together with an scFv linker by PCR and cloned into a phagemid vector (*e.g.*, p CANTAB 6 or pComb 3 HSS). The vector is electroporated in *E. coli* and the *E. coli* is infected with helper phage. Phage used in these methods are typically filamentous phage including fd and M13 and the V_H and V_L domains are usually recombinantly fused to either the phage gene III or gene VIII. Phage expressing an antigen-binding domain that binds to a DLL4 antigen can be selected or identified with antigen, *e.g.*, recombinant DLL4. Examples of phage display methods that can be used to make the antibodies by phage display include those disclosed, for example, in Brinkman *et al.* (1995) *J. Immunol. Methods* 182:41-50; Ames *et al.* (1995) *J. Immunol. Methods* 184:177-186; Kettleborough *et al.* (1994) *Eur. J. Immunol.* 24:952-958; Persic *et al.* (1997) *Gene* 187:9-18; Burton *et al.* (1994) *Advances in Immunology* 57:191-280; PCT application No. PCT/GB91/O1 134; PCT publication Nos. WO 90/02809, WO 91/10737, WO 92/01047, WO 92/18619, WO 93/1 1236, WO 95/15982, WO 95/20401, and WO97/13844; and U.S. Pat. Nos. 5,698,426, 5,223,409, 5,403,484, 5,580,717, 5,427,908, 5,750,753, 5,821,047, 5,571,698, 5,427,908, 5,516,637, 5,780,225, 5,658,727, 5,733,743 and 5,969,108; each of which is incorporated herein by reference in its entirety.

As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including human antibodies, or any other desired antigen-binding fragment, and expressed in any desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, *e.g.*, as described herein. Techniques to recombinantly produce Fab, Fab' and F(ab')2 fragments can also be employed using methods known in the art such as those disclosed in PCT publication No. WO 92/22324; Mullinax *et al.* (1992) *BioTechniques* 12(6):864-869; Sawai *et al.* (1995) *AJRI* 34:26-34; and Better *et al.* (1988) *Science* 240: 1041-1043.

The resulting phagemid library can be manipulated to increase and/or alter the immunospecificities of the antibodies or antibody fragment of the library to produce and subsequently identify additional antibodies with improved properties, such as increased binding to a target antigen. For example, either or both the H and L chain encoding DNA can be mutagenized in a complementarity determining region (CDR) of the variable region of the immunoglobulin polypeptide, and subsequently screened

for desirable immunoreaction and neutralization capabilities. In order to identify candidate hypervariable region sites for modification, alanine scanning mutagenesis can be performed to identify hypervariable region residues contributing significantly to antigen binding. Alternatively, or additionally, it can be beneficial to analyze a crystal structure of the antigen-antibody complex to identify contact points between the antibody and antigen. Such contact residues and neighboring residues are candidates for substitution according to the techniques elaborated herein. Once such variants are generated, the panel of variants is subjected to screening as described herein and antibodies with superior properties in one or more relevant assays can be selected for further development.

E. METHODS OF GENERATING OR IDENTIFYING ANTI-DLL4 ANTIBODIES

Anti-DLL4 antibodies provided herein an be generated or identified using any method known to one of skill in the art. For example, an anti-DLL4 antibody can be generated using conventional immunization and hybridoma screening methods. In other examples, an anti-DLL4 antibody is identified by any of a variety of screening methods known to one of skill in the art, such as any described herein. Identified or generated antibodies also can be further optimized using antibody engineering and affinity maturation methods.

1. Immunization and Hybridoma Screening

Antibodies specific for DLL4 can be made using the hybridoma method first described by Kohler et al. (1975) *Nature*, 256:495, or made by recombinant DNA methods (U.S. Patent No. 4,816,567).

In the hybridoma method, a mouse or other appropriate host animal, such as a hamster, is immunized to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the protein used for immunization. Antibodies to a target antigen can be raised in animals by multiple subcutaneous (sc) or intraperitoneal (ip) injections of protein antigen and an adjuvant. Two weeks later, animals are boosted. 7 to 14 days later animals are bled and the serum is assayed for antibody titer specific for the target antigen. Animals are boosted until titers plateau.

Alternatively, lymphocytes can be immunized *in vitro*. Lymphocytes then are fused with myeloma cells using a suitable fusing agent, such as polyethylene glycol,

to form a hybridoma cell (Goding, Monoclonal Antibodies: Principles and Practice, pp. 59-103 (Academic Press, 1986)).

The hybridoma cells that are prepared are seeded and grown in a suitable culture medium that generally contains one or more substances that inhibit the growth or survival of the unfused, parental myeloma cells. For example, if the parental myeloma cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine (HAT medium), which substances prevent the growth of HGPRT-deficient cells.

Myeloma cells include those that fuse efficiently, support stable high-level production of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. Among these, myeloma cell lines are murine myeloma lines, such as those derived from MOPC-21 and MPC-11 mouse tumors available from the Salk Institute Cell Distribution Center, San Diego, CA, USA, and SP-2 or X63-Ag8-653 cells available from the American Type Culture Collection (ATCC), Rockville, Md., USA. Human myeloma and mouse-human heterocyeloma cells lines also have been described for the production of human monoclonal antibodies (Kozbor, (1984) *J. Immunol.*, 133:3001; and Brodeur et al., Monoclonal Antibody Production Techniques and Applications, pp. 51-63 (Marcel Dekker, Inc., New York, 1987)).

Culture medium in which hybridoma cells are growing is assayed for production of monoclonal antibodies directed against the target antigen. The binding specificity of monoclonal antibodies produced by hybridoma cells can be determined by any method known to one of skill in the art (e.g. as described in Section E.1), for example, by immunoprecipitation or by an *in vitro* binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoadsorbent assay (ELISA). The binding affinity also can be determined, for example, using Scatchard analysis.

After hybridoma cells are identified that produce antibodies of the desired specificity, affinity, and/or activity, the clones can be subcloned by limiting dilution procedures and grown by standard methods (Goding, Monoclonal Antibodies: Principles and Practice, pp. 59-103 (Academic Press, 1986)). Suitable culture media

for this purpose include, for example, D-MEM or RPMI-1640 medium. In addition, the hybridoma cells can be grown *in vivo* as ascites tumors in an animal.

The monoclonal antibodies secreted by the subclones are suitably separated from the culture medium, ascites fluid, or serum by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography.

DNA-encoding the hybridoma-derived monoclonal antibody can be readily isolated and sequenced using conventional procedures. For example, sequencing can be effected using oligonucleotide primers designed to specifically amplify the heavy and light chain coding regions of interest from the hybridoma. Once isolated, the DNA can be placed into expression vectors, which are then transfected into host cells such as *E. coli* cells, simian COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein to obtain the synthesis of the desired monoclonal antibodies in the recombinant host cells.

2. Screening Assays

Anti-DLL4 antibodies can be identified using antibody libaries to screen for antibody clones with the desired activity or activities.

a. Display Libraries

Typical of screening methods are high throughput screening of antibody libraries. For example, antibody libraries are screened using a display technique, such that there is a physical link between the individual molecules of the library (phenotype) and the genetic information encoding them (genotype). These methods include, but are not limited to, cell display, including bacterial display, yeast display and mammalian display, phage display (Smith, G. P. (1985) *Science* 228:1315-1317), mRNA display, ribosome display and DNA display. Using display techniques, the identity of each of the individual antibodies is unknown prior to screening, but the phenotype-genotype link allows for facile identification of selected antibodies.

Typically, in the libraries, nucleic acids encoding antibody gene fragments are obtained from immune cells harvested from humans or animals. If a library biased in favor of an antigen-specific antibody is desired, the subject is immunized with the target antigen to generate an antibody response, and spleen cells and/or circulating B cells or other peripheral blood lymphocytes (PBLs) are recovered for library

construction. Additional enrichment for antigen-specific antibody reactive cell populations can be obtained using a suitable screening procedure to isolate B cells expressing antigen-specific membrane bound antibody, e.g. by cell separation with antigen affinity chromatography or adsorption of cells to fluorochrome-labeled antigen followed by fluorescence-activated cell sorting (FACs).

Alternatively, the use of spleen cells and/or B cells or other PBLs from an unimmunized donor provides a better representation of the possible antibody repertoire, and also permits the construction of an antibody library using any animal (human or non-human) species in which the target antigen is not antigenic. For libraries incorporating *in vitro* antibody gene construction, stem cells are harvested from the subject to provide nucleic acids encoding unrearranged antibody gene segments. The immune cells of interest can be obtained from a variety of animal species, such as human, mouse, rat, lagomorpha, lupine, canine, feline, porcine, bovine, equine, and avian species.

Nucleic acid encoding antibody variable gene segments (including VH and VL segments) can be recovered from the cells of interest and amplified. In the case of rearranged VH and VL gene libraries, the desired DNA can be obtained by isolating genomic DNA or mRNA from lymphocytes followed by polymerase chain reaction (PCR) with primers matching the 5' and 3' ends of rearranged VH and VL genes as described in Orlandi *et al.*, (1989) *Proc. Natl. Acad. Sci. (USA)*, 86:3833-3837, thereby making diverse V gene repertoires for expression. The V genes can be amplified from cDNA and genomic DNA, with back primers at the 5' end of the exon encoding the mature V-domain and forward primers based within the J-segment as described in Orlandi *et al.*, (1989) and in Ward *et al.*, (1989) *Nature*, 341:544-546. For amplifying from cDNA, however, back primers can also be based in the leader exon as described in Jones *et al.*, (1991) *Biotechnology*, 9:88-89, and forward primers within the constant region as described in Sastry *et al.*, (1989) *Proc. Natl. Acad. Sci. (USA)*, 86:5728-5732. To maximize complementarity, degeneracy can be incorporated in the primers as described in Orlandi *et al.* (1989) or Sastry *et al.* (1989). The library diversity can be maximized by using PCR primers targeted to each V-gene family in order to amplify all available VH and VL arrangements present in the immune cell nucleic acid sample, e.g. as described in the method of Marks *et*

al., (1991) *J. Mol. Biol.*, 222:581-597, or as described in the method of Orum *et al.*, (1993) *Nucleic Acids Res.*, 21:4491-4498. For cloning of the amplified DNA into expression vectors, rare restriction sites can be introduced within the PCR primer as a tag at one end as described in Orlandi *et al.* (1989), or by further PCR amplification with a tagged primer as described in Clackson *et al.*, (1991) *Nature*, 352:624-628.

In another example of generating an antibody library, repertoires of synthetically rearranged V genes can be derived *in vitro* from V gene segments. Most of the human VH-gene segments have been cloned and sequenced (see e.g. Tomlinson *et al.*, (1992) *J. Mol. Biol.*, 227:776-798), and mapped (see e.g. Matsuda *et al.*, (1993) *Nature Genet.*, 3:988-94). These segments can be used to generate diverse VH gene repertoires with PCR primers encoding H3 loops of diverse sequence and length as described in Hoogenboom and Winter (1992) *J. Mol. Biol.*, 227:381-388. VH repertoires also can be made with all of the sequence diversity focused in a long H3 loop of a single length as described in Barbas *et al.*, (1992) *Proc. Natl. Acad. Sci. USA*, 89:4457-4461. Human Vκ and Vλ segments have been cloned and sequenced (see e.g. Williams and Winter (1993) *Eur. J. Immunol.*, 23:1456-1461) and can be used to make synthetic light chain repertoires. Synthetic V gene repertoires, based on a range of VH and VL folds, and L3 and H3 lengths, encode antibodies of considerable structural diversity. Following amplification of V-gene encoding DNAs, germline V-gene segments can be rearranged *in vitro* according to the methods of Hoogenboom and Winter (1992) *J. Mol. Biol.*, 227:381-388.

Repertoires of antibody fragments can be constructed by combining VH and VL gene repertoires together in several ways. Each repertoire can be created in different vectors, and the vectors recombined *in vitro* (see e.g. Hogrefe *et al.*, (1993) *Gene*, 128:119-126), or in vivo by combinatorial infection, for example, using the lox P system (Waterhouse *et al.*, (1993) *Nucl. Acids Res.*, 21:2265-2266). The *in vivo* recombination approach exploits the two-chain nature of Fab fragments to overcome the limit on library size imposed by *E. coli* transformation efficiency. Alternatively, the repertoires can be cloned sequentially into the same vector (see e.g. Barbas *et al.*, (1991) *Proc. Natl. Acad. Sci. USA*, 88:7978-7982), or assembled together by PCR and then cloned (see e.g. Clackson *et al.*, (1991) *Nature*, 352:624-628). PCR assembly can also be used to join VH and VL DNAs with DNA encoding a flexible peptide spacer

to form single chain Fv (scFv) repertoires. In another technique, "in cell PCR assembly" can be used to combine VH and VL genes within lymphocytes by PCR and then clone repertoires of linked genes (see e.g. Embleton (1992) *Nucl. Acids Res.*, 20:3831-3837).

In typical display libraries, the repertoire of VH and VL chains are constructed as one-pot libraries, such that the sequence of each member of the library is not known. Accordingly, sequencing is required following identification of a antibody specific for DLL4. Thus, as above for hybridoma-generated antibodies, DNA-encoding antibody clones identified from a display library can be readily isolated and sequenced using conventional procedures. For example, sequencing can be effected using oligonucleotide primers designed to specifically amplify the heavy and light chain coding regions of interest from a DNA template, e.g. phage DNA template.

Exemplary of such antibody libraries that can be used for screening are those described in any of the following: European Patent Application Nos. EP0368684 and EP89311731; International Published Patent Application Nos. WO92/001047, WO 02/38756, WO 97/08320, WO 2005/023993, WO 07/137616 and WO 2007/054816; United States Patent Nos. US 6,593,081 and US 6,989,250; United States Published Patent Application Nos. US 2002/0102613, US 2003/153038, US 2003/0022240, US 2005/0119455, US 2005/0079574 and US 2006/0234302; and Orlandi *et al.* (1989) *Proc Natl. Acad. Sci. U.S.A.,* 86:3833-3837; Ward *et al.* (1989) *Nature*, 341:544-546; Huse *et al.* (1989) *Science,* 246:1275-1281; Burton *et al.* (1991) *Proc. Natl. Acad. Sci., U.S.A.*, 88:10134-10137; Marks *et al.* (1991) *J Mol Biol*, 222:581-591; Hoogenboom *et al.* (1991) *J Mol Biol*, 227:381-388; Nissim *et al.* (1994) *EMBO J*, 13:692-698; Barbas *et al.* (1992) *Proc. Natl. Acad. Sci., U.S.A.*, 89:4457-4461; Akamatsu *et al.* (1993) *J. Immunol.*, 151:4651-1659; Griffiths *et al.* (1994) *EMBO J,* 13:3245-3260; Fellouse (2004) PNAS, 101:12467-12472; Persson *et al.* (2006) J. Mol. Biol. 357:607-620; Knappik *et al.* (2000) J. Mol. Biol. 296:57-86; Rothe *et al.* (2008) J. Mol. Biol. 376:1182-1200; Mondon *et al.* (2008) *Frontiers in Bioscience*, 13:1117-1129; and Behar, I. (2007) *Expert Opin. Biol. Ther.*, 7:763-779.

Phage Display Libraries

For example, natural or synthetic antibodies are selected by screening phage libraries containing phage that display various fragments of antibody variable region

(Fv) fused to phage coat protein. Variable domains can be displayed functionally on phage, either as single-chain Fv (scFv) fragments, in which VH and VL are covalently linked through a short, flexible peptide, or as Fab fragments, in which they are each fused to a constant domain and interact non-covalently, as described in Winter *et al.*, (1994) *Ann. Rev. Immunol.*, 12:433-455. Such phage libraries are panned by affinity chromatography against the desired antigen. Clones expressing Fv fragments capable of binding to the desired antigen are bound to the antigen and thus separated from the non-binding clones in the library. The binding clones are then eluted from the antigen, and can be further enriched by additional cycles of antigen binding/elution. Any antibody can be obtained by designing a suitable antigen screening procedure to select for the phage clone of interest followed by construction of a full length antibody clone using the Fv sequences from the phage clone of interest and suitable constant region (Fc) sequences described in Kabat *et al.*, Sequences of Proteins of Immunological Interest, Fifth Edition, NIH Publication 91-3242, Bethesda Md. (1991), vols. 1-3.

Repertoires of VH and VL genes can be separately cloned by polymerase chain reaction (PCR) and recombined randomly in phage libraries, which can then be searched for antigen-binding clones as described in Winter *et al.*, *Ann. Rev. Immunol.*, 12: 433-455 (1994). Libraries from immunized sources provide high-affinity antibodies to the immunogen without the requirement of constructing hybridomas. Alternatively, the naive repertoire can be cloned to provide a single source of human antibodies to a wide range of non-self and also self antigens without any immunization as described by Griffiths *et al.*, *EMBO J.* 12: 725-734 (1993). Finally, naive libraries can also be made synthetically by cloning the unrearranged V-gene segments from stem cells, and using PCR primers containing random sequence to encode the highly variable CDR3 regions and to accomplish rearrangement *in vitro* as described by Hoogenboom and Winter, *J. Mol. Biol.*, 227: 381-388 (1992).

VH and VL repertoires are cloned separately, one into a phagemid and the other into a phage vector. The two libraries are then combined by phage infection of phagemid-containing bacteria so that each cell contains a different combination and the library size is limited only by the number of cells present (about 10^{12} clones). Both vectors contain *in vivo* recombination signals so that the VH and VL genes are recombined onto a single replicon and are co-packaged into phage virions. The

libraries can provide a large number of diverse antibodies of good affinity (Kd^{-1} of about 10^{-8} M).

Filamentous phage is used to display antibody fragments by fusion to a coat protein, for example, the minor coat protein pIII. The antibody fragments can be displayed as single chain Fv fragments, in which VH and VL domains are connected on the same polypeptide chain by a flexible polypeptide spacer, e.g. as described by Marks *et al.*, *J. Mol. Biol.*, 222: 581-597 (1991), or as Fab fragments, in which one chain is fused to pIII and the other is secreted into the bacterial host cell periplasm where assembly of a Fab-coat protein structure which becomes displayed on the phage surface by displacing some of the wild type coat proteins, e.g. as described in Hoogenboom *et al.*, *Nucl. Acids Res.*, 19: 4133-4137 (1991).

b. Addressable Libraries

Another method of identifying anti-DLL4 antibodies, or fragments thereof, that have a desired specificity and/or activity for a target protein includes addressable combinatorial antibody libraries as described in U.S. Provisional Application Nos. 61/198,764 and 61/211,204, incorporated by reference herein. An advantage of addressable combinatorial libraries compared to display libraries is that each loci represents a different library member whose identity is known by virtue of its address. In such libraries, each individual member of the library is individually generated, and thus the sequence of each member is known. Display of the members of the library can be achieved on any desired format, which permits screening the members not only for binding but also for function. The "Hits" can be quickly identified, including by sequence, coincident with the screening results. Sequencing is not required to obtain structural information about an identified antibody since the sequence of an identified "Hit" is known *a priori*.

Addressable combinatorial antibody libraries contain antibodies with variable heavy chain and variable light chains composed of recombined human germline segments. Antibody combinatorial diversity in the library exists from recombination of individual V, D and J segments that make up the variable heavy chains and of individual V (V_κ or V_λ) and J (J_κ or J_λ) segments that make up the variable light chains. Additional combinatorial diversity derives from the pairing of different variable heavy chains and variable light chains.

The nucleic acid molecules encoding each VH chain and/or VL chain are individually synthesized, using standard DNA synthesis techniques, in an addressable format, whereby the identity of the nucleic acid sequence of each VH chain and/or VL chain in each locus is known. VH chains and VL chains are then paired, also in an addressable format, such that the identity of each member of the library is known based on its locus or "address". The addressable combinatorial antibody libraries can be screened for binding or activity against a target protein, such as DLL4, to identify antibodies or portions thereof that bind to a target protein and/or modulate an activity of a target protein. By virtue of the fact that these libaries are arrayed, the identity of each individual member in the collection is known during screening, thereby allowing facile comparison of "Hit" and related "non-Hit" antibodies.

Method of Generating a Combinatorial Addressable Antibody Library

U.S. Provisional Appl. Nos. 61/198,764 and 61/211,204, incorporated by reference herein, provide a method of generating a combinatorial antibody library where the identity of every antibody is known at the time of screening by virtue of the combinatorial generation of antibody members. In the combinatorial addressable libraries, variable heavy (VH) and variable light (VL) chain members of the libraries are generated, recombinantly or synthetically by DNA synthesis, from known germline antibody sequences or modified sequences thereof. Antibody combinatorial diversity in the library exists from recombination of individual V, D and J segments that make up the variable heavy chains and of individual V (V_κ or V_λ) and J (J_κ or J_λ) segments that make up the variable light chains. Additional combinatorial diversity derives from the pairing of different variable heavy chains and variable light chains.

Each VL chain of the antibodies in the library is encoded by a nucleic acid molecule that comprises a V_κ and a J_κ human germline segment or degenerate codons thereof, or a V_λ and a J_λ human germline segment or degenerate codons thereof, whereby the segments are linked in-frame. The germline segments are joined such that the V_L segment is 5' of the J_L segment. Each VH chain of the antibodies in the library is encoded by a nucleic acid molecule that comprises a V_H, D_H and a J_H germline segment, whereby the segments are linked in-frame. The germline segments

are joined such that the V_H segment is 5' of the D_H segment, which is 5' of the J_H segment.

The recombination is effected so that each gene segment is in-frame, such that resulting recombined nucleic acid molecules encodes a functional VH or VL polypeptide. For example, recombined segments are joined such that the recombined full length nucleic acid is in frame with the 5' start codon (ATG), thereby allowing expression of a full length polypeptide. Any combination of a V(D)J can be made, and junctions modified accordingly in order to generate a compiled V(D)J sequence that is in-frame, while preserving reading frames of each segment. The choice of junction modification is a function of the combination of V(D)J that will be joined, and the proper reading frame of each gene segment. In some examples, the nucleic acid molecule encoding a VH chain and/or a VL chain are further modified to remove stop codons and/or restriction enzyme sites so that the resulting encoded polypeptide is in-frame and functional.

A nucleic acid that encodes a variable heavy chain or a variable light chain is generated as follows. In the first step, individual germline segments (V_H, D_H and J_H for a heavy chain or V_κ and a J_κ, or V_λ and J_λ for a light chain) are selected for recombination (see e.g. Tables 3-5 herein and the Sequence Listing for exemplary germline segments). The germline segments can be human germline segments, or dgenerate sequences thereof, or alternatively the germline segments can be modified. For example, the D_H segment of a variable heavy chain can be translated in any open reading frame, or alternatively, the D_H segment can be the reverse complement of a D_H germline segment. Once selected, the germline segments are joined such that the recombined full length nucleic acid is in frame with the 5' start codon (ATG), thereby allowing expression of a full length polypeptide. Any combination of a V(D)J can be made, and junctions modified accordingly in order to generate a compiled V(D)J sequence that is in-frame, while preserving reading frames of each segment. The V segment is always reading frame 1. The reading frame of the J segment is selected so the correct amino acids are encoded. The D segment can be in any reading frame, but typically, the reading frame is chosen such that the resulting amino acids are predominately hydrophobic. As necessary, nucleic acid modifications are made at the junctions between the gene segments such that each segment is in the desired reading

frame. For example, at the V-D junction, one or more nucleotides can be deleted from the 5' end of the D, one or more nucleotides can be deleted from the 3' end of the V or one or more nucleotides can be inserted between the V and D (e.g. a nucleotide can be added to the 3' end of the V). Once the junctions are formed, the sequence is modified to remove any stop codons by substitution of nucleotides, such that stop codon TAA is replaced by codon TAT; stop codon TAG is replaced by codon TAT, and stop codon TGA is replaced by codon TCA. Finally, the nucleic acid can be further modified to, for example, remove unwanted restriction sites, splicing donor or acceptor sites, or other nucleotide sequences potentially detrimental to efficient translation. Modifications of the nucleic acid sequences include replacements or substitutions, insertions, or deletions of nucleotides, or any combination thereof.

The nucleic acid molecules encoding each VH chain and/or VL chain are individually synthesized, using standard DNA synthesis techniques, in an addressable format, whereby the identity of the nucleic acid sequence of each VH chain and/or VL chain in each locus is known.

VH chains and VL chains are then paired, also in an addressable format, such that the identity of each member of the library is known based on its locus or "address". For example, resulting members of the library are produced by co-expression of nucleic acid molecules encoding the recombined variable region genes together, such that when expressed, a combinatorial antibody member is generated minimally containing a VH and VL chain, or portions thereof. In some examples of the methods, the nucleic acid molecule encoding the VH and VL chain can be expressed as a single nucleic acid molecule, whereby the genes encoding the heavy and light chain are joined by a linker. In another example of the methods, the nucleic acid molecules encoding the VH and VL chain can be separately provided for expression together. Thus, upon expression from the recombined nucleic acid molecules, each different member of the library represents a germline encoded antibody, whereby diversity is achieved by combinatorial diversity of V(D)J segments and pairing diversity of heavy and light chains.

A library of antibodies can be generated upon co-expression of a nucleic acid molecule encoding the VH chain and a nucleic acid encoding the VL chain to

generate a combinatorial library containing a plurality of different members. The antibodies within the combinatorial addressable germline antibody libraries contain all or a portion of the variable heavy chain (VH) and variable light chain (VL), as long as the resulting antibody is sufficient to form an antigen binding site. Typically, the combinatorial addressable germline antibodies are Fabs. The combinatorial addressable antibody library can be screened to identify a "Hit" antibody against any target antigen, for example, against DLL4.

3. Optimization and Affinity Maturation

Anti-DLL4 antibodies, such as any that are generated or identified by any of the above methods or other methods known to one of skill in the art, can be optimized or improved by engineering or affinity maturation methods. For example, the binding affinity to DLL4 can be optimized or improved. Such methods include, for example, generating and screening antibody libraries using the previously identified antibody as a template by introducing mutations at random *in vitro* by using error-prone PCR (Zhou et al., *Nucleic Acids Research* (1991) 19(21):6052; and US2004/0110294); randomly mutating one or more CDRs, e.g. using PCR with primers carrying random sequence spanning the CDR of interest, in selected individual Fv clones and screening for higher affinity clones (WO 96/07754); oligonucleotide directed mutagenesis (Rosok et al., *The Journal of Immunology*, (1998) 160:2353-2359); codon cassette mutagenesis (Kegler-Ebo et al., *Nucleic Acids Research,* (1994) 22(9):1593-1599); degenerate primer PCR, including two-step PCR and overlap PCR (U.S. Patent Nos. 5,545,142, 6,248,516, and 7,189,841; Higuchi et al., *Nucleic Acids Research* (1988); 16(15):7351-7367; and Dubreuil et al., *The Journal of Biological Chemistry* (2005) 280(26):24880-24887); and recombining the VH or VL domains selected by phage display with repertoires of naturally occurring V domain variants obtained from unimmunized donors and screening for higher affinity in several rounds of chain reshuffling as described in Marks *et al., Biotechnology,* 10: 779-783 (1992).

Affinity maturation methods also include rationale methods of affinity maturation as described in U.S. Provisional Application No. [Attorney Docket No. 3800016-00004/p702], incorporated by reference herein. For example, the structure-affinity/activity relationship (SAR) of a parent or template antibody can be used to rationally optimize or improve the binding affinity or activity of an antibody.

Generally, in the method of affinity maturation, residues to mutagenize in the antibody are identified either by scanning mutagenesis described below or by comparison of the amino acid sequence of the variable heavy or light chain of the antibody with a respective variable heavy or light chain of a related antibody that exhibits reduced activity for the target antigen. This structure-affinity/activity relationship analysis between the antibody and a related antibody or antibodies reveals target regions of the antibody polypeptide that are important for activity. The affinity maturation method provided herein can be performed iteratively to further optimize binding affinity.

For example, SAR can be effected by scanning mutagenesis (e.g. alanine scanning mutagenesis), across the full-length sequence of a variable heavy or light chain or in a region (e.g. CDR) of the variable heavy or light chain. The scanning mutagenesis can reveal each residues contribution to binding to the target antigen. Residues that are essential for activity (e.g. binding), i.e. those whose mutagenesis decreases activity to the target antigen, are not subjected to full or partial saturation mutagenesis. Residues that are not essential for binding, i.e. those whose mutagenesis preserves or increases binding to the target antigen, are subjected to full or partial saturation mutagenesis; mutants are tested for binding to the target antigen to identify mutations that increase binding affinity to the target antigen.

F. ASSESSING ANTI-DLL4 ANTIBODY PROPERTIES AND ACTIVITIES

The anti-DLL4 antibodies provided herein can be characterized in binding or other activities using assays well known to one of skill in the art. For example, the anti-DLL4 antibodies can be assayed for the ability to immunospecifically bind to DLL4. The affinity and specificity for DLL4 also can be determined. In addition, in vitro assays and in vivo animal models using the anti-DLL4 antibodies provided herein can be employed for assessing their effects, generally their antagnositic effects for inhibiting the activity of DLL4.

1. Binding

The anti-DLL4 antibodies provided herein can be assessed for their ability to specifically bind DLL4 (e.g. cell-surface expressed DLL4 or an isolated, synthetically generated or recombinantly expressed protein or peptide (e.g. epitope)) and the

specifity determined by any method known to one of skill in the art. Exemplary assays are described herein below. Binding assays can be performed in solution, suspension or on a solid support. Negative controls can be included in such assays as a measure of background binding. Binding affinities also can be determined using Scatchard analysis (Munson *et al.*, *Anal. Biochem.*, 107:220 (1980)), surface plasmon resonance, isothermal calorimetry, or other methods known to one of skill in the art.

a. Binding Assays

Generally, binding is detected using a detectable moiety or label (e.g. an enzyme, a radionuclide, a fluorescent probe, electrochemiluminescent label, or a color dye) typically attached to the target or, if desired, directly to the antibody. Alternatively, binding can be detected by a further third reagent that itself is labeled or detectable. For example, detection of an antibody bound to a target protein can be achieved using a labeled capture molecule in a sandwich assay format. Other proteins capable of specifically binding immunoglobulin constant regions, such as protein A or protein G also can be used as the label agent. These proteins exhibit a strong non-immunogenic reactivity with immunoglobulin constant regions from a variety of species (see, e.g., Kronval *et al.*, (1973) *J. Immunol.* 111:1401-1406; Akerstrom *et al.*, (1985) *J. Immunol.* 135:2589-2542). The detection agent can be modified with a detectable moiety, such as biotin, to which another molecule can specifically bind, such as streptavidin. A variety of detectable moieties are well known to those skilled in the art.

The choice of label or detectable group used in the assay is not critical, as long as it does not significantly interfere with the specific binding of the antibody used in the assay. Generally, the choice depends on sensitivity required, ease of conjugation with the compound, stability requirements, available instrumentation, and disposal provisions. One of skill in the art is familiar with labels and can identify a detectable label suitable for and compatible with the assay employed.

The detectable group can be any material having a detectable physical or chemical property. Such detectable labels have been well-developed in the field of immunoassays and, in general, most any label useful in such methods can be applied. Thus, a label is any composition detectable by spectroscopic, photochemical, biochemical, immunochemical, electrical, optical or chemical means. Useful labels

include magnetic beads (e.g., DYNABEADS™), fluorescent dyes (e.g., fluorescein isothiocyanate, Texas red, rhodamine, and the like), radiolabels (e.g., 3H, 125I, 35S, 14C, or 32P), enzymes (e.g., horse radish peroxidase, alkaline phosphatase and others commonly used in an ELISA), chemiluminescent labels (luciferin and 2,3-dihydrophtahlazinediones, e.g., luminol), and colorimetric labels such as colloidal gold or colored glass or plastic beads (e.g., polystyrene, polypropylene, latex, etc.). For a review of various labeling or signal producing systems that can be used, see e.g. United States Patent No. 4,391,904.

Means of detecting labels are well known to those of skill in the art. Thus, for example, where the label is a radioactive label, means for detection include a scintillation counter or photographic film as in autoradiography. Where the label is a fluorescent label, it can be detected by exciting the fluorochrome with the appropriate wavelength of light and detecting the resulting fluorescence. The fluorescence can be detected visually, by the use of electronic detectors such as charge coupled devices (CCDs) or photomultipliers and the like. Similarly, enzymatic labels can be detected by providing the appropriate substrates for the enzyme and detecting the resulting reaction product. Finally simple colorimetric labels can be detected simply by observing the color associated with the label.

Some assay formats do not require the use of labeled components. For instance, agglutination assays can be used to detect the presence of the target antibodies. In this case, antigen-coated particles are agglutinated by samples containing the target antibodies. In this format, none of the components need be labeled and the presence of the target antibody is detected by simple visual inspection.

Alternatively, the antibodies provided herein can be screened for their ability to bind to cells, using whole cell panning, with or without subtractive panning. Screening can be done against live cells or against intact, mildly fixed target cells. Methods for whole cell panning have been described previously (see e.g. Siegel *et al.* (1997) *J. Immunol. Methods* 206:73-85 incorporated herein by reference). Other techniques for screening which can be applied include fluorescent activated cell sorting (FACs). Example 8 exemplifies a binding assay for anti-DLL4 binding to DLL4 expressed on the surface of cells.

For high-throughput screening, assays can be multiplexed. Thus, the binding affinities of antibodies to a number of different target proteins can be determined at once. In one example, different target proteins can be separately labeled with different detectable moieities. For example, different antigens can be coupled to color-coded beads (Schwenk *et al.* (2007) *Mol. Cell. Prot.*, 6:125-132). In another example, multi-spot plates can be used that permit assay multiplexing by absorption of of up to 100 proteins in a locus of the plate (e.g. using Multi-Array or Multi-Spot plates from Meso Scale Discovery; MSD, Gaithersburg, MD). In such an example, antibodies can be screened by addition of a different antibody to each well of a multi-spot plate. The assay readily permits the screening of thousands of antibodies at once against numerous target proteins. Example 3 exemplifies a binding assay to identify antibodies that bind to DLL4 using a Multispot electrochemiluminescence (ECL) binding assay.

For example, DLL4-expressing cells can be incubated first with an anti-DLL4 antibody followed by a second incubation with a secondary antibody that recognizes the primary antibody and is conjugated with a detectable label such as FITC. After labeling, the cells can be counted with a flow cytometer to analyze the antibody binding. In another example, a DLL4 antigen can be immobilized to a solid support (*e.g.* a carbon or plastic surface, a tissue culture dish or chip) and contacted with antibody. Unbound antibody or target protein can be washed away and bound complexes can then be detected. Binding assays can be performed under conditions to reduce nonspecific binding, such as by using a high ionic strength buffer (*e.g.* 0.3-0.4 M NaCl) with nonionic detergent (*e.g.* 0.1% Triton X-100 or Tween 20) and/or blocking proteins (*e.g.* bovine serum albumin or gelatin).

Other immunoassays also can be used to analyze immunospecific binding and cross-reactivity including, but not limited to, competitive and non-competitive assay systems using techniques such as, but not limited to, western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), Meso Scale Discovery (MSD, Gaithersburg, Maryland), "sandwich" immunoassays, immunoprecipitation assays, ELISPOT, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, protein A immunoassays,

immunohistochemistry, or immuno-electron microscopy. Such assays are routine and well known in the art (see, *e.g.*, Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, which is incorporated by reference herein in its entirety). Other assay formats include liposome immunoassays (LIA), which use liposomes designed to bind specific molecules (e.g., antibodies) and release encapsulated reagents or markers. The released chemicals are then detected according to standard techniques (see Monroe *et al.*, (1986) *Amer. Clin. Prod. Rev.* 5:34-41). Exemplary immunoassays not intended by way of limitation are described briefly below.

Immunoprecipitation protocols generally comprise lysing a population of cells in a lysis buffer such as RIPA buffer (1% NP-40 or Triton X-100, 1% sodium deoxycholate, 0.1% SDS, 0.15 M NaCl, 0.01 M sodium phosphate at pH 7.2, 1% Trasylol) supplemented with protein phosphatase and/or protease inhibitors (*e.g.*, EDTA, PMSF, aprotinin, sodium vanadate), adding the antibody or antigen-binding fragment thereof of interest to the cell lysate, incubating for a period of time (*e.g.*, 1 to 4 hours) at 40°C., adding protein A and/or protein G sepharose beads to the cell lysate, incubating for about an hour or more at 40°C., washing the beads in lysis buffer and resuspending the beads in SDS/sample buffer. The ability of the antibody of interest to immunoprecipitate a particular antigen can be assessed by, *e.g.*, western blot analysis. One of skill in the art is knowledgeable as to the parameters that can be modified to increase the binding of the antibody to an antigen and decrease the background (*e.g.*, pre-clearing the cell lysate with sepharose beads). For further discussion regarding immunoprecipitation protocols see, *e.g.*, Ausubel *et al.*, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.16.1.

Western blot analysis generally involves preparing cell extracts, in particular of cells that express DLL4, electrophoresis of the samples in a polyacrylamide gel (*e.g.*, 8%-20% SDS-PAGE depending on the molecular weight of the antigen) or via 2-D gel electrophoresis, transferring the sample from the polyacrylamide gel to a membrane such as nitrocellulose, PVDF or nylon, blocking the membrane in blocking solution (*e.g.*, PBS with 3% BSA or non-fat milk), washing the membrane in washing buffer (*e.g.*, PBS-Tween 20), probing the membrane with primary antibody (*i.e.* the

antibody of interest) diluted in blocking buffer, washing the membrane in washing buffer, probing the membrane with a secondary antibody (which recognizes the primary antibody, *e.g.*, an anti-human antibody) conjugated to an enzymatic substrate (*e.g.*, horseradish peroxidase or alkaline phosphatase) or radioactive molecule (*e.g.*, ^{32}P or ^{125}I) diluted in blocking buffer, washing the membrane in wash buffer, and detecting the presence of the antigen. One of skill in the art is knowledgeable as to the parameters that can be modified to increase the signal detected and to reduce the background noise. For further discussion regarding western blot protocols see, *e.g.*, Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.8.1.

ELISAs also can be used to assess binding. ELISAs generally involve preparing antigen (generally a recombinant or synthetic protein or peptide thereof, such as containing an epitope), coating the well of a 96 well microtiter plate with the antigen, adding the antibody of interest conjugated to a detectable compound such as an enzymatic substrate (*e.g.*, horseradish peroxidase or alkaline phosphatase) to the well and incubating for a period of time, and detecting the presence of the antigen. In ELISAs, the antibody of interest does not have to be conjugated to a detectable compound; instead, a second antibody (which recognizes the antibody of interest) conjugated to a detectable compound can be added to the well. Further, instead of coating the well with the antigen, the antibody can be coated to the well. In this case, a second antibody conjugated to a detectable compound can be added following the addition of the antigen of interest to the coated well. One of skill in the art is knowledgeable as to the parameters that can be modified to increase the signal detected as well as other variations of ELISAs known in the art. For further discussion regarding ELISAs see, *e.g.*, Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 11.2.1. Example 7 exemplifies an ELISA binding assay to assess the dose-dependent binding of anti-DLL4 antibodies to DLL4.

Immunohistochemistry can be used. Immunohistochemistry involves preparing a tissue sample (*e.g.* from a DLL4-expressing cell), fixing the tissue to preserve protein molecules in their native conformation, bathing the sample in a permeabilization reagent (e.g. Tween, Nonidet P40) to penetrate the tissue, blocking

the sample with blocking solution (*e.g.*, PBS with 3% BSA or non-fat milk), washing the sample in washing buffer (*e.g.*, PBS-Tween 20), probing the sample with primary antibody (*i.e.* the antibody of interest) diluted in blocking buffer, washing the sample in washing buffer, probing the sample with a secondary antibody (which recognizes the primary antibody, *e.g.*, an anti-human antibody) conjugated to a fluorescent dye (e.g. fluoresein isothiocynate, alexa fluor, rhodamine) diluted in blocking buffer, washing the sample in wash buffer, and detecting the presence of the antigen via fluorescent microscopy. One of skill in the art is knowledgeable as to the parameters that can be modified to increase the signal detected and to reduce the background noise.

In any of the above binding assays, competition experiments can be performed. For example, anti-DLL4 antibodies can be assessed for their ability to block binding of Notch receptors to DLL4. Thus, assays also include binding assasys to assess the inhibition of DLL4-Notch interaction in the presence of an anti-DLL4 antibody. Such assays can be used to identify anagonist antibodies. This is exemplified in Example 10 and Example 11.

b. Binding Affinity

The binding affinity of an antibody to an antigen can be determined. Any method known to one of skill in the art can be used to measure the binding affinity of an antibody. For example, the binding properties of an antibody can be assessed by performing a saturation binding assay, for example, a saturation ELISA, whereby binding to a target protein is assessed with increasing amounts of antibody. In such experiments, it is possible to assess whether the binding is dose-dependent and/or saturable. In addition, the binding affinity can be extrapolated from the 50% binding signal. Typically, apparent binding affinity is measured in terms of its association constant (Ka) or dissociation constant (Kd) and determined using Scatchard analysis (Munson *et al.*, *Anal. Biochem.*, 107:220 (1980).

For example, binding affinity to a target protein can be assessed in a competition binding assay in where increasing concentrations of unlabeled protein is added, such as by radioimmunoassay (RIA) or ELISA. Binding affinity also can be analyzed surface plasmon resonance, e.g. using BIAcore kinetic analysis. This involves analyzing the binding and dissociation of an antibody member from chips

containing immobilized target proteins on their surface. The Biacore evaluation software generates the values of Ka and Kd by fitting the data to interaction models.

It is understood that the binding affinity of an antibody can vary depending on the assay and conditions employed, although all assays for binding affinity provide a rough approximation. By performing various assays under various conditions it is possible to estimate the binding affinity of an antibody. In addition, binding affinities can differ depending on the target source, whether as a cell-expressed target antigen or as a recombinant or synthetically produced antigen. Thus, the binding affinity of an anti-DLL4 antibody for DLL4 expressed on the surface of a cells can differ from the binding affinity determined using an isolated or purfied DLL4 protein. Further, binding affinities can differ depending on the structure of an antibody. For example, generally a bivalent antibody, for example a bivalent $F(ab')_2$ fragment or full-length IgG, has a better binding affinity then a monovalent Fab antibody. Hence, it is understood that where a Fab has a specified binding affinity for a particular target, it is excepted that the binding affinity is even greater for a full-lenth IgG that is bivalent.

Example 6 exemplifies assessing binding affinity using surface plasmon resonance.

2. Functional Activity

Anti-DLL4 antibodies provided herein can be screened for modulation of an functional acitivity of DLL4 using in vitro or in vivo assays known to one of skill in the art. Assays for functional activity include those that assess activation of Notch signaling by DLL4 by assaying for signal transduction and/or down stream functional activities such as are described above. Activiation of Notch can be achieved, for example, by coincubation with cells that express DLL4 and/or immobilization of DLL4, and assays performed in the presence of antibody members. In such assays, for example, the effects of antibodies on endothelial cell proliferation (e.g. HUVECs) induced by DLL4 can be assessed (see e.g., Ridgway *et al.* (2006) Nature, 444:1083). In some examples, antibodies can be used to assess effects on cell differentiation of a cell expressing Notch. The cells can be co-cultured with cells expressing a ligand for Notch, for example, DLL4 or Jag1. To identify antibodies that promote differentiation (i.e. interfere with Notch activation), antibodies can be added to the assay.

For cell-based assays, assays are generally performed using cell lines that are known to express the target of interest (Notch or a Notch ligand, e.g. DLL4). Such cells are known to one of skill in the art. For example, one can consult the ATCC Catalog (atcc.org) to identify cell lines. Also, if a particular cell type is desired, the means for obtaining such cells, and/or their instantly available source is known to those in the art. An analysis of the scientific literature can readily reveal appropriate choice of cells expressing any desired target. In addition, cells lines expressing a target of interest can be generated by transient or stable transfection with an expression vector expressing a target of interest. Methods of transfection and expression are known to those of skill in the art (see e.g., Kaufman R.J. (1990) *Methods in Enzymology* 185:537-566). In addition, any primary cell or cell line can be assessed for expression of a particular target (e.g. cell surface marker). Cell surface markers can be assayed using fluorescently labeled antibodies and FACS. Suitable cell lines include A549 (lung), HeLa, Jurkat, BJAB, Colo205, H1299, MCF7, MDA-MB-231, PC3, HUMEC, HUVEC, and PrEC. Exemplary assays to assess the effects of modulation of anti-DLL4 antibodies on a functional activity are set forth in Example 13 and Example 14.

Other assays that can be used to assess anti-DLL4 antibodies include any assay that models angiogenesis. For example, a human umbilical vein endothelial cells (HUVECs) can be grown in fibrin gels in the presence of co-cultured human skin fibroblast (SF) cells to generate sprouts (see e.g. published U.S. Application No. 20080175847; see also Nakatsu et al. *Microvasc. Res.* 66:102-12 (2003)). In such an assay, Cytodex™ 3 beads (Amersham Phamacia Biotech) are coated with HUVEC cells. HUVEC-coated beads are imbedded in a fibrin clot in one well of a 12-well culture plate. SF cells (e..g 8×10^4) are plated on top of the clot. Anti-DLL4 antibodies can be added. After a designated time (e.g. between days 7 and 9) the assay can be terminated and the length and number of sprouts can be assessed by immunostaining and/or imaging, for example, using an anti-CD31 antibody (clone EM59; eBioscience).

Anti-DLL4 antibodies provided herein that contain a modification in the Fc region also can be assessed to determine effector functions of the antibody. For example, the Fc activities of the produced antibody are measured to ensure that only

the desired properties are maintained. In vitro and/or in vivo cytotoxicity assays can be conducted to confirm the reduction/depletion of CDC and/or ADCC activites. For example, Fc receptor (FcR) binding assays can be conducted to ensure tha thte antibody lacks FcγR bomdomg (hence likely lacking ADCC activity), but retains FcRn binding ability. The primary cells for mediating ADCC, NK cells, express FcγRIII only, whereas monocytes express FcγRI, FcγRII and FcγRIII. FcR expression on hematopoietic cells is summarized in Table 3 on page 464 of Ravetch and Kinet, *Annu. Rev. Immunol.*, 9:457-92 (1991). An example of an in vitro assay to assess ADCC activity of a molecule of interest is described in U.S. Patent Nos. 5,500,362 or 5,821,337. Useful effector cells for such assays include peripheral blood mononuclear cells (PBMC) and Natural Killer (NK) cells. Alternatively, or additionally, ADCC activity of the molecule of interest can be assessed in vivo, e.g., in an animal model such as that disclosed in Clynes et al. *Proc. Natl. Acad. Sci. USA* 95:652-656 (1998). C1q binding assays can also be carried out to confirm that the antibody is unable to bind C1q and hence lacks CDC activity. To assess complement activation, a CDC assay, e.g. as described in Gazzano-Santoro et al. *J. Immunol. Methods* 202:163 (1996) can be performed. FcRn binding and in vivo clearance/half-life deteminations can also be performed using method known in the art.

3. Animal Models

Anti-DLL4 antibodies, for example any provided herein, can be assessed in vivo assays associated with aberrant activity of DLL4 or its receptor Notch. In general, the method involves administering an antibody to a subject, generally a non-human animal model for a disease or condition and determining the effect of the antibody on the on the disease or condition of the model animal. *In vivo* assays include controls, where suitable controls include a sample in the absence of the antibody.

Generally, assays in animals include those that assess the effects of antibodies on angiogenesis or tumor growth. Exemplay of such assays are described in published U.S. Application No. 20090035308 and 2008 0175847. In one example, *in vivo* angiogenesis can by assayed using a matrigel plug assay. For example, a matrigel plug can be injected into the ventral abdominal subcutaneous tissue of mice, in the presence or absence of anti-DLL4 antibodies and/or VEGF. After a designated

time, e.g. six days, the matrigel plug can be recovered, weighed, and assessed for hemoglobin measurement and immunohistochemical analysis. For example, vascular identity of infiltrating cells can be established with PECAM immunostaining. In such examples, the VEGF samples contain recruited endothelial cells and various stages of vascular structures formed throughout the plug. Vascularization can be assessed in the presence and absence of anti-DLL4 antibodies.

In another example, a tumor xenograft model can be used to assess the activity of anti-DLL4 antibodies on tumor growth. For example, tumor cells such as HT29 (human colon carcinoma cell line) and KS-SLK (human Kaposi's sarcoma cell line) cells can implanted into mice subcutancously. If study of local effects is desired, cells can be premixed with matrigel and implanted subcutaneously. The antibody can be administered before or coincident with establishment of the tumor, or after tumor establishment. The antibodies also can be administered in combination with anti-VEGF or other combination treatment. In some examples, antibody is administered days to weeks after establishment of the turmor. In other examples, for study of local effects, cells can be premixed with matrigel-containing vehicle control or anti-DLL4 antibody. The size of the tumors can be monitored over hours, days and weeks by sacrificing the animal and isolating the tumor. Thc blood vessel density, branching of the tumors and tumor vascular perfusion also can be assessed and compared to tumors from mice injected with control. A tumor xenograft model also can be induced using MDA-MB-435, HM7, Colo205 or Calu6 cells (see e.g. U.S. published application No. US20080175847). In addition, pre-clinical tumor mdoesl also can be used, including but not limited to, MV-522, WEHI3, SK-OV-3X1, LL2, EL4, H11299, SKMES-1, MX-1, SW620, and LS174T xenograft tumor models (see e.g. U.S. published application No. US20080175847).

In a further example, endothelial cell proliferation and arterial development in the the vasculature in vivo can be assessed, for example in the vasculature of the retina. In such an example, anti-DLL4 antibody or control can be injected intraperitoneally into mice. Eyes can be collected at various time points and fixed with 4% paraformaldehyde. Retinas can be dissected and incubated with various antibodies. For example, proliferation can be assessed by labeling with Ki67 (e.g. clone Sp6; Lab Vision) in the presence or absence of anti-DLL4 antibody. Also, anti-

α smooth muscle actin (ASMA; Sigma-Aldrich) staining, which is associated with the retinal artieries, can be used to assess the morphology of arteries. Generally, a hyperproliferation phenotype of retinal endothelial cells in observed by blockade of DLL4. Further, disruption of radially alternating arteries and veins also is observed.

G. METHODS OF PRODUCTION OF ANTIBODIES

Antibodies provided herein can be expressed in host cells and produced therefrom. The antibodies can be expressed as full-length, or as antibodies that are less then full length, for example, as antibody fragments. Nucleic acid molecules and antibodies provided herein can be made by any method known to one of skill in the art. Such procedures are routine and are well known to the skill artisan. They include routine molecular biology techniques including gene synthesis, PCR, ligation, cloning, transfection and purification techniques. A description of such procedures is provided below.

For example, nucleic acid sequences can be constructed using gene synthesis techniques. Gene synthesis or routine molecular biology techniques also can be used to effect insertion, deletion, addition or replacement of nucleotides. For example, additional nucleotide sequences can be joined to a nucleic acid sequence. In one example linker sequences can be added, such as sequences containing restriction endonuclease sites for the purpose of cloning the synthetic gene into a vector, for example, a protein expression vector or a vector designed for the amplification of the antibody constant region coding DNA sequences. Furthermore, additional nucleotide sequences specifying functional DNA elements can be operatively linked to a recombined germline encoding nucleic acid molecule. Examples of such sequences include, but are not limited to, promoter sequences designed to facilitate intracellular protein expression, and leader peptide sequences designed to facilitate protein secretion. Additional nucleotide sequences such as sequences specifying protein binding regions also can be linked to nucleic acid sequences. Such regions include, but are not limited to, sequences to facilitate uptake of recombined antibodies or fragments thereof into specific target cells, or otherwise enhance the pharmacokinetics of the synthetic gene.

The nucleic acids encoding antibody polypeptides are typically cloned into a vector before transformation into prokaryotic or eukaryotic cells. Choice of vector

can depend on the desired application. For example, after insertion of the nucleic acid, the vectors typically are used to transform host cells, for example, to amplify the antibody genes for replication and/or expression thereof. In such examples, a vector suitable for high level expression is used.

Generally, nucleic acid encoding the heavy chain of an antibody is cloned into a vector and the nucleic acid encoding the light chain of an antibody is cloned into the vector. The genes can be cloned into a single vector for dual expression thereof, or into separate vectors. If desired, the vectors also can contain further sequences encoding additional constant region(s) or hinge regions to generate other antibody forms.

In one example, nucleic acid encoding the heavy chain of an antibody, is ligated into a first expression vector and nucleic acid encoding the light chain of an antibody, is ligated into a second expression vector. The expression vectors can be the same or different, although generally they are sufficiently compatible to allow comparable expression of proteins (heavy and light chain) therefrom. The first and second expression vectors are generally co-transfected into host cells, typically at a 1:1 ratio. Exemplary of vectors include, but are not limited to, pγ1HC and pκLC (Tiller et al. (2008) *J Immunol. Methods*, 329:112-24). Other expression vectors include the light chain expression vector pAG4622 and the heavy chain expression vector pAH4604 (Coloma et al. (1992) *J Immunol. Methods*, 152:89-104). The pAG4622 vector contains the genomic sequence encoding the C-region domain of the human κ L chain and the gpt selectable marker. The pAH4604 vectors contains the hisD selectable marker and sequences encoding the human H chain γ1 C-region domain. In another example, the heavy and light chain can be cloned into a single vector that has expression cassettes for both the heavy and light chain. Other exemplary expression vectors include Plasmids A, C, D and E, described elsewhere herein.

Expression can be in any cell expression system known to one of skill in the art. Exemplary cells for expression include, but are not limited to, 293FS cells, HEK293-6E cells or CHO cells. Other expression vectors and host cells are described below.

Hence, antibodies provided herein can be generated or expressed as full-length antibodies or as antibodies that are less than full length, including, but not limited to Fabs, Fab hinge fragment, scFv fragment, scFv tandem fragment and scFv hinge and scFv hinge(ΔE) fragments. Various techniques have been developed for the production of antibody fragments. Traditionally, these fragments were derived via proteolytic digestion of intact antibodies (see e.g. Morimoto et al. (1992) *Journal of Biochemical and Biophysical Methods*, 24:107-117; Brennance et al. (1985) *Science*, 229:81). Fragments also can be produced directly by recombinant host cells. Fab, Fv and scFv antibody fragments can all be expressed in and secreted from host cells, such as *E. coli*, thus allowing the facile production of large amounts of these fragments. Also, Fab'-SH fragments can be chemically coupled to form $F(ab')_2$ fragments (Carter et al. (1992) *Bio/Technology*, 10:163-167). According to another approach, $F(ab')_2$ fragments can be isolated directly from recombinant host cell culture. In other examples, the antibody of choice is a single chain Fv fragment (scFv) (see e.g. WO93/16185; US Patent No. 5,571,894 and U.S. Patent No. 5,587,458. Fv and sFv are the only species with intact combining sites that are devoid of constant regions; thus, they are suitable for reduced nonspecific binding during in vivo use. sFv fusion proteins can be constructed to yield fusion of an effector protein at either the amino or the carboxy terminius of an sFv. The antibody fragment can also be a llinear antibody (see e.g. U.S. Patent No. 5,641,870). Such linear antibody fragments can be monospecific or bispecific. Other techniques for the production of antibody fragments are known to one of skill in the art.

For example, upon expression, antibody heavy and light chains pair by disulfide bond to form a full-length antibody or fragments thereof. For example, for expression of a full-length Ig, sequences encoding the V_H-C_H1-hinge-C_H2- C_H3 can be cloned into a first expression vector and sequences encoding the V_L-C_L domains can be cloned into a second expression vector. Upon co-expression with the second expression vector encoding the V_L-C_L domains, a full-length antibody is expressed. In another example, to generate a Fab, sequences encoding the V_H-C_H1 can be cloned into a first expression vector and sequences encoding the V_L-C_L domains can be cloned into a second expression vector. The heavy chain pairs with a light chain and a Fab monomer is generated. In this example, exemplary vectors include Plasmids A,

C, D and E as described elsewhere herein. Sequences of C_H1, hinge, C_H2 and/or C_H3 of various IgG sub-types are known to one of skill in the art (see e.g. U.S. Published Application No. 20080248028; see also SEQ ID NO: 891). Similarly, sequences of CL, lambda or kappa, also is known (see e.g. U.S. Published Application No. 20080248028; see also SEQ ID NOS: 892-893).

1. Vectors

Provided herein are vectors that contain nucleic acid encoding the recombined antibodies or portions thereof. The nucleic acids encoding antibody polypeptides are typically cloned into a intermediate vector before transformation into prokaryotic or eukaryotic cells. Choice of vector can depend on the desired application. For example, after insertion of the nucleic acid, the vectors typically are used to transform host cells, for example, to amplify the recombined antibody genes for replication and/or expression thereof. In such examples, a vector suitable for high level expression is used. In other cases, a vector is chosen that is compatible with display of the expressed polypeptide on the surface of the cell.

Many expression vectors are available and known to those of skill in the art for the expression of recombined antibodies or portions thereof. The choice of an expression vector is influenced by the choice of host expression system. Such selection is well within the level of skill of the skilled artisan. In general, expression vectors can include transcriptional promoters and optionally enhancers, translational signals, and transcriptional and translational termination signals. Expression vectors that are used for stable transformation typically have a selectable marker which allows selection and maintenance of the transformed cells. In some cases, an origin of replication can be used to amplify the copy number of the vectors in the cells. Vectors also generally can contain additional nucleotide sequences operably linked to the ligated nucleic acid molecule (e.g. His tag, Flag tag). For purposes herein, vectors generally include sequences encoding the constant region. Thus, recombined antibodies or portions thereof also can be expressed as protein fusions. For example, a fusion can be generated to add additional functionality to a polypeptide. Examples of fusion proteins include, but are not limited to, fusions of a signal sequence, an epitope tag such as for localization, e.g. a his_6 tag or a myc tag, or a tag for

purification, for example, a GST fusion, and a sequence for directing protein secretion and/or membrane association.

For example, expression of the proteins can be controlled by any promoter/enhancer known in the art. Suitable bacterial promoters are well known in the art and described herein below. Other suitable promoters for mammalian cells, yeast cells and insect cells are well known in the art and some are exemplified below. Selection of the promoter used to direct expression of a heterologous nucleic acid depends on the particular application. Promoters which can be used include but are not limited to eukaryotic expression vectors containing the SV40 early promoter (Bernoist and Chambon, *Nature 290*:304-310 (1981)), the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto *et al. Cell 22*:787-797 (1980)), the herpes thymidine kinase promoter (Wagner *et al.*, *Proc. Natl. Acad. Sci. USA 78*:1441-1445 (1981)), the regulatory sequences of the metallothionein gene (Brinster *et al.*, *Nature 296*:39-42 (1982)); prokaryotic expression vectors such as the β-lactamase promoter (Jay *et al.*, (1981) *Proc. Natl. Acad. Sci. USA 78*:5543) or the *tac* promoter (DeBoer *et al.*, *Proc. Natl. Acad. Sci. USA 80*:21-25 (1983)); see also "Useful Proteins from Recombinant Bacteria": in Scientific American *242*:79-94 (1980)); plant expression vectors containing the nopaline synthetase promoter (Herrara-Estrella *et al.*, *Nature 303*:209-213 (1984)) or the cauliflower mosaic virus 35S RNA promoter (Gardner *et al.*, *Nucleic Acids Res. 9*:2871 (1981)), and the promoter of the photosynthetic enzyme ribulose bisphosphate carboxylase (Herrera-Estrella *et al.*, *Nature 310*:115-120 (1984)); promoter elements from yeast and other fungi such as the Gal4 promoter, the alcohol dehydrogenase promoter, the phosphoglycerol kinase promoter, the alkaline phosphatase promoter, and the following animal transcriptional control regions that exhibit tissue specificity and have been used in transgenic animals: elastase I gene control region which is active in pancreatic acinar cells (Swift *et al.*, *Cell 38*:639-646 (1984); Ornitz *et al.*, *Cold Spring Harbor Symp. Quant. Biol. 50*:399-409 (1986); MacDonald, *Hepatology 7*:425-515 (1987)); insulin gene control region which is active in pancreatic beta cells (Hanahan *et al.*, *Nature 315*:115-122 (1985)), immunoglobulin gene control region which is active in lymphoid cells (Grosschedl *et al.*, *Cell 38*:647-658 (1984); Adams *et al.*, *Nature 318*:533-538 (1985); Alexander *et al.*, *Mol. Cell Biol. 7*:1436-1444 (1987)),

mouse mammary tumor virus control region which is active in testicular, breast, lymphoid and mast cells (Leder *et al.*, *Cell 45*:485-495 (1986)), albumin gene control region which is active in liver (Pinckert *et al.*, *Genes and Devel. 1*:268-276 (1987)), alpha-fetoprotein gene control region which is active in liver (Krumlauf *et al.*, *Mol. Cell. Biol. 5*:1639-1648 (1985); Hammer *et al.*, *Science 235*:53-58 1987)), alpha-1 antitrypsin gene control region which is active in liver (Kelsey *et al.*, *Genes and Devel. 1*:161-171 (1987)), beta globin gene control region which is active in myeloid cells (Magram *et al.*, *Nature 315*:338-340 (1985); Kollias *et al.*, *Cell 46*:89-94 (1986)), myelin basic protein gene control region which is active in oligodendrocyte cells of the brain (Readhead *et al.*, *Cell 48*:703-712 (1987)), myosin light chain-2 gene control region which is active in skeletal muscle (Shani, *Nature 314*:283-286 (1985)), and gonadotrophic releasing hormone gene control region which is active in gonadotrophs of the hypothalamus (Mason *et al.*, *Science 234*:1372-1378 (1986)).

In addition to the promoter, the expression vector typically contains a transcription unit or expression cassette that contains all the additional elements required for the expression of the antibody, or portion thereof, in host cells. A typical expression cassette contains a promoter operably linked to the nucleic acid sequence encoding the germline antibody chain and signals required for efficient polyadenylation of the transcript, ribosome binding sites and translation termination. Additional elements of the cassette can include enhancers. In addition, the cassette typically contains a transcription termination region downstream of the structural gene to provide for efficient termination. The termination region can be obtained from the same gene as the promoter sequence or can be obtained from different genes.

Some expression systems have markers that provide gene amplification such as thymidine kinase and dihydrofolate reductase. Alternatively, high yield expression systems not involving gene amplification are also suitable, such as using a baculovirus vector in insect cells, with a nucleic acid sequence encoding a germline antibody chain under the direction of the polyhedron promoter or other strong baculovirus promoter.

For purposes herein, vectors are provided that contain a sequence of nucleotides that encodes a constant region of an antibody operably linked to the nucleic acid sequence encoding the recombined variable region of the antibody. The

vector can include the sequence for one or all of a CH1, CH2, hinge, CH3 or CH4 and/or CL. Generally, such as for expression of Fabs, the vector contains the sequence for a CH1 (amino acids 1-103 of SEQ ID NO:891) or CL (for kappa light chains, see SEQ ID NO:892; for lambda light chains, see SEQ ID NO:893). The sequences of constant regions or hinge regions are known to one of skill in the art (see e.g. U.S. Published Application No. 20080248028 and SEQ ID NOS:891-893, including CH1 (amino acids 1-103 of SEQ ID NO:891), IgG1 hinge region (amino acids 104-119 of SEQ ID NO:891), IgG1 CH2 (amino acids 120-223 of SEQ ID NO:891), IgG1 CH3 (amino acids 224-330 of SEQ ID NO:891), CL kappa (SEQ ID NO:892) and CL lambda (SEQ ID NO:893). Exemplary of such vectors containing a heavy chain constant region gene (e.g. CH1) are plasmids A and D, described herein. Exemplary of such vectors containing a light chain constant region genes are plasmids C and E, described herein.

Exemplary expression vectors include any mammalian expression vector such as, for example, pCMV. For bacterial expression, such vectors include pBR322, pUC, pSKF, pET23D, and fusion vectors such as MBP, GST and LacZ. Exemplary of such a vector are bacterial expression vectors such as, for example, plasmid A, plasmid C, plasmid D and plasmid E, described herein. Other eukaryotic vectors, for example any containing regulatory elements from eukaryotic viruses can be used as eukaryotic expression vectors. These include, for example, SV40 vectors, papilloma virus vectors, and vectors derived from Epstein-Bar virus. Other exemplary eukaryotic vectors include pMSG, pAV009/A+, pMT010/A+, pMAMneo-5, baculovirus pDSCE, and any other vector allowing expression of proteins under the direction of the CMV promoter, SV40 early promoter, SV40 late promoter, metallothionein promoter, murine mammary tumor virus promoter, Rous sarcoma virus promoter, polyhedron promoter, or other promoters shown effective for expression in eukaryotes.

Exemplary plasmid vectors for transformation of *E. coli* cells, include, for example, the ColE1 replication vectors described herein. Several features common to all these vectors include (a) a pBAD inducible promoter; (b) an AraC gene, which controls the pBAD promoter; (c) a synthetic ribosomal binding site (RBS) for efficient translation; (d) a ColE1 origin of replication, allowing for high copy

expression; (e) a STII leader sequence, allowing for expressed proteins to be translocated to the periplasm; (f) a f1 origin of replication; and (g) a gene for conferring antibiotic resistance. Such plasmids include plasmid A (SEQ ID NO:84), plasmid C (SEQ ID NO:86), plasmid D (SEQ ID NO:85) and plasmid E (SEQ ID NO:87). Plasmid A and Plasmid D are utilized for expression of heavy chain antibody genes in as they contain a gene for the heavy chain constant region (CH1) operably linked to the inserted gene for the heavy chain variable region. The vectors contain NheI and NcoI restriction sites to allow for cloning of the recombined antibody genes described herein. Both vectors contain a pUC origin of replication, a ColE1 type origin of replication, and an aminoglycoside phosphotransferase gene conferring kanamycin resistance. Plasmid A contains a $(His)_6$ Tag and a Flag Tag for protein purification. Plasmid D contains both a $(His)_6$ Tag and a Flag Tag, and an additional LPETG tag, which allows for covalent attachment of the resulting protein using a sortase. Plasmid C and Plasmid E are utilized for expression of light chain antibody genes in as they contain a gene for the light chain constant region (CL) operably linked to the inserted gene for the light chain variable region. Plasmid C is specific for kappa light chains and contains BseWI and NcoI restriction sites to allow for cloning of the recombined antibody genes described herein. Plasmid E is specific for lambda light chains and contains AcrII and NcoI restriction sites to allow for cloning of the recombined antibody genes described herein. Both vectors contain a 3.3 origin of replication, a ColE1 type origin of replication, and a gene conferring chloramphenicol resistance. The vectors described above are designed to be utilized in a dual vector system, in which a light chain vector and a heavy chain vector are co-transformed. Thus, they contain two different but compatible ColE1 origins of replication utilized, one for heavy chains and one light chain. This allows for efficient expression of both chains of the antibody when the vectors are co-transformed and expressed.

Any methods known to those of skill in the art for the insertion of DNA fragments into a vector can be used to construct expression vectors containing a nucleic acid encoding an antibody chain. These methods can include *in vitro* recombinant DNA and synthetic techniques and *in vivo* recombinants (genetic recombination). The insertion into a cloning vector can, for example, be

accomplished by ligating the DNA fragment into a cloning vector which has complementary cohesive termini. If the complementary restriction sites used to fragment the DNA are not present in the cloning vector, the ends of the DNA molecules can be enzymatically modified. Alternatively, any site desired can be produced by ligating nucleotide sequences (linkers) onto the DNA termini; these ligated linkers can contain specific chemically synthesized nucleic acids encoding restriction endonuclease recognition sequences.

2. Cells and Expression Systems

Cells containing the vectors also are provided. Generally, any cell type that can be engineered to express heterologous DNA and has a secretory pathway is suitable. Expression hosts include prokaryotic and eukaryotic organisms such as bacterial cells (e.g. *E. coli*), yeast cells, fungal cells, Archea, plant cells, insect cells and animal cells including human cells. Expression hosts can differ in their protein production levels as well as the types of post-translational modifications that are present on the expressed proteins. Further, the choice of expression host is often related to the choice of vector and transcription and translation elements used. For example, the choice of expression host is often, but not always, dependent on the choice of precursor sequence utilized. For example, many heterologous signal sequences can only be expressed in a host cell of the same species (i.e., an insect cell signal sequence is optimally expressed in an insect cell). In contrast, other signal sequences can be used in heterologous hosts such as, for example, the human serum albumin (hHSA) signal sequence which works well in yeast, insect, or mammalian host cells and the tissue plasminogen activator pre/pro sequence which has been demonstrated to be functional in insect and mammalian cells (Tan *et al.*, (2002) *Protein Eng.* 15:337). The choice of expression host can be made based on these and other factors, such as regulatory and safety considerations, production costs and the need and methods for purification. Thus, the vector system must be compatible with the host cell used.

Expression in eukaryotic hosts can include expression in yeasts such as *Saccharomyces cerevisiae* and *Pichia pastoris*, insect cells such as *Drosophila* cells and *lepidopteran* cells, plants and plant cells such as tobacco, corn, rice, algae, and lemna. Eukaryotic cells for expression also include mammalian cells lines such as

Chinese hamster ovary (CHO) cells or baby hamster kidney (BHK) cells. Eukaryotic expression hosts also include production in transgenic animals, for example, including production in serum, milk and eggs.

Recombinant molecules can be introduced into host cells via, for example, transformation, transfection, infection, electroporation and sonoporation, so that many copies of the gene sequence are generated. Generally, standard transfection methods are used to produce bacterial, mammalian, yeast, or insect cell lines that express large quantity of antibody chains, which is then purified using standard techniques (see e.g., Colley *et al.* (1989) *J. Biol. Chem.*, 264:17619-17622; Guide to Protein Purification, in Methods in Enzymology, vol. 182 (Deutscher, ed.), 1990). Transformation of eukaryotic and prokaryotic cells are performed according to standard techniques (see, e.g., Morrison (1977) *J. Bact.* 132:349-351; Clark-Curtiss and Curtiss (1983) *Methods in Enzymology,* 101, 347-362). For example, any of the well-known procedures for introducing foreign nucleotide sequences into host cells can be used. These include the use of calcium phosphate transfection, polybrene, protoplast fusion, electroporation, biolistics, liposomes, microinjection, plasma vectors, viral vectors and any other the other well known methods for introducing cloned genomic DNA, cDNA, synthetic DNA or other foreign genetic material into a host cell. Generally, for purposes herein, host cells are transfected with a first vector encoding at least a VH chain and a second vector encoding at least a VL chain. Thus, it is only necessary that the particular genetic engineering procedure used be capable of successfully introducing at least both genes into the host cell capable of expressing germline, or modified form thereof, antibody polypeptide.

Transformation of host cells with recombinant DNA molecules that incorporate the isolated recombined variable region gene, cDNA, or synthesized DNA sequence enables generation of multiple copies of the gene. Thus, the gene can be obtained in large quantities by growing transformants, isolating the recombinant DNA molecules from the transformants and, when necessary, retrieving the inserted gene from the isolated recombinant DNA. Generally, After the expression vector is introduced into the cells, the transfected cells are cultured under conditions favoring expression of the germline chain, which is recovered from the culture using standard purification techniques identified below.

Antibodies and portions thereof can be produced using a high throughput approach by any methods known in the art for protein production including *in vitro* and *in vivo* methods such as, for example, the introduction of nucleic acid molecules encoding recombined antibodies or portions thereof into a host cell or host animal and expression from nucleic acid molecules encoding recombined antibodies *in vitro*. Prokaryotes, especially *E. coli*, provide a system for producing large amounts of recombined antibodies or portions thereof, and are particularly desired in applications of high-throughput expression and purification of proteins. Transformation of *E. coli* is a simple and rapid technique well known to those of skill in the art. *E. coli* host strains for high throughput expression include, but are not limited to, BL21 (EMD Biosciences) and LMG194 (ATCC). Exemplary of such an *E. coli* host strain is BL21. Vectors for high throughput expression include, but are not limited to, pBR322 and pUC vectors. Exemplary of such vectors are the vectors described herein, including plasmid A, plasmid C, plasmid D and plasmid E. Automation of expression and purification can facilitate high-throughput expression. For example, use of a Piccolo™ system , a fully automatic system that combines cell culture with automated harvesting, lysing and purification units, or other similar robotic system can be employed.

a. Prokaryotic Expression

Prokaryotes, especially *E. coli*, provide a system for producing large amounts of recombined antibodies or portions thereof. Transformation of *E. coli* is a simple and rapid technique well known to those of skill in the art. Expression vectors for *E. coli* can contain inducible promoters that are useful for inducing high levels of protein expression and for expressing proteins that exhibit some toxicity to the host cells. Examples of inducible promoters include the lac promoter, the trp promoter, the hybrid tac promoter, the T7 and SP6 RNA promoters and the temperature regulated λP_L promoter.

Recombined antibodies or portions thereof can be expressed in the cytoplasmic environment of *E. coli*. The cytoplasm is a reducing environment and for some molecules, this can result in the formation of insoluble inclusion bodies. Reducing agents such as dithiothreitol and β-mercaptoethanol and denaturants (e.g., such as guanidine-HCl and urea) can be used to resolubilize the proteins. An

exemplary alternative approach is the expression of recombined antibodies or fragments thereof in the periplasmic space of bacteria which provides an oxidizing environment and chaperonin-like and disulfide isomerases leading to the production of soluble protein. Typically, a leader sequence is fused to the protein to be expressed which directs the protein to the periplasm. The leader is then removed by signal peptidases inside the periplasm. There are three major pathways to translocate expressed proteins into the periplasm, namely the Sec pathway, the SRP pathway and the TAT pathway. Examples of periplasmic-targeting leader sequences include the pelB leader from the pectate lyase gene, the StII leader sequence, and the DsbA leader sequence. An exemplary leader sequence is a DsbA leader sequence. In some cases, periplasmic expression allows leakage of the expressed protein into the culture medium. The secretion of proteins allows quick and simple purification from the culture supernatant. Proteins that are not secreted can be obtained from the periplasm by osmotic lysis. Similar to cytoplasmic expression, in some cases proteins can become insoluble and denaturants and reducing agents can be used to facilitate solubilization and refolding. Temperature of induction and growth also can influence expression levels and solubility. Typically, temperatures between 25 °C and 37 °C are used. Mutations also can be used to increase solubility of expressed proteins. Typically, bacteria produce aglycosylated proteins. Thus, if proteins require glycosylation for function, glycosylation can be added *in vitro* after purification from host cells.

b. Yeast

Yeasts such as *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, *Yarrowia lipolytica*, *Kluyveromyces lactis,* and *Pichia pastoris* are useful expression hosts for recombined antibodies or portions thereof. Yeast can be transformed with episomal replicating vectors or by stable chromosomal integration by homologous recombination. Typically, inducible promoters are used to regulate gene expression. Examples of such promoters include AOX1, GAL1, GAL7, and GAL5 and metallothionein promoters such as CUP1. Expression vectors often include a selectable marker such as LEU2, TRP1, HIS3, and URA3 for selection and maintenance of the transformed DNA. Proteins expressed in yeast are often soluble. Co-expression with chaperonins such as Bip and protein disulfide isomerase can

improve expression levels and solubility. Additionally, proteins expressed in yeast can be directed for secretion using secretion signal peptide fusions such as the yeast mating type alpha-factor secretion signal from Saccharomyces cerevisae and fusions with yeast cell surface proteins such as the Aga2p mating adhesion receptor or the *Arxula adeninivorans* glucoamylase. A protease cleavage site such as for the Kex-2 protease, can be engineered to remove the fused sequences from the expressed polypeptides as they exit the secretion pathway. Yeast also is capable of glycosylation at Asn-X-Ser/Thr motifs.

c. Insects

Insect cells, particularly using baculovirus expression, are useful for expressing antibodies or portions thereof. Insect cells express high levels of protein and are capable of most of the post-translational modifications used by higher eukaryotes. Baculovirus have a restrictive host range which improves the safety and reduces regulatory concerns of eukaryotic expression. Typical expression vectors use a promoter for high level expression such as the polyhedrin promoter and p10 promoter of baculovirus. Commonly used baculovirus systems include the baculoviruses such as *Autographa californica* nuclear polyhedrosis virus (AcNPV), and the *Bombyx mori* nuclear polyhedrosis virus (BmNPV) and an insect cell line such as Sf9 derived from *Spodoptera frugiperda* and TN derived from *Trichoplusia ni*. For high-level expression, the nucleotide sequence of the molecule to be expressed is fused immediately downstream of the polyhedrin initiation codon of the virus. To generate baculovirus recombinants capable of expressing human antibodies, a dual-expression transfer, such as pAcUW51 (PharMingen) is utilized. Mammalian secretion signals are accurately processed in insect cells and can be used to secrete the expressed protein into the culture medium

An alternative expression system in insect cells is the use of stably transformed cells. Cell lines such as Sf9 derived cells from *Spodoptera frugiperda* and TN derived cells from *Trichoplusia ni* can be used for expression. The baculovirus immediate early gene promoter IE1 can be used to induce consistent levels of expression. Typical expression vectors include the pIE1-3 and pI31-4 transfer vectors (Novagen). Expression vectors are typically maintained by the use of selectable markers such as neomycin and hygromycin.

d. Mammalian Cells

Mammalian expression systems can be used to express antibodies or portions thereof. Expression constructs can be transferred to mammalian cells by viral infection such as adenovirus or by direct DNA transfer such as liposomes, calcium phosphate, DEAE-dextran and by physical means such as electroporation and microinjection. Expression vectors for mammalian cells typically include an mRNA cap site, a TATA box, a translational initiation sequence (Kozak consensus sequence) and polyadenylation elements. Such vectors often include transcriptional promoter-enhancers for high-level expression, for example the SV40 promoter-enhancer, the human cytomegalovirus (CMV) promoter and the long terminal repeat of Rous sarcoma virus (RSV). These promoter-enhancers are active in many cell types. Tissue and cell-type promoters and enhancer regions also can be used for expression. Exemplary promoter/enhancer regions include, but are not limited to, those from genes such as elastase I, insulin, immunoglobulin, mouse mammary tumor virus, albumin, alpha fetoprotein, alpha 1 antitrypsin, beta globin, myelin basic protein, myosin light chain 2, and gonadotropic releasing hormone gene control. Selectable markers can be used to select for and maintain cells with the expression construct. Examples of selectable marker genes include, but are not limited to, hygromycin B phosphotransferase, adenosine deaminase, xanthine-guanine phosphoribosyl transferase, aminoglycoside phosphotransferase, dihydrofolate reductase and thymidine kinase. Antibodies are typically produced using a NEO^R/G418 system, a dihydrofolate reductase (DHFR) system or a glutamine synthetase (GS) system. The GS system uses joint expression vectors, such as pEE12/pEE6, to express both heavy chain and light chain. Fusion with cell surface signaling molecules such as TCR-ζ and $Fc_\varepsilon RI$-γ can direct expression of the proteins in an active state on the cell surface.

Many cell lines are available for mammalian expression including mouse, rat human, monkey, chicken and hamster cells. Exemplary cell lines include but are not limited to CHO, Balb/3T3, HeLa, MT2, mouse NS0 (nonsecreting) and other myeloma cell lines, hybridoma and heterohybridoma cell lines, lymphocytes, fibroblasts, Sp2/0, COS, NIH3T3, HEK293, 293S, 2B8, and HKB cells. Cell lines also are available adapted to serum-free media which facilitates purification of

secreted proteins from the cell culture media. One such example is the serum free EBNA-1 cell line (Pham *et al.*, (2003) *Biotechnol. Bioeng. 84*:332-42.)

e. Plants

Transgenic plant cells and plants can be used to express proteins such as any antibody or portion thereof described herein. Expression constructs are typically transferred to plants using direct DNA transfer such as microprojectile bombardment and PEG-mediated transfer into protoplasts, and with agrobacterium-mediated transformation. Expression vectors can include promoter and enhancer sequences, transcriptional termination elements and translational control elements. Expression vectors and transformation techniques are usually divided between dicot hosts, such as *Arabidopsis* and tobacco, and monocot hosts, such as corn and rice. Examples of plant promoters used for expression include the cauliflower mosaic virus CaMV 35S promoter, the nopaline synthase promoter, the ribose bisphosphate carboxylase promoter and the maize ubiquitin-1 (*ubi*-1) promoter promoters. Selectable markers such as hygromycin, phosphomannose isomerase and neomycin phosphotransferase are often used to facilitate selection and maintenance of transformed cells. Transformed plant cells can be maintained in culture as cells, aggregates (callus tissue) or regenerated into whole plants. Transgenic plant cells also can include algae engineered to produce proteases or modified proteases (see for example, Mayfield *et al.* (2003) *PNAS 100*:438-442). Because plants have different glycosylation patterns than mammalian cells, this can influence the choice of protein produced in these hosts.

3. Purification

Antibodies and portions thereof are purified by any procedure known to one of skill in the art. The recombined germline antibodies can be purified to substantial purity using standard protein purification techniques known in the art including but not limited to, SDS-PAGE, size fraction and size exclusion chromatography, ammonium sulfate precipitation, chelate chromatography, ionic exchange chromatography or column chromatography. For example, antibodies can be purified by column chromatography. Exemplary of a method to purify antibodies is by using column chromatography, wherein a solid support column material is linked to Protein G, a cell surface-associated protein from *Streptococcus*, that binds immunoglobulins

with high affinity. The antibodies can be purified to 60%, 70%, 80% purity and typically at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% purity. Purity can be assessed by standard methods such as by SDS-PAGE and coomassie staining.

Methods for purification of recombined antibodies or portions thereof from host cells depend on the chosen host cells and expression systems. For secreted molecules, proteins are generally purified from the culture media after removing the cells. For intracellular expression, cells can be lysed and the proteins purified from the extract. When transgenic organisms such as transgenic plants and animals are used for expression, tissues or organs can be used as starting material to make a lysed cell extract. Additionally, transgenic animal production can include the production of polypeptides in milk or eggs, which can be collected, and if necessary further the proteins can be extracted and further purified using standard methods in the art.

When antibodies are expressed by transformed bacteria in large amounts, typically after promoter induction, although expression can be constitutive, the polypeptides can form insoluble aggregates. There are several protocols that are suitable for purification of polypeptide inclusion bodies known to one of skill in the art. Numerous variations will be apparent to those of skill in the art.

For example, in one method, the cell suspension is generally centrifuged and the pellet containing the inclusion bodies resuspended in buffer which does not dissolve but washes the inclusion bodies, e.g., 20 mM Tris-HCL (pH 7.2), 1 mM EDTA, 150 mM NaCl and 2% Triton-X 100, a non-ionic detergent. It can be necessary to repeat the wash step to remove as much cellular debris as possible. The remaining pellet of inclusion bodies can be resuspended in an appropriate buffer (e.g., 20 mM sodium phosphate, pH 6.8, 150 mM NaCl). Other appropriate buffers are apparent to those of skill in the art.

Alternatively, antibodies can be purified from bacteria periplasm. Where the polypeptide is exported into the periplasm of the bacteria, the periplasmic fraction of the bacteria can be isolated by cold osmotic shock in addition to other methods known to those of skill in the art. For example, in one method, to isolate recombinant polypeptides from the periplasm, the bacterial cells are centrifuged to form a pellet. The pellet is resuspended in a buffer containing 20% sucrose. To lyse the cells, the

bacteria are centrifuged and the pellet is resuspended in ice-cold 5 mM $MgSO_4$ and kept in an ice bath for approximately 10 minutes. The cell suspension is centrifuged and the supernatant decanted and saved. The recombinant polypeptides present in the supernatant can be separated from the host proteins by standard separation techniques well known to those of skill in the art. These methods include, but are not limited to, the following steps: solubility fractionation, size differential filtration, and column chromatography.

H. FORMULATIONS, ADMINISTRATION AND ARTICLES OF MANUFACTURE/KITS

1. Formulations

The antibodies provided herein can be provided as a formulation for administration. While it is possible for the active ingredient to be administered alone, it generally presented as a pharmaceutical formulation. Formulations comprise at least one active ingredient, together with one or more acceptable carriers thereof. Each carrier must be both pharmaceutically and physiologically acceptable in the sense of being compatible with the other ingredients and not injurious to the patient. Formulations include those suitable for oral, rectal, nasal, or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. The formulations can conveniently be presented in unit dosage form and can be prepared by methods well known in the art of pharmacy. See, e.g., Gilman, *et al.* (eds. 1990) Goodman and Gilman's: The Pharmacological Bases of Therapeutics, 8th Ed., Pergamon Press; and Remington's Pharmaceutical Sciences, 17th ed. (1990), Mack Publishing Co., Easton, Pa.; Avis, *et al.* (eds. 1993) Pharmaceutical Dosage Forms: Parenteral Medications Dekker, NY; Lieberman, *et al.* (eds. 1990) Pharmaceutical Dosage Forms: Tablets Dekker, NY; and Lieberman, *et al.* (eds. 1990) Pharmaceutical Dosage Forms: Disperse Systems Dekker, NY.

The route of antibody administration is in accord with known methods, e.g., injection or infusion by intravenous, intraperitoneal, intracerebral, intramuscular, subcutaneous, intraocular, intraarterial, intrathecal, inhalation or intralesional routes, topical or by sustained release systems as noted below. The antibody can be administered continuously by infusion or by bolus injection. One can administer the antibodies in a local or systemic manner.

The antibodies provided herein can be prepared in a mixture with a pharmaceutically acceptable carrier. Techniques for formulation and administration of the compounds of the instant application can be found in "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, Pa., latest edition. This therapeutic composition can be administered intravenously or through the nose or lung, for example as a liquid or powder aerosol (lyophilized). The composition also can be administered parenterally or subcutaneously as desired. When administered systematically, the therapeutic composition generally is sterile, pyrogen-free and in a parenterally acceptable solution having due regard for pH, isotonicity, and stability. These conditions are known to those skilled in the art.

Therapeutic formulations can be administered in many conventional dosage formulations. Briefly, dosage formulations of the antibodies provided herein are prepared for storage or administration by mixing the compound having the desired degree of purity with physiologically acceptable carriers, excipients, or stabilizers. Such materials are non-toxic to the recipients at the dosages and concentrations employed, and can include buffers such as TRIS HCl, phosphate, citrate, acetate and other organic acid salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) peptides such as polyarginine, proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidinone; amino acids such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, mannose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium and/or nonionic surfactants such as TWEEN, PLURONICS or polyethyleneglycol.

When used for in vivo administration, the antibody formulation must be sterile and can be formulated according to conventional pharmaceutical practice. This is readily accomplished by filtration through sterile filtration membranes, prior to or following lyophilization and reconstitution. The antibody ordinarily will be stored in lyophilized form or in solution. Other vehicles such as naturally occurring vegetable oil like sesame, peanut, or cottonseed oil or a synthetic fatty vehicle like ethyl oleate or the like can be desired. Buffers, preservatives, antioxidants and the like can be incorporated according to accepted pharmaceutical practice.

Pharmaceutical compositions suitable for use include compositions wherein one or more rationally designed antibodies are contained in an amount effective to achieve their intended purpose. Determination of a therapeutically effective amount is well within the capability of those skilled in the art. Therapeutically effective dosages can be determined by using in vitro and in vivo methods.

An effective amount of antibody to be employed therapeutically will depend, for example, upon the therapeutic objectives, the route of administration, and the condition of the patient. For example, antibodies provided herein include agonist and antagonist antibodies. In addition, the attending physician takes into consideration various factors known to modify the action of drugs including severity and type of disease, body weight, sex, diet, time and route of administration, other medications and other relevant clinical factors. Accordingly, it will be necessary for the therapist to titer the dosage and modify the route of administration as required to obtain the optimal therapeutic effect. Typically, the clinician will administer antibody until a dosage is reached that achieves the desired effect. The progress of this therapy is easily monitored by conventional assays.

For any antibody containing a peptide, the therapeutically effective dose can be estimated initially from cell culture assays. For example, a dose can be formulated in animal models to achieve a circulating concentration range that includes the EC50 as determined in cell culture (e.g., the concentration of the test molecule which promotes or inhibits cellular proliferation or differentiation). Such information can be used to more accurately determine useful doses in humans.

Toxicity and therapeutic efficacy of the antibody molecules described herein can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD50 and ED50. Molecules which exhibit high therapeutic indices can be used. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage of such molecules lies within a range of circulating concentrations that include the ED50 with little or no toxicity. The dosage can vary within this range

depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. (See e.g., Fingl *et al.*, 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1, p.1).

Dosage amount and interval can be adjusted individually to provide plasma levels of the antibody which are sufficient to promote or inhibit cellular proliferation or differentiation or minimal effective concentration (MEC). The MEC will vary for each antibody, but can be estimated from in vitro data using described assays. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. HPLC assays or bioassays can be used to determine plasma concentrations. Dosage intervals can also be determined using MEC value. Antibody molecules can be administered using a regimen which maintains plasma levels above the MEC for 10-90% of the time, generally between 30-90%, for example between 50-90%. In cases of local administration or selective uptake, the effective local concentration of the antibody can not be related to plasma concentration.

The antibody is suitably administered to the patient at one time or over a series of treatments. Depending on the type and severity of the disease, from about 0.001 mg/kg to abut 1000 mg/kg, for example about 0.01 mg to 100 mg/kg, such as 0.010 to 20 mg/kg of the antibody, in particular about 1 μg/kg to 15 mg/kg (e.g. 0.1 mg/kg-10 mg/kg) is an initial candidate dosage for administration to the patient, whether, for example, by one or more separate administrations, or by continuous infusion. One typical daily dosage might range from about 1 μg/kg to 1000 mg/kg or more, for example, 1 μg/kg to 100 mg/kg or more, depending on the factors mentioned above. For repeated administrations over several days or longer, depending on the condition, the treatment is sustained until a desired suppression of disease symptoms occurs. One exemplary dosage of the antibody is in the range from about 0.05 mg/kg to about 10 mg/kg. Thus, one or more doses of about 0.5 mg/kg, 2.0 mg/kg, 4.0 mg/kg or 10 mg/kg (or any combination thereof) can be administered to the patient. Such doses can be administered intermittently, e.g. every week or every three weeks (e.g. such that the patient receives from about two to about twenty, e.g. about six doses of the antibody). An initial higher loading dose, followed by one or more lower doses can be administered. An exemplary dosing regimen includes administering an initial loading

dose of about 4 mg/kg, followed by a weekly maintenance dose of about 2 mg/kg of the antibody. Other dosage regimens also can be employed. The progress of this therapy is readily monitored by conventional techniques and assays. Typically, the clinician administers the molecule until a dosage is reached that achieves the desired effect.

2. Articles of Manufacture and Kits

Pharmaceutical compounds of selected antibodies or nucleic acids encoding selected antibodies, or a derivative or a biologically active portion thereof can be packaged as articles of manufacture containing packaging material, a pharmaceutical composition which is effective for treating the disease or disorder, and a label that indicates that selected antibody or nucleic acid molecule is to be used for treating the disease or disorder.

The articles of manufacture provided herein contain packaging materials. Packaging materials for use in packaging pharmaceutical products are well known to those of skill in the art. See, for example, U.S. Patent Nos. 5,323,907, 5,052,558 and 5,033,252, each of which is incorporated herein in its entirety. Examples of pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, tubes, inhalers, pumps, bags, vials, containers, syringes, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment. A wide array of formulations of the compounds and compositions provided herein are contemplated as are a variety of treatments for any EPO-mediated disease or disorder or therapeutic polypeptide-mediated disease or disorder.

Antibodies and nucleic acid molecules encoding the antibodies thereof also can be provided as kits. Kits can include a pharmaceutical composition described herein and an item for administration. For example, a selected antibody can be supplied with a device for administration, such as a syringe, an inhaler, a dosage cup, a dropper, or an applicator. The kit can, optionally, include instructions for application including dosages, dosing regimens and instructions for modes of administration. Kits also can include a pharmaceutical composition described herein and an item for diagnosis. For example, such kits can include an item for measuring the concentration, amount or activity of the antibody in a subject.

I. METHODS AND USES OF ANTIBODIES

The antibodies or portions thereof provided herein can be used in a variety of methods or uses based on the ability of the antibodies to specifically bind to DLL4. For example, antibodies provided herein that modulate an activity of DLL4 can be used for the treatment or prevention of disease states associated with expression and/or activity of DLL4. Antibodies also can be provided in combination with other therapeutic agents. Hence, combinations of anti-DLL4 antibodies and other therapeutic agents can be used in methods of treatment herein. Antibodies provided herein also can be used in detection or diagnostic methods.

1. Methods of Treatment and Uses

Provided herein are methods of treatment of uses of anti-DLL4 antibodies provided herein that specifically bind and/or modulate an activity of DLL4, such as increased expression and/or activity or undesired expression and/or activity (see e.g., U.S. Published Application Serial No. US20080175847 and International Published PCT Appl. No. WO2008060705, WO2008091222). Treatment includes neoplastic and non-neoplastic disorders. For example, the antibodies or portions thereof can be used to treat a tumor, a cancer (e.g. colon cancer, lung cancer or breast cancer) and/or a cell proliferative disorder and/or conditions associated with angiogenesis (e.g. intraocular neovascular disease). In particular, the antibodies or portions thereof can be used in combination with anti-VEGF therapies and/or in treatments that are resistant to anti-VEGF treatment.

Angiogenesis is implicated in the pathogenesis of a variety of disorders. These include solid tumors and metastasis, atherosclerosis, retrolental fibroplasia, hemangiomas, chronic inflammation, intraocular neovascular diseases such as proliferative retinopathies, e.g., diabetic retinopathy, age-related macular degeneration (AMD), neovascular glaucoma, immune rejection of transplanted corneal tissue and other tissues, rheumatoid arthritis, and psoriasis. Folkman et al., *J. Biol. Chem.* 267:10931-34 (1992); Klagsbrun et al., *Annu. Rev. Physiol.* 53:217-39 (1991); and Garner A., "Vascular diseases," In: Pathobiology of Ocular Disease. A Dynamic Approach, Garner A., Klintworth G K, eds., 2nd Edition (Marcel Dekker, NY, 1994), pp 1625-1710.

In the case of tumor growth, angiogenesis appears to be crucial for the transition from hyperplasia to neoplasia, and for providing nourishment for the growth and metastasis of the tumor. Folkman et al., *Nature* 339:58 (1989). The neovascularization allows the tumor cells to acquire a growth advantage and proliferative autonomy compared to the normal cells. A tumor usually begins as a single aberrant cell which can proliferate only to a size of a few cubic millimeters due to the distance from available capillary beds, and it can stay 'dormant' without further growth and dissemination for a long period of time. Some tumor cells then switch to the angiogenic phenotype to activate endothelial cells, which proliferate and mature into new capillary blood vessels. These newly formed blood vessels not only allow for continued growth of the primary tumor, but also for the dissemination and recolonization of metastatic tumor cells. Accordingly, a correlation has been observed between density of microvessels in tumor sections and patient survival in breast cancer as well as in several other tumors. Weidner et al., *N. Engl. J. Med.* 324:1-6 (1991); Horak et al., *Lancet* 340:1120-24 (1992); Macchiarini et al., *Lancet* 340:145-46 (1992). The precise mechanisms that control the angiogenic switch is not well understood, but it is believed that neovascularization of tumor mass results from the net balance of a multitude of angiogenesis stimulators and inhibitors (Folkman, *Nat. Med.* 1(1):27-31 (1995)).

In addition, antibodies or portions thereof can be used to treat non-neoplastic disorders including, but not limited to, undesired or aberrant hypertrophy, arthritis, rheumatoid arthritis (RA), psoriasis, psoriatic plaques, sarcoidosis, atherosclerosis, atherosclerotic plaques, edema from myocardial infarction, diabetic and other proliferative retinopathies including retinopathy of prematurity, retrolental fibroplasia, neovascular glaucoma, age-related macular degeneration, diabetic macular edema, corneal neovascularization, corneal graft neovascularization, corneal graft rejection, retinal/choroidal neovascularization, neovascularization of the angle (rubeosis), ocular neovascular disease, vascular restenosis, arteriovenous malformations (AVM), meningioma, hemangioma, angiofibroma, thyroid hyperplasias (including Grave's disease), corneal and other tissue transplantation, chronic inflammation, lung inflammation, acute lung injury/ARDS, sepsis, primary pulmonary hypertension, malignant pulmonary effusions, cerebral edema (e.g., associated with acute

stroke/closed head injury/trauma), synovial inflammation, pannus formation in RA, myositis ossificans, hypertropic bone formation, osteoarthritis (OA), refractory ascites, polycystic ovarian disease, endometriosis, 3rd spacing of fluid diseases (pancreatitis, compartment syndrome, burns, bowel disease), uterine fibroids, premature labor, chronic inflammation such as IBD (Crohn's disease and ulcerative colitis), renal allograft rejection, inflammatory bowel disease, nephrotic syndrome, undesired or aberrant tissue mass growth (non-cancer), obesity, adipose tissue mass growth, hemophilic joints, hypertrophic scars, inhibition of hair growth, Osier-Weber syndrome, pyogenic granuloma retrolental fibroplasias, scleroderma, trachoma, vascular adhesions, synovitis, dermatitis, preeclampsia, ascites, pericardial effusion (such as that associated with pericarditis), and pleural effusion.

Combination Therapy

As indicated above, anti-DLL4 antibodies provided herein can be administered in combined therapies in which an anti-DLL4 antibody is administered with another therapy. US2009For example, anti-DLL4 antibodies are used in combinations with anti-cancer therapeutics or anti-neovascularization therapeutics to treat various neoplastic or non-neoplastic conditions. In one embodiment, the neoplastic or non-neoplastic condition is characterized by pathological disorder associated with aberrant or undesired angiogenesis. Exemplary combination therapies also include any set forth in U.S. Published application No. 20090246199. The anti-DLL4 antibody can be administered serially or in combination with another agent that is effective for those purposes, either in the same composition or as separate compositions. The anti-DLL4 antibodies can be administered sequentially, simultaneously or intermittently with a therapeutic agent. Alternatively, or additionally, multiple inhibitors of DLL4 can be administered.

The administration of the anti-DLL4 antibody can be done simultaneously, e.g., as a single composition or as two or more distinct compositions using the same or different administration routes. Alternatively, or additionally, the administration can be done sequentially, in any order. In certain embodiments, intervals ranging from minutes to days, to weeks to months, can be present between the administrations of the two or more compositions. For example, the anti-cancer agent can be administered

first, followed by the DLL4 inhibitor. Simultaneous administration or administration of the anti-DLL4 antibody first also is contemplated.

The effective amounts of therapeutic agents administered in combination with an anti-DLL4 antibody will be at the physician's or veterinarian's discretion. Dosage administration and adjustment is done to achieve maximal management of the conditions to be treated. The dose will additionally depend on such factors as the type of therapeutic agent to be used and the specific patient being treated. Suitable dosages for the anti-cancer agent are those presently used and can be lowered due to the combined action (synergy) of the anti-cancer agent and the anti-DLL4 antibody. In certain embodiments, the combination of the inhibitors potentiates the efficacy of a single inhibitor.

Typically, the anti-DLL4 antibodies and anti-cancer agents are suitable for the same or similar diseases to block or reduce a pathological disorder such as tumor growth or growth of a cancer cell. In one embodiment the anti-cancer agent is an anti-angiogenesis agent. Antiangiogenic therapy in relationship to cancer is a cancer treatment strategy aimed at inhibiting the development of tumor blood vessels required for providing nutrients to support tumor growth. Because angiogenesis is involved in both primary tumor growth and metastasis, the antiangiogenic treatment is generally capable of inhibiting the neoplastic growth of tumor at the primary site as well as preventing metastasis of tumors at the secondary sites, therefore allowing attack of the tumors by other therapeutics.

Many anti-angiogenic agents have been identified and are known in the arts, including those listed herein, e.g., listed under Definitions, and by, e.g., Carmeliet and Jain, *Nature* 407:249-257 (2000); Ferrara et al., *Nature Reviews. Drug Discovery,* 3:391-400 (2004); and Sato *Int. J. Clin. Oncol.*, 8:200-206 (2003). See also, US Patent Application US20030055006. In one embodiment, an anti-DLL4 antibody is used in combination with an anti-VEGF neutralizing antibody (or fragment) and/or another VEGF antagonist or a VEGF receptor antagonist including, but not limited to, for example, soluble VEGF receptor (e.g., VEGFR-1, VEGFR-2, VEGFR-3, neuropillins (e.g., NRP1, NRP2)) fragments, aptamers capable of blocking VEGF or VEGFR, neutralizing anti-VEGFR antibodies, low molecule weight inhibitors of VEGFR tyrosine kinases (RTK), antisense strategies for VEGF, ribozymes against VEGF or

VEGF receptors, antagonist variants of VEGF; and any combinations thereof. Alternatively, or additionally, two or more angiogenesis inhibitors can optionally be co-administered to the patient in addition to VEGF antagonist and other agent. In certain embodiment, one or more additional therapeutic agents, e.g., anti-cancer agents, can be administered in combination with anti-DLL4 antibody, the VEGF antagonist, and an anti-angiogenesis agent.

In certain aspects, other therapeutic agents useful for combination tumor therapy with a anti-DLL4 antibody include other cancer therapies, (e.g., surgery, radiological treatments (e.g., involving irradiation or administration of radioactive substances), chemotherapy, treatment with anti-cancer agents listed herein and known in the art, or combinations thereof). Alternatively, or additionally, two or more antibodies binding the same or two or more different antigens disclosed herein can be co-administered to the patient. Sometimes, it can be beneficial to also administer one or more cytokines to the patient.

For example, a method of blocking or reducing tumor growth or growth of a cancer cell, includes administering effective amounts of an antagonist of DLL4 and/or an angiogenesis inhibitor(s) and one or more chemotherapeutic agents to a patient susceptible to, or diagnosed with, cancer. A variety of chemotherapeutic agents can be used in the combined treatment methods. As will be understood by those of ordinary skill in the art, the appropriate doses of chemotherapeutic agents will be generally around those already employed in clinical therapies wherein the chemotherapeutics are administered alone or in combination with other chemotherapeutics. Variation in dosage will likely occur depending on the condition being treated. The physician administering treatment will be able to determine the appropriate dose for the individual subject.

2. Diagnosis and Detection

The anti-DLL4 antibodies provided herein are useful in assays detecting DLL4 expression (such as diagnostic or prognostic assays), for example, in specicific cells or tissues. In such exaples, antibodies can be labeled and/or immoblilized on an insoluble matrix. For example, methods of diagnosing a disorder associated with DLL4 expression and/or activity is provided herein. The methods involve detecting DLL4-anti-DLL4 antibody complex in a biological sample from a paitent having or

suspected of having the disorder. In some embodiments, the DLL4 expression is increased expression or abnormal (undesired) expression. In some embodiments, the disorder is a tumor, cancer and/or a cell proliferative disorder.

In detection methods provided herein, the anti-DLL4 antibody is labeled generally with a detectable label (e.g. biotin, rubidium, fluorescent label or other label). Anti-DLL4 antibodies can be used for the detection of DLL4 in any one of a number of well known detection assay methods. For example, a biological sample can be assayed for DLL4 by obtaining the sample from a desired source (e.g. blood or serum or cellular preoparation), admixing the sample with anti-DLL4 antibody to allow the antibody to form antibody/DLL4 complex with any DLL4 present in the mixture, and detecting any antibody/DLL4 complex present in the mixture. The biological sample can be prepared fro assay by methods known in the art that are suitable for the particular sample. The methods of admixing the sample with antibodies and the methods of detecting antibody/DLL4 complex are chosen according to the type of assay used. Such assays include immunohistochemistry, competititve and sandwich assays and seteric inhibition assays.

The label can be any detectable functionality that does nto interfere with the binding of DLL4 ant anti-DLL4 antibody. Numerous labels are known for use in immunoassay. Exemplary labels include moieties that can be detected directly, such as fluorochrome, chemiluminescent and radioactive labels, as well as moieties, such as enzymes, that must be reatcted or derivatized to be detected. Examples of usch labels include the radioisotopes ^{32}P, ^{14}C, ^{125}I, ^{3}H, and ^{131}I, flurophores such as rare earth chelates or flurescein and its derivatives, rhodamine and its derivatives, dansyl, umbelliferone, luciferases, e.g. firefly luciferase and bacterial luciferase (U.S. Patent No. 4,737,456), lucifrein, 2,3,-dihydrophthalazinediones, horseradish peroxidase (HRP), alkaline phosphatase, β-galactosidase, glucoamylase, lysozyme, saccharide oxidases, e.g. glucose oxidase, galactose oxidase, and glucose-6-phosphate dehydrogenase, heterocyclic oxidases such as uricase and xanthine oxidase, couples with an enzyme that employs hydrogen peroxide to osidize a dye precursor suc as HRP, lactoperoxidase, or microperoxidase, biotin/avidin, spin labels, bacteriophge labels and free radicals.

Conventional methods are available to bind these labels covalently to proteins or polypeptides. For instance, coupling agents such as dialdehydes, carbodiimides, dimaleimides, bis-imidates, bis-diazotized benzidine, can be used to tag the antibodies with the above-described fluorescent, chemiluminescent, and enzyme labels. See, for example, U.S. Pat. Nos. 3,940,475 (fluorimetry) and 3,645,090 (enzymes); Hunter et al., *Nature*, 144: 945 (1962); David et al., *Biochemistry*, 13: 1014-1021 (1974); Pain et al., *J. Immunol. Methods*, 40: 219-230 (1981); and Nygren, *J. Histochem. and Cytochem.*, 30: 407-412 (1982). Examples of labels are enzymes such as horseradish peroxidase and alkaline phosphatase. The conjugation of such label, including the enzymes, to the antibody is a standard manipulative procedure for one of ordinary skill in immunoassay techniques. See, for example, O'Sullivan et al., "Methods for the Preparation of Enzyme-antibody Conjugates for Use in Enzyme Immunoassay," in *Methods in Enzymology*, ed. J. J. Langone and H. Van Vunakis, Vol. 73 (Academic Press, New York, N.Y., 1981), pp. 147-166.

Immobilization of reagents is required for certain assay methods. Immobilization entails separating the anti-DLL4 antibody from any DLL4 that remains free in solution. This conventionally is accomplished by either insolubilizing the anti-DLL4 antibody or DLL4 analogue before the assay procedure, as by adsorption to a water-insoluble matrix or surface (Bennich et al., U.S. Pat. No. 3,720,760), by covalent coupling (for example, using glutaraldehyde cross-linking), or by insolubilizing the anti-DLL4 antibody or DLL4 analogue afterward, e.g., by immunoprecipitation.

The expression of proteins in a sample can be examined using immunohistochemistry and staining protocols. Immunohistochemical staining of tissue sections has been shown to be a reliable method of assessing or detecting presence of proteins in a sample. Immunohistochemistry ("IHC") techniques utilize an antibody to probe and visualize cellular antigens in situ, generally by chromogenic or fluorescent methods. For sample preparation, a tissue or cell sample from a mammal (typically a human patient) can be used. Examples of samples include, but are not limited to, cancer cells such as colon, breast, prostate, ovary, lung, stomach, pancreas, lymphoma, and leukemia cancer cells. The sample can be obtained by a variety of procedures known in the art including, but not limited to surgical excision,

aspiration or biopsy. The tissue can be fresh or frozen. In one embodiment, the sample is fixed and embedded in paraffin. The tissue sample can be fixed (i.e. preserved) by conventional methodology. One of ordinary skill in the art will appreciate that the choice of a fixative is determined by the purpose for which the sample is to be histologically stained or otherwise analyzed. One of ordinary skill in the art will also appreciate that the length of fixation depends upon the size of the tissue sample and the fixative used.

IHC can be performed in combination with additional techniques such as morphological staining and/or fluorescence in-situ hybridization. Two general methods of IHC are available; direct and indirect assays. According to the first assay, binding of antibody to the target antigen (e.g., DLL4) is determined directly. This direct assay uses a labeled reagent, such as a fluorescent tag or an enzyme-labeled primary antibody, which can be visualized without further antibody interaction. In a typical indirect assay, unconjugated primary antibody binds to the antigen and then a labeled secondary antibody binds to the primary antibody. Where the secondary antibody is conjugated to an enzymatic label, a chromogenic or fluorogenic substrate is added to provide visualization of the antigen. Signal amplification occurs because several secondary antibodies can react with different epitopes on the primary antibody. The primary and/or secondary antibody used for immunohistochemistry typically are labeled with a detectable moiety. Numerous labels are available which can be generally grouped into the following categories:

Aside from the sample preparation procedures discussed above, further treatment of the tissue section prior to, during or following IHC can be desired. For example, epitope retrieval methods, such as heating the tissue sample in citrate buffer can be carried out (see, e.g., Leong et al. *Appl. Immunohistochem.* 4(3):201 (1996)).

Following an optional blocking step, the tissue section is exposed to primary antibody for a sufficient period of time and under suitable conditions such that the primary antibody binds to the target protein antigen in the tissue sample. Appropriate conditions for achieving this can be determined by routine experimentation. The extent of binding of antibody to the sample is determined by using any one of the detectable labels discussed above. The label can be an enzymatic label (e.g. HRP) which catalyzes a chemical alteration of the chromogenic substrate such as 3,3'-

diaminobenzidine chromogen. The enzymatic label can be conjugated to antibody which binds specifically to the primary antibody (e.g. the primary antibody is rabbit polyclonal antibody and secondary antibody is goat anti-rabbit antibody). Specimens thus prepared are mounted and coverslipped.

Slide evaluation is then determined, e.g. using a microscope, and staining intensity criteria, routinely used in the art, can be employed. For exampel, a score of 2+ indicates weak to moderate staining observed in more than 10% of the cells. A score of 3+ is given where there is moderate to strong staining observed in more than 10% of the cells. Lesser scores are given for lesser staining, such as no staining (score of 0) or faint or barely perceptible staining (1+). Typically, a staining pattern score of about 2+ or higher in an IHC assay is diagnostic and/or prognostic. In some embodiments, a staining pattern score of about 1+ or higher is diagnostic and/or prognostic. In other embodiments, a staining pattern score of about 3 of higher is diagnostic and/or prognostic. It is understood that when cells and/or tissue from a tumor or colon adenoma are examined using IHC, staining is generally determined or assessed in tumor cell and/or tissue (as opposed to stromal or surrounding tissue that can be present in the sample).

Other assay methods, known as competitive or sandwich assays, are well established and widely used in the commercial diagnostics industry. For example, competitive assays rely on the ability of a tracer DLL4 analogue to compete with the test sample DLL4 for a limited number of anti-DLL4 antibody antigen-binding sites. The anti-DLL4 antibody generally is insolubilized before or after the competition and then the tracer and DLL4 bound to the anti-DLL4 antibody are separated from the unbound tracer and DLL4. This separation is accomplished by decanting (where the binding partner was preinsolubilized) or by centrifuging (where the binding partner was precipitated after the competitive reaction). The amount of test sample DLL4 is inversely proportional to the amount of bound tracer as measured by the amount of marker substance. Dose-response curves with known amounts of DLL4 are prepared and compared with the test results to quantitatively determine the amount of DLL4 present in the test sample. These assays are called ELISA systems when enzymes are used as the detectable markers.

Another example of a competitive assay, called a "homogeneous" assay, does not require a phase separation. Here, a conjugate of an enzyme with the DLL4 is prepared and used such that when anti-DLL4 antibody binds to the DLL4 the presence of the anti-DLL4 antibody modifies the enzyme activity. In this case, the DLL4 or its immunologically active fragments are conjugated with a bifunctional organic bridge to an enzyme such as peroxidase. Conjugates are selected for use with anti-DLL4 antibody so that binding of the anti-DLL4 antibody inhibits or potentiates the enzyme activity of the label. This method per se is widely practiced under the name of EMIT.

Steric conjugates are used in steric hindrance methods for homogeneous assay. These conjugates are synthesized by covalently linking a low-molecular-weight hapten to a small DLL4 fragment so that antibody to hapten is substantially unable to bind the conjugate at the same time as anti-DLL4 antibody. Under this assay procedure the DLL4 present in the test sample will bind anti-DLL4 antibody, thereby allowing anti-hapten to bind the conjugate, resulting in a change in the character of the conjugate hapten, e.g., a change in fluorescence when the hapten is a fluorophore.

Sandwich assays particularly are useful for the determination of DLL4 or anti-DLL4 antibodies. In sequential sandwich assays an immobilized anti-DLL4 antibody is used to adsorb test sample DLL4, the test sample is removed as by washing, the bound DLL4 is used to adsorb a second, labeled anti-DLL4 antibody and bound material is then separated from residual tracer. The amount of bound tracer is directly proportional to test sample DLL4. In "simultaneous" sandwich assays the test sample is not separated before adding the labeled anti-DLL4. A sequential sandwich assay using an anti-DLL4 monoclonal antibody as one antibody and a polyclonal anti-DLL4 antibody as the other is useful in testing samples for DLL4.

J. EXAMPLES

The following examples are included for illustrative purposes only and are not intended to limit the scope of the invention.

EXAMPLE 1

Cloning of Germline Fab Antibodies

In this Example, Fab antibodies were generated by cloning heavy or light chain variable region DNA into their respective plasmids.

A. Generation of Heavy and Light Chain Germline Recombined DNA Sequences

Germline-derived antibodies were generated as described in U.S. Provisional Application Serial Nos. 61/198,764 and 61/211,204, incorporated by reference herein. Briefly, V_H, D_H and J_H germline segments were compiled, in frame, to generate a nucleic acid sequence encoding a VH chain. Following compilation of germline segment sequences, restriction enzyme sites NcoI (SEQ ID NO:108) and NheI (SEQ ID NO:109) were included at the 5' and 3' end, respectively, of the nucleic acid sequence encoding the VH chain to allow for subcloning into appropriate vectors as described below. Similarly, Vκ and Jκ or V_λ and J_λ were compiled, in frame, to generate a nucleic acid sequence encoding a VL chain. Following compilation of Vκ and Jκ germline segment sequences, restriction enzyme sites for NcoI and BsiWI (SEQ ID NO:110) were included at the 5' and 3' end, respectively, of the nucleic acid sequence encoding the VL chain to allow for subcloning into appropriate vectors. Alternatively, following compilation of V_λ and J_λ germline segment sequences, restriction enzyme sites NcoI and Avr II (SEQ ID NO:111) were included at the 5' and 3' end, respectively, of the nucleic acid sequence encoding the VL chain to allow for subcloning into appropriate vectors. The compiled nucleic acid sequences were sent to a DNA synthesis vendor (Genscript Corp.) to generate synthetic antibody variable heavy and light chain sequences. Exemplary nucleic acid sequences encoding VH chain are set forth in Table 9. Exemplary nucleic acid sequences encoding VL chain are set forth in Table 10.

TABLE 9: Exemplary Compiled Heavy Chain Nucleic Acid Sequences

Heavy Chain	SEQ ID NO
VH1-46_IGHD6-6*01_IGHJ1*01	88
VH5-51_IGHD5-18*01>3_IGHJ4*01	89
VH6-1_IGHD3-3*01_IGHJ4*01	90
VH1-46_IGHD6-13*01_IGHJ4*01	92
VH4-34_IGHD7-27*01_IGHJ4*01	94
VH1-3_IGHD4-23*01_IGHJ4*01	95
VH1-46_IGHD2-15*01_IGHJ2*01	93
VH1-46_IGHD3-10*01_IGHJ4*01	91
VH1-8_IGHD2-2*01_IGHJ6*01	96
VH4-31_IGHD2-15*01_IGHJ2*01	97

TABLE 10: Exemplary Compiled Light Chain Nucleic Acid Sequences	
Light Chain	**SEQ ID NO**
L6_IGKJ1*01	98
V3-4_IGLJ1*01	99
V4-3_IGLJ4*01	100
L2_IGKJ1*01	102
L5_IGKJ1*01	103
A27_IGKJ1*01	101
L12_IGKJ1*01	104
O1_IGKJ1*01	105
V1-4_IGLJ4*01	106
V4-6_IGLJ4*01	107

B. Cloning of Variable Heavy and Light Chains

DNA encoding a heavy or light chain variable region was cloned into plasmids containing constant heavy or light chains as appropriate for co-transformation and expression of combinatorial Fabs. Plasmid A (SEQ ID NO:84) and plasmid D (SEQ ID NO:85) contain heavy chain constant regions sequences. Plasmid C (SEQ ID NO:86) contains a kappa light chain constant region sequence and Plasmid E (SEQ ID NO:87) contains a lambda light chain constant region sequence.

DNA encoding a variable heavy chain was digested with Nhe I and Nco I and ligated into Plasmid A with a StII leader sequence using standard molecular techniques. DNA encoding a variable kappa light chain was digested with NcoI and BsiWI and DNA encoding a variable lambda chain was digested with NcoI and AvrII, and were ligated into Plasmid C or Plasmid E, respectively, with a StII leader sequence, using standard molecular biology techniques.

Example 2

Expression and Purification of Antibody Fabs

A. Co-Transformation

Plasmid A and one of either Plasmid C or Plasmid E, each containing various combinations of variable heavy and light chains, were co-transformed into *E. coli*. The process was repeated for all combinations of heavy and light chains. Briefly, plasmid A (encoding a Fab heavy chain) and plasmid C or Plasmid E (encoding a Fab light chain) were resuspended separately in TE buffer to a final concentration of 1 ng/μl. One (1) μL of heavy chain plasmid and 1 μL of light chain plasmid were combined in a PCR tube or a PCR plate and were mixed with 20 μL ice cold LMG194

competent cells. The transformation reaction was incubated on ice for 10 minutes followed by heat shock in a preheated PCR block at 42 °C for 45 seconds. The tube was then placed on ice for an additional 2 minutes followed by addition of 200 µL SOC medium. The cells were allowed to recover for 1.5 hours at 37 °C. A 100 µL aliquot of the transformation culture was used to inoculate 0.9 mL LB (Luria-Bertani Broth) containing 0.4% (w/v) glucose, 17 µg/mL kanamycin (Sigma Aldrich) and 34 µg/mL chloramphenicol (Sigma Aldrich). The culture was grown at 30 °C with vigorous shaking for 20 hours. The transformation culture was grown and purified using the Piccolo™ system as described in Example 10.

B. High throughput Growth and Purification of Fab antibodies

Following transformation, the cells were grown overnight in 2 ml deep well 96-well plates (VWR) block covered with breathable tape. The overnight culture was used directly for inoculation in Piccolo™ (Wollerton *et al.* (2006) JALA, 11:291-303.)

High throughput, parallel expression and purification of Fab antibodies was performed using Piccolo™ (The Automation Partnership (TAP)), which automates protein expression and purification. The expression and purification parameters for Piccolo™ were prepared using Run Composer software (TAP). A 'Strain File' was generated mapping the location of each clone in the seed culture plate. This was submitted to the Run Composer software and the basic machine settings were set as follows: Pre-induction Incubator set at 30° C; Expression Incubator 1 set at 16 °C; Centrifuge set at 6 °C and 5000 x *g*; Media Pump 1 primed with TB (Terrific Broth; per liter contains 12 g tryptone, 24 g yeast extract, 9.4 g potassium phosphate, dibasic, and 2.2 g potassium phosphate, monobasic) (EMD Biosciences; catalog No. 71754), 50 µg/mL kanamycin (Sigma Aldrich), 35 µg/mL chloramphenicol (Sigma Aldrich), 0.4% (w/v) glucose (Sigma Aldrich) and 0.015% (v/v) Antifoam 204 (Sigma Aldrich); Inducer Pump 1 primed with 0.2% (w/v) arabinose (EMD Biosciences); Incubator Gassing Rate set at 2 sec with 51% oxygen, 0.1 mL inoculation volume; Induction Statistic Mean set w/o Outliers (i.e. block mean OD_{600} determined after excluding the 3 highest and 3 lowest values); culture vessel blocks (CVB) pre-induction delay set at 1 hr 20 min and Expression Incubator Acclimatization set at 30 min.

The seed cultures were prepared and loaded into Piccolo™ along with the necessary labware: 24-well culture vessel blocks (CVBs; The Automation Partnership), 24-well Filter Plates (The Automation Partnership), 24-well Output Plates (Seahorse Bioscience) and Pipette Tip Boxes (MBP) as specified by the manufacturer. The TB media supplemented as described above, arabinose inducer and associated pumps were prepared under sterile conditions and attached to the machine. The centrifuge counterbalance weight was set and placed inside the centrifuge. Lastly, purification reagents were prepared and attached to the system pumps (lysis buffer, resin, wash buffer and elution buffer as described below). Once this was complete, the machine was started and processing began.

Before inoculation, the inocula were mapped to specific wells of 24-well CVB, and expression and induction conditions were set as described below. Each well of the CVBs was filled with 10 mL of TB media supplemented as described above prior to inoculation from the seed plate. Each well of each CVB was inoculated with 0.1 mL seed culture and then returned to the storage carousel to await scheduled admission to pre-induction incubation. Once a CVB was queued to begin pre-induction incubation it was removed from the storage carousel and coupled to an aeration assembly (which provides agitation, well sealing and a means for controlled administration of oxygen/air) and then placed in the pre-induction incubator set at 30 °C. OD_{600} readings were taken upon commencement of incubation and approximately every 30 minutes thereafter. Piccolo operation control software monitors the OD_{600} measurements to predict when each CVB will reach the 1.0 OD_{600} set point. Approximately 30 minutes prior to the CVB reaching the OD_{600} set point the assembly was moved to the expression incubator to equilibrate to the expression temperature of 20 °C, and then the cultures in the CVB were induced by addition of 0.032% arabinose inducer followed by 45 hours of expression.

Following culture inoculation and growth induction of cultures, the cells were harvested and lysed for purification of Fabs. Piccolo™ was used for purification of the expressed Fab proteins using an automated expression and purification 'Lifecycle' of a whole culture purification. After controlled expression, CVBs were chilled for 30 minutes at 6 °C in the storage carousel prior to lysis. The CVB was moved to the liquid handling bed and lysis buffer (2.5 mL of Popculture with 1:1000 Lysonase

(EMD Biosciences)) was added to each well with thorough mixing. The lysis proceeded for 10 minutes and then the CVB was centrifuged for 10 minutes at 5000 x *g* to pellet cell debris. During centrifugation, a Filter Plate was placed in the filter bed and resin (2 mL of a 50% slurry of Ni-charged His-Bind resin (EMD Biosciences)) was added to each well. Soluble lysate was added to the corresponding wells of the filter plate containing resin and allowed to bind for 10 minutes prior to draining to waste. Wash buffer (12 mL of wash buffer (50 mM Sodium Phosphate, 300 mM NaCl, 30 mM Imidazole, pH 8.0)) was added in two steps to each well and allowed to drain to waste. Finally, an Output Plate was placed under the Filter Plate in the filter bed and IMAC elution buffer (50 mM Sodium Phosphate, 300 mM NaCl, 500 mM Imidazole) was added in two steps draining into the output plate. The output plate was returned to the storage carousel as was all other labware. Once this process was complete for each CVB in the designed run, the machine was unloaded.

C. Orthogonal Secondary Purification of Fab antibodies

To rapidly further purify partially pure Fabs generated after the Piccolo™ process, an orthogonal method of purification was developed. Fabs were expressed and purified as described above using the Piccolo™ machine.

Two different affinity resins were used depending on the light chain classes. Fabs with a kappa light chain were further purified on Protein G column (GE Healthcare), and Fabs with a lambda light chain were further purified on CaptureSelect Fab Lambda affinity column (BAC, Netherlands). First, the protein samples were transferred to a deep well 96-well block (VWR). Approximately 1.8 mL of the IMAC elution per Fab sample was purified on either a 1 mL Hi-Trap Protein G column or a 0.5 mL CaptureSelect Fab Lambda affinity column at 4 °C using the Akta purifier (GE Healthcare) and A-905 autosampler (GE Healthcare) according to the manufacturer's protocol. Protein concentration was determined by measuring absorbance at A280 on a Molecular Dynamic plate reader and calculated from the exctinction coefficient of the corresponding Fab. Extinction coefficients are calculated based on the total numbers of Tyrosine + Tryptophane + Phenylalanine in the Fab heavy and light chains. Following purification using the Piccolo™ system, expressed protein was generally less than 20% pure. After orthogonal purifiation with protein G, Fab purity was greater than 95% pure as indicated by SDS-PAGE.

EXAMPLE 3

Identification of Anti-DLL4 Antibodies Derived from Germline Segments

Antibodies derived from germline segments were generated and purified as described in Examples 1 and 2 and testing for binding to DLL4 using a Multispot electrochemiluminescence (ECL) binding assay. In the ECL binding assay, germline-derived Fab antibodies were screened for binding to nine different antigens, including the human epidermal growth factor 2 receptor (ErbB2), epidermal growth factor receptor (EGF R), hepatocyte growth factor receptor (HGF R/c-Met), Notch-1, CD44, insulin-like growth factor-1 soluble receptor (IGF-1 sR), P-cadherin, erythropoietin receptor (Epo R) and delta-like protein 4 (DLL4). In an ECL assay, an antigen-antibody interaction is detected by addition of a detection antibody labeled with ruthenium tri-bispyridine-(4-methysulfone) ($Ru(bpy)_2^{2+}$). Upon application of an electric current, the $Ru(bpy)_2^{2+}$-label undergoes an oxidation-reduction cycle in the presence of a co-reactant and light is emitted. A signal is only generated when the $Ru(bpy)_2^{2+}$-label is in close proximity to the electrode, eliminating the need for washing. Detected light intensity is proportional to the amount of captured protein. Those antibodies that showed an ECL signal for DLL4 that was 4 times the signal to a blank well containing no protein antigen were identified.

Recombinant proteins were immobilized onto each well of a 96-well plate by spotting 50 nanoliters (nl) of each protein (of a 60 μg/mL antigen) on the surface of a 96-well Multi-Spot 10 Highbind plate (Meso Scale Discovery; Gaithersburg MD). Spot 10 was left blank as a control. The recombinant human proteins were obtained from R&D Systems and included: rHuman ErbB2/Fc Chimera, CF (Cat# 1129-ER); rHuman EGF R/Fc Chimera, CF (Cat# 344-ER); rHuman HGF R/c-MET/Fc Chimera, CF (Cat# 358-MT/CF); rHuman Notch-1/Fc Chimera, CF (Cat# 3647-TK); rHuman CD44/Fc Chimera, CF (Cat# 3660-CD); rHuman IGF-1 sR,(IGF-1 sR), CF (Cat# 391-GR); rHuman P-Cadherin/Fc Chimera, CF (Cat# 861-PC); rHuman Erythropoietin R/Fc Chimera, CF (Cat# 963-ER); and Recombinant Human DLL4 (Cat# 1506-D4/CF).

An 150 μl aliquot of 1% Bovine Serum Albumin (BSA) in Tris-buffered Saline Tween (TBST) was added to each well and allowed to incubate for 30 min at

20 °C followed by washing and tap drying to completely remove any residual solution. Subsequently, a 12.5 µl aliquot of 1% BSA TBST was added to each well followed by the addition of a 12.5 µl aliquot of a purified Fab. The plate was sealed and incubated for 1 hour at 20 °C with shaking.

Detection antibodies were prepared by individually conjugating both goat anti-human Kappa light chain polyclonal antibody (K3502-1MG, Sigma-Aldrich) and goat anti-human Lambda light chain polyclonal antibody (L1645-1ML, Sigma-Aldrich) with Ruthenium (II) tris-bipyridine-(4-methylsulfone)-N-hydroxysuccinimide (SULFO-TAG NHS-ester, Meso Scale Discovery) according to the manufacturer's instructions. TAG-detection antibody at 25 µl was added to each well and allowed to incubate for 1 hour at 20 °C with shaking. Finally, 15 µl of Read Buffer P with Surfactant (Cat # R92PC-1, Meso Scale Discovery) was added to each well. The electrochemiluminescence was measured using a Sector Imager 2400 (Meso Scale Discovery). Data was analyzed by comparing the ECL signals for an antigen to the blank of each well. A signal to blank ratio of 4 or more was considered a "Hit" Fab.

Table 11, below, lists the Fabs (including the heavy chain and light chain) that were identified as "hits" in the initial ECL screen and the target(s) of the identified Fab "hit." All of the Fabs bind to DLL4. Additionally, as is indicated in Table 11 below, several Fabs were identified that bind to multiple targets. For example, Fab VH1-46_IGHD2-15*01_IGHJ2*01 & L12_IGKJ1*01 binds to EGF R, Epo R and DLL4 and Fab VH1-46_IGHD3-10*01_IGHJ4*01 & L12_IGKJ1*01 binds to Notch-1, P-cadherin and DLL4.

TABLE 11: IDENTIFIED FAB "HITS"

Target	Heavy Chain	SEQ ID NO	Light Chain	SEQ ID NO
rHuman DLL4	VH1-46_IGHD6-6*01_IGHJ1*01	131	L6_IGKJ1*01	141
rHuman DLL4	VII5-51_IGIID5-18*01>3_IGHJ4*01	132	V3-4_IGLJ1*01	142
rHuman DLL4	VH6-1_IGHD3-3*01_IGHJ4*01	133	V4-3_IGLJ4*01	143
EGF R/Fc chimera, Notch-1/Fc chimera, P-cadherin/Fc chimera, Epo R/Fc chimera and rHuman DLL4	VH1-46_IGHD6-13*01_IGHJ4*01	135	L2_IGKJ1*01	145
rHuman DLL4	VH4-34_IGHD7-27*01_IGHJ4*01	137	L5_IGKJ1*01	146

Notch-1/Fc chimera, P-cadherin/Fc chimera, Epo R/Fc chimera and rHuman DLL4	VH1-46_IGHD6-13*01_IGHJ4*01	135	A27_IGKJ1*01	144
rHuman DLL4	VH1-3_IGHD4-23*01_IGHJ4*01	138	L12_IGKJ1*01	147
EGF R/Fc chimera, Epo R/Fc chimera and rHuman DLL4	VH1-46_IGHD2-15*01_IGHJ2*01	136	L12_IGKJ1*01	147
Notch-1/Fc chimera, P-cadherin/Fc chimera and rHuman DLL4	VH1-46_IGHD3-10*01_IGHJ4*01	134	L12_IGKJ1*01	147
rHuman DLL4	VH1-8_IGHD2-2*01_IGHJ6*01	139	L12_IGKJ1*01	147
Epo R/Fc chimera and rHuman DLL4	VH1-46_IGHD6-13*01_IGHJ4*01	135	O1_IGKJ1*01	148
rHuman DLL4	VH4-34_IGHD7-27*01_IGHJ4*01	137	V1-4_IGLJ4*01	149
rHuman DLL4	VH4-31_IGHD2-15*01_IGHJ2*01	140	V1-4_IGLJ4*01	149
rHuman DLL4	VH4-34_IGHD7-27*01_IGHJ4*01	137	V4-6_IGLJ4*01	150

To confirm a "Hit" from the initial Multispot ECL screening, a Fab concentration dependent titration was carried out to determine the Fab-antigen binding affinity. The Multispot ECL assay procedure was the same as described above, except that the concentration of Fab antibody was varied between wells from 0.1 nM to 2.4 μM as indicated in the Tables below depending on each Fab tested. The data are set forth in Tables 12-25 below.

Table 12. Binding affinity of Fab VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01

Fab[nM]	**2383**	**595.8**	**148.9**	**37.2**	**9.3**	**2.3**	**0.6**	**0.1**
ErbB2/Fc	454	321	247	384	354	291	215	306
EGF R/Fc	621	403	290	228	424	289	309	311
HGF R/Fc	762	353	205	207	324	253	256	286
Notch-1/Fc	690	306	375	402	492	333	337	378
CD44/Fc	559	372	348	356	396	317	238	323
IGF-1 sR	527	335	322	295	315	231	313	241
P-Cadherin/Fc	728	617	687	649	452	401	321	235
EPO R/Fc	658	378	373	315	306	429	337	373
DLL4	11794	17203	16253	16717	13210	3055	508	317
Blank	344	285	218	199	287	234	226	201

Table 13. Binding affinity of Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 & V3-4_IGLJ1*01				
Fab[nM]	**154**	**51**	**17**	**6**
ErbB2/Fc	1593	1248	1033	873
EGF R/Fc	1398	816	805	742
HGF R/Fc	1520	1044	914	831
Notch-1/Fc	929	685	558	464
CD44/Fc	960	651	518	547
IGF-1 sR	1396	1051	872	854
P-Cadherin/Fc	1733	854	542	358
EPO R/Fc	1195	750	620	548
DLL4	40392	17025	7158	1946
Blank	447	335	143	191

Table 14. Binding affinity of Fab VH6-1_IGHD3-3*01_IGHJ4*01 & V4-3_IGLJ4*01								
Fab[nM]	**480**	**240**	**120**	**60**	**30**	**15**	**7.5**	**3.8**
ErbB2/Fc	965	833	822	777	726	713	695	714
EGF R/Fc	877	690	658	679	585	584	582	511
HGF R/Fc	951	834	785	623	640	694	558	519
Notch-1/Fc	545	368	472	415	425	508	392	383
CD44/Fc	541	470	442	434	484	454	444	419
IGF-1 sR	741	625	813	654	697	705	642	463
P-Cadherin/Fc	596	383	450	372	440	351	352	281
EPO R/Fc	621	478	431	423	325	397	443	407
DLL4	1532	1273	938	875	736	690	598	462
Blank	362	316	363	237	213	261	217	198

Table 15. Binding affinity of Fab VH1-46_IGHD6-13*01_IGHJ4*01 & L2_IGKJ1*01				
Fab[μM]	**1.19**	**0.2975**	**0.07438**	**0.01859**
ErbB2/Fc	38410	15111	7551	5531
EGF R/Fc	62454	42213	16605	11750
HGF R/Fc	45494	17396	6611	4566
Notch-1/Fc	72018	37503	21990	17565
CD44/Fc	47145	28601	10922	7322
IGF-1 sR	35187	17389	5804	3779
P-Cadherin/Fc	69710	26043	14807	11672
EPO R/Fc	192967	167064	153692	188065
DLL4	74900	34726	20719	18888
Blank	24999	5019	2504	1776

Table 16. Binding affinity of Fab VH4-34_IGHD7-27*01_IGHJ4*01 & L5_IGKJ1*01				
Fab[μM]	**0.51**	**0.1275**	**0.03188**	**0.00797**
ErbB2/Fc	1532	857	584	493
EGF R/Fc	2363	1061	694	530
HGF R/Fc	1989	853	693	419
Notch-1/Fc	2773	1497	849	654
CD44/Fc	2012	926	653	490
IGF-1 sR	2236	1045	765	564
P-Cadherin/Fc	2389	957	775	502
EPO R/Fc	2624	1067	789	566
DLL4	5183	2382	1282	872
Blank	1096	530	536	364

Table 17. Binding affinity of Fab VH1-46_IGHD6-13*01_IGHJ4*01 & A27_IGKJ1*01			
Fab[μM]	**0.48**	**0.096**	**0.0192**
ErbB2/Fc	11287	3365	2313
EGF R/Fc	14638	4509	3115
HGF R/Fc	8002	2328	1582
Notch-1/Fc	15931	4802	3041
CD44/Fc	13445	4320	2915
IGF-1 sR	8927	2449	1826
P-Cadherin/Fc	15595	6654	5040
EPO R/Fc	70938	57356	62037
DLL4	16065	5586	3555
Blank	2945	917	751

Table 18. Binding affinity of Fab VH1-3_IGHD4-23*01_IGHJ4*01 & L12_IGKJ1*01				
Fab[nM]	**60**	**15**	**3.75**	**0.9375**
ErbB2/Fc	2155	740	291	268
EGF R/Fc	2563	842	371	224
HGF R/Fc	2298	743	394	243
Notch-1/Fc	2886	1058	375	348
CD44/Fc	2355	748	307	251
IGF-1 sR	2666	859	314	204
P-Cadherin/Fc	2662	837	331	191
EPO R/Fc	3214	970	358	238
DLL4	17270	7728	1569	453
Blank	1433	536	191	153

Table 19. Binding affinity of Fab VH1-46_IGHD2-15*01_IGHJ2*01 & L12_IGKJ1*01				
Fab[nM]	**280**	**70**	**17.5**	**4.375**
ErbB2/Fc	3953	1358	541	384
EGF R/Fc	6667	2574	1305	542
HGF R/Fc	3564	1289	565	193
Notch-1/Fc	4382	1492	680	480
CD44/Fc	4069	1370	664	424
IGF-1 sR	3533	1319	626	369
P-Cadherin/Fc	5400	1817	949	469
EPO R/Fc	8496	2485	1262	594
DLL4	8111	2747	1219	558
Blank	1691	635	304	305

Table 20. Binding affinity of Fab VH1-46_IGHD3-10*01_IGHJ4*01 & L12_IGKJ1*01				
Fab[nM]	**920**	**230**	**57.5**	**14.375**
ErbB2/Fc	10924	4078	2447	1594
EGF R/Fc	13406	5723	3858	2672
HGF R/Fc	10708	3934	2297	1600
Notch-1/Fc	20086	9737	5886	4206
CD44/Fc	9698	3817	2313	1488
IGF-1 sR	10246	4764	2833	1746
P-Cadherin/Fc	16666	6484	4110	2318
EPO R/Fc	16429	6949	4038	2718
DLL4	73638	119436	144126	125422
Blank	4082	1656	954	738

Table 21. Binding affinity of Fab VH1-8_IGHD2-2*01_IGHJ6*01 & L12_IGKJ1*01				
Fab[nM]	**130**	**32.5**	**8.1**	**2.0**
ErbB2/Fc	1533	556	557	382
EGF R/Fc	1746	645	560	424
HGF R/Fc	1882	525	551	356
Notch-1/Fc	1759	706	612	539
CD44/Fc	1754	573	528	447
IGF-1 sR	1973	561	518	367
P-Cadherin/Fc	1845	556	573	250
EPO R/Fc	2151	673	660	433
DLL4	7738	2989	1548	605
Blank	1153	473	435	316

Table 22. Binding affinity of Fab VH1-46_IGHD6-13*01_IGHJ4*01 & O1_IGKJ1*01				
Fab[nM]	**930**	**232.5**	**58.1**	**14.5**
ErbB2/Fc	2225	779	322	274
EGF R/Fc	3110	803	444	357
HGF R/Fc	2344	790	432	373
Notch-1/Fc	2206	778	388	317
CD44/Fc	1917	607	375	212
IGF-1 sR	1915	569	343	234
P-Cadherin/Fc	2438	655	478	277
EPO R/Fc	3009	1472	829	660
DLL4	8162	3586	1876	1149
Blank	1206	460	225	117

Table 23. Binding affinity of Fab VH4-34_IGHD7-27*01_IGHJ4*01 & V1-4_IGLJ4*01				
Fab[nM]	**580**	**145**	**36.3**	**9.1**
ErbB2/Fc	1712	1123	1029	987
EGF R/Fc	1631	856	831	800
HGF R/Fc	2341	1173	1065	894
Notch-1/Fc	1585	860	633	754
CD44/Fc	1228	692	629	607
IGF-1 sR	1364	794	799	788
P-Cadherin/Fc	2240	850	684	589
EPO R/Fc	1579	845	722	697
DLL4	4420	2140	1399	1030
Blank	679	357	314	276

Table 24. Binding affinity of Fab VH4-31_IGHD2-15*01_IGHJ2*01 & V1-4_IGLJ4*01				
Fab[nM]	**210**	**52.5**	**13.1**	**3.3**
ErbB2/Fc	1977	1511	930	1031
EGF R/Fc	1617	1109	824	847
HGF R/Fc	2060	1286	981	849
Notch-1/Fc	1972	1323	669	726
CD44/Fc	1395	897	708	621
IGF-1 sR	1431	911	814	743
P-Cadherin/Fc	4410	2161	1062	678
EPO R/Fc	2123	1319	776	695
DLL4	4108	1951	1107	922
Blank	833	467	376	359

Table 25. Binding affinity of Fab VH4-34_IGHD7-27*01_IGHJ4*01 & V4-6_IGLJ4*01				
Fab[nM]	**340**	**170**	**85.0**	**42.5**
ErbB2/Fc	1226	964	844	866
EGF R/Fc	1208	826	1001	528
HGF R/Fc	1238	757	998	607
Notch-1/Fc	1209	816	780	649
CD44/Fc	959	660	693	522
IGF-1 sR	1042	832	891	646
P-Cadherin/Fc	1160	744	709	421
EPO R/Fc	1255	790	817	494
DLL4	2332	1462	1311	877
Blank	554	262	292	162

Example 4

Germline-Modified anti-DLL4 Antibodies

Anti-DLL4 antibodies derived from germline segments were used to generate germline-modified anti-DLL4 antibodies. Modifications were made in the VH and/or VL chains of germline-derived anti-DLL4 antibodies as described in U.S. provisional

Application No. [nickname 3800016-00004/ p702], and incorporated by reference herein.

A. Alignment with non-Hit and alanine-scanning mutagenesis

Briefly, the amino acid sequence of the heavy and/or light chain of a germline-derived antibody identified as a "Hit" by binding to DLL4 was compared to the amino acid sequence of the heavy and/or light chain of a germline-derived antibody that was identified as a "non-Hit" for DLL4. The region of the antibody containing amino acid residues that differed between the "Hit" and "non-Hit" was subjected to alanine-scanning mutagenesis. Alanine mutants were generated by overlapping PCR using the parent heavy or light chain DNA as a template. Forward and reverse primers that specifically generate the desire mutation at the target codon were used to amplify the parent DNA in the appropriate plasmid. In the first round of PCR, two separate PCR reactions with different primer pairs were used to amplify two segments of the gene. The first reaction used the specific reverse primer with an EcoRI forward primer and amplified the first half of the gene. The second reaction used the specific forward primer with an FLXhoI reverse primer and amplified the second half of the gene. The gene segments were generated using 20 cycles of PCR with the following conditions: 94 °C for 30 sec; 50 °C for 30 sec; and 72 °C for 90 sec. The PCR products were isolated and purified from 1% agarose gel and mixed together as a template for the second round of PCR. In the second round of PCR, EcoRI forward and FLXhoI reverse primers were used to amplify the full length gene product. The gene product was generated using 20 cycles of PCR with the following conditions: 94 °C for 30 sec; 55 °C for 30 sec; and 72 °C for 90 sec.

The PCR product was isolated and subsequently digested with EcoRI and XhoI (New England Biolabs) and ligated into the similarly digested plasmid. After transformation of the ligation product in *E. coli* DH5α and plating, individual colonies were selected and grown in a 96-well block containing 1.5 ml of Terrific Broth (EMD, San Diego, CA) supplemented with 50 μg/ml Kanamycin, and 0.4 % glucose, and grown at 37 °C overnight. The DNA was isolated using a mini-prep kit (Qiagen) and alanine mutations were confirmed by DNA sequencing.

As an example, Table 26 sets forth primer pairs used to generate the mutant VH5-51_IGHD5-18*01>3_IGHJ4*01 R99A and VH1-46_IGHD6-6*01_IGHJ1*01

E100A. Primers R99A_F and R99A_R were utilized to specifically amplify the R99 to alanine mutation. Primers E100A_F and E100A_R were utilized to specifically amplify the E100 to alanine mutation. Primers EcoRI_F and FLXhoI_R were utilized to amplify the remaining segments of the gene.

5

Table 26. Example primer pairs for alanine scanning mutagenesis		
Primer	**Sequence**	**SEQ ID NO**
VH5-51_IGHD5-18*01>3_IGHJ4*01		
R99A_F	GCCATGTATTACTGTGCGAGAGCCGGATACAGCTATGGTTACGAC	1
R99A_R	GTCGTAACCATAGCTGTATCCGGCTCTCGCACAGTAATACATGGC	2
VH1-46_IGHD6-6*01_IGHJ1*01		
E100A_F	GTGTATTACTGTGCGAGAGAGGCCTATAGCAGCTCGTCCGCTG	3
E100A_R	CAGCGGACGAGCTGCTATAGGCCTCTCTCGCACAGTAATACAC	4
Plasmid A and D		
EcoRI_F	TTGGGCGAATTCCCTAGATAATTAATTAGGAGG	5
FLXhoI_R	TTAAACCTCGAGCCGCGGTTCATTAAAG	6

B. NNK mutagenesis by overlapping PCR

Following alanine scanning mutagenesis, expressed Fab antibodies were tested for binding to DLL4 using the ECL assay described in Example 3 above. The Fab antibodies that contained modifications in the VH and/or VL chain that did not affect or increased binding to DLL4 were subjected to further mutagenesis. NNK mutagenesis by overlapping PCR was carried out as described above for alanine scanning mutagenesis, with initial primers that generate the desired NNK mutations. Therefore, in the first round of PCR, specific primer pairs were used in which the target codon was replaced with NNK (forward) and MNN (reverse). For example, Table 27 below sets forth forward and reverse primers used to generate VH5-51_IGHD5-18*01>3_IGHJ4*01 G100 NNK mutants and VH1-46_IGHD6-6*01_IGHJ1*01 S102 NNK mutants.

Individual clones were subjected to DNA sequencing (by BATJ, Inc., San Diego, CA) to identify the amino acid substitution. Depending on the number of colonies picked per NNK mutation reaction, mutation rate varies—as low as 4 to 5 amino acid changes, and as high as 18 to 19 amino acid changes per mutation were observed.

Table 27. Example primer pairs for NNK mutagenesis		
Primer	Sequence	SEQ ID NO
VH5-51_IGHD5-18*01>3_IGHJ4*01		
G100_NNK_F	GTATTACTGTGCGAGACGTNNKTACAGCTATGGTTACGAC	7
G100_NNK_R	GTCGTAACCATAGCTGTAMNNACGTCTCGCACAGTAATAC	8
VH1-46_IGHD6-6*01_IGHJ1*01		
S102_NNK_F	TGCGAGAGAGGGGTATNNKAGCAGCTGGTACGACT	9
S102_NNK_R	AGTCGTACCAGCTGCTMNNATACCCCTCTCTCGCA	10

C. Cassette Mutagenesis

Following identification of modifications in the VH and/or VL chain that optimized binding to DLL4, cassette mutagenesis was used to generate particular combination mutants. Briefly, Fab mutants were generated in a high-throughput manner by cloning of specific synthetic CDR1, CDR2 and/or CDR3 sequences into plasmids previously modified to contain BsaI cloning sites. Specifically, for each heavy or light chain, three vectors each were generated whereby a BsaI restriction site was incorporated at both the 5' and 3' end of each CDR region. To generate Fab mutants, forward and reverse primers encoding a CDR with specific mutations and additionally BsaI overlapping ends were synthesized and annealed. These cassettes, or mutated CDR regions, were then ligated into the corresponding BsaI digested vector, thereby generating a plasmid containing a specifically modified CDR region.

For example, specific primers were synthesized (IDT, see Table 28 below) and used to generate three vectors each for germline-derived heavy chains VH1-46_IGHD6-6*01_IGHJ1*01 and VH5-51_IGHD5-18*01>3_IGHJ4*01 and light chains L6_IGKJ1*01 and V3-4_IGLJ1*01, to incorporate a BsaI site at the beginning and end of CDR1, CDR2 and CDR3. The vectors were generated as described above using the specific forward and reverse primers in the first round of PCR and the parent heavy or light chain DNA as a template. Individual clones were subjected to DNA sequencing (by BATJ, Inc., San Diego, CA) to confirm the incorporation of two BsaI sites in each CDR.

Subsequentely, each BsaI containing plasmid was digested with BsaI (New England Biolabs) and the DNA was gel purified. Specific primers were synthesized (IDT) to generate desired mutants. Briefly, 1 µl of each forward and reverse primer were annealed by heating to 95 °C in TE for 2 min, followed by slow cooling to room

temperature. 1 µl of the annealed primers were then ligated with 2 ng of the BsaI digested vector and transformed into *E. coli* DH5a cell. Mutations were confirmed by DNA sequencing. The ligation reactions can be carried out in a 96-well plate thereby allowing for high-throughput mutagenesis.

For example, Tables 28-29 below set forth primers to generate VH1-46_IGHD6-6*01_IGHJ1*01_APFF CDR2 mutants set forth in Example 5, Table 30 below.

Table 28. BsaI restriction enzyme mutagenesis primers

Primer	Sequence	SEQ ID NO
VH1-46_C DR1_F	gagacctactatggttcgggtctctgggtgcgacaggcc	11
VH1-46_C DR2_F	gagacctactatggttcgggtctcaagttccagggcagagtcac	12
VH1-46_C DR3_F	gagacctactatggttcgggtctctggggccagggcac	13
VH5-51_C DR1_F	gagacctactatggttcgggtctctgggtgcgccagatg	14
VH5-51_C DR2_F	gagacctactatggttcgggtctccaggtcaccatctcagccg	15
VH5-51_C DR3_F	gagacctactatggttcgggtctctggggccaaggaaccc	16
L6_CDR1_F	gagacctactatggttcgggtctctggtaccaacagaaacctggc	17
L6_CDR2_F	gagacctactatggttcgggtctcggcatcccagccagg	18
L6_CDR3_F	gagacctactatggttcgggtctcttcggccaagggacca	19
V3-4_CDR1_F	gagacctactatggttcgggtctctggtaccagcagacccca	20
V3-4_CDR2_F	gagacctactatggttcgggtctcggggtccctgatcgcttc	21
V3-4_CDR3_F	gagacctactatggttcgggtctcttcggaactgggaccaag	22
Lambda_BSA_F	gagtggagacgaccacaccc	23
VH1-46_C DR1_R	GAGACCCGAACCATAGTAGGTCTCAGATGCCTTGCAGGAAACC	24
VH1-46_C DR2_R	GAGACCCGAACCATAGTAGGTCTCTCCCATCCACTCAAGCCC	25
VH1-46_C DR3_R	GAGACCCGAACCATAGTAGGTCTCTCTCGCACAGTAATACACGGC	26
VH5-51_C DR1_R	GAGACCCGAACCATAGTAGGTCTCAGAACCCTTACAGGAGATCTTCA	27
VH5-51_C DR2_R	GAGACCCGAACCATAGTAGGTCTCCCCCATCCACTCCAGGC	28
VH5-51_C DR3_R	GAGACCCGAACCATAGTAGGTCTCTCTCGCACAGTAATACATGGC	29
L6_CDR1_R	GAGACCCGAACCATAGTAGGTCTCGCAGGAGAGGGTGGCTC	30
L6_CDR2_R	GAGACCCGAACCATAGTAGGTCTCATAGATGAGGAGCCTGGGAG	31
L6_CDR3_R	GAGACCCGAACCATAGTAGGTCTCACAGTAATAAACTGCAAAATCTTCAG	32
V3-4_CDR1_R	GAGACCCGAACCATAGTAGGTCTCACAAGTGAGTGTGACTGTCCCT	33
V3-4_CDR2_R	GAGACCCGAACCATAGTAGGTCTCGTAGATGAGCGTGCGTGG	34
V3-4_CDR3_R	GAGACCCGAACCATAGTAGGTCTCACAGTAATAATCAGATTCATCATCTGC	35

Table 29. VH1-46_IGHD6-6*01_IGHJ1*01_APFF_CDR2 BsaI mutagenesis primers

Primer	Sequence	SEQ ID NO
A_ILPTH_F	tgggaataattctcctactggtcatagcacaagctacgcacaga	36

A_VLPTH_F	tgggaatagtgctccctactggtcatagcacaagctacgcacaga	37
A_ALPTH_F	tgggaatagctctccctactggtcatagcacaagctacgcacaga	38
A_GLPTH_F	tgggaataggcctccctactggtcatagcacaagctacgcacaga	39
A_TLPTH_F	tgggaataaccctccctactggtcatagcacaagctacgcacaga	40
A_SLPTH_F	tgggaatatccctccctactggtcatagcacaagctacgcacaga	41
A_YLPTH_F	tgggaatatacctccctactggtcatagcacaagctacgcacaga	42
A_WLPTH_F	tgggaatatggctccctactggtcatagcacaagctacgcacaga	43
A_HLPTH_F	tgggaatacacctccctactggtcatagcacaagctacgcacaga	44
A_RLPTH_F	tgggaatacgcctccctactggtcatagcacaagctacgcacaga	45
A_ELPTH_F	tgggaatagaactccctactggtcatagcacaagctacgcacaga	46
A_NLPTH_F	tgggaataaacctccctactggtcatagcacaagctacgcacaga	47
A_TLVTH_F	tgggaataaccctcgtgactggtcatagcacaagctacgcacaga	48
A_TLATH_F	tgggaataaccctcgctactggtcatagcacaagctacgcacaga	49
A_TLGTH_F	tgggaataaccctcggcactggtcatagcacaagctacgcacaga	50
A_TLTTH_F	tgggaataaccctcaccactggtcatagcacaagctacgcacaga	51
A_TLSTH_F	tgggaataaccctctccactggtcatagcacaagctacgcacaga	52
A_TLYTH_F	tgggaataaccctctacactggtcatagcacaagctacgcacaga	53
A_TLWTH_F	tgggaataaccctctggactggtcatagcacaagctacgcacaga	54
A_TLHTH_F	tgggaataaccctccacactggtcatagcacaagctacgcacaga	55
A_TLRTH_F	tgggaataaccctccgcactggtcatagcacaagctacgcacaga	56
A_TLETH_F	tgggaataaccctcgaaactggtcatagcacaagctacgcacaga	57
A_TLNTH_F	tgggaataaccctcggcactggtcatagcacaagctacgcacaga	58
A_TLMTH_F	tgggaataaccctcatgactggtcatagcacaagctacgcacaga	59
A_ILPTH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTAGGGAGAATTATT	60
A_VLPTH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTAGGGAGCACTATT	61
A_ALPTH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTAGGGAGAGCTATT	62
A_GLPTH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTAGGGAGGCCTATT	63
A_TLPTH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTAGGGAGGGTTATT	64
A_SLPTH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTAGGGAGGGATATT	65
A_YLPTH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTAGGGAGGTATATT	66
A_WLPTH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTAGGGAGCCATATT	67
A_HLPTH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTAGGGAGGTGTATT	68
A_RLPTH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTAGGGAGGCGTATT	69
A_ELPTH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTAGGGAGTTCTATT	70
A_NLPTH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTAGGGAGGTTTATT	71
A_TLVTH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTCACGAGGGTTATT	72
A_TLATH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTAGCGAGGGTTATT	73
A_TLGTH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTGCCGAGGGTTATT	74
A_TLTTH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTGGTGAGGGTTATT	75
A_TLSTH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTGGAGAGGGTTATT	76
A_TLYTH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTGTAGAGGGTTATT	77
A_TLWTH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTCCAGAGGGTTATT	78
A_TLHTH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTGTGGAGGGTTATT	79
A_TLRTH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTGCGGAGGGTTATT	80
A_TLETH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTTTCGAGGGTTATT	81
A_TLNTH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTGCCGAGGGTTATT	82
A_TLMTH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTCATGAGGGTTATT	83

Example 5

Germline-Modified anti-DLL4 Antibodies

Table 30 sets forth germline-modified anti-DLL4 antibodies derived from parent anti-DLL4 antibody encoded by VH chain germline segments VH1-

46_IGHD6-6*01_IGHJ1*01 and VL chain germline segments L6_IGKJ1*01. Table 31 sets forth germline-modified anti-DLL4 antibodies derived from parent anti-DLL4 antibody encoded by VH chain germline segments VH5-51_IGHD5-18*01>3_IGHJ4*01 and VL chain germline segments V3-4_IGLJ1*01. The amino acid mutation(s) is numbered according to its amino acid position in the parent wild-type antibody. The SEQ ID NO corresponding to the amino acid sequence of each heavy chain and light chain is provided.

Table 30. VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01 DLL4 antibodies

	Nickname	Heavy Chain VH1-46_IGHD6-6*01_IGHJ1*01	SEQ ID NO	Light Chain L6_IGKJ1*01	SEQ ID NO
1		wildtype	131	wildtype	141
2	H:S104F & L:wt	S104F	151	wildtype	141
3	H:S104A & L:wt	S104A	152	wildtype	141
4	H:S103P & L:wt	S103P	153	wildtype	141
5	H:S102A & L:wt	S102A	154	wildtype	141
6	H:APF & L:wt	S102A/S103P/S104F	155	wildtype	141
7	H:APFF & L:wt	S102A/S103P/S104F/H111F	156	wildtype	141
8	H:APFY & L:wt	S102A/S103P/S104F/H111Y	157	wildtype	141
9	H:APYY & L:wt	S102A/S103P/S104Y/H111Y	158	wildtype	141
10	H:APF & L:wt	S102A/S103P/S104F	155	S28P	264
11	H:APF & L:wt	S102A/S103P/S104F	155	S30N	265
12	H:APF & L:wt	S102A/S103P/S104F	155	S31K	266
13	H:E100A & L:wt	E100A	159	wildtype	141
14	H:Y101A & L:wt	Y101A	160	wildtype	141
15	H:S103A & L:wt	S103A	161	wildtype	141
16	H:S105A & L:wt	S105A	162	wildtype	141
17	H:E107A & L:wt	E107A	163	wildtype	141
18	H:Q110A & L:wt	Q110A	164	wildtype	141
19	H:H111A & L:wt	H111A	165	wildtype	141
20	H:S102Q & L:wt	S102Q	166	wildtype	141
21	H:S102V & L:wt	S102V	167	wildtype	141
22	H:S102I & L:wt	S102I	168	wildtype	141
23	H:S102G & L:wt	S102G	169	wildtype	141
24	H:S103L & L:wt	S103L	170	wildtype	141
25	H:S103W & L:wt	S103W	171	wildtype	141
26	H:S103F & L:wt	S103F	172	wildtype	141
27	H:S103N & L:wt	S103N	173	wildtype	141
28	H:S103H & L:wt	S103H	174	wildtype	141
29	H:S103C & L:wt	S103C	175	wildtype	141
30	H:S103G & L:wt	S103G	176	wildtype	141
31	H:S104G & L:wt	S104G	177	wildtype	141
32	H:S104C & L:wt	S104C	178	wildtype	141
33	H:S104H & L:wt	S104H	179	wildtype	141
34	H:S104L & L:wt	S104L	180	wildtype	141
35	H:S104R & L:wt	S104R	181	wildtype	141
36	H:APF G55W & L:wt	S102A/S103P/S104F G55W	182	wildtype	141
37	H:APF G55D & L:wt	S102A/S103P/S104F G55D	183	wildtype	141

38	H:APF A106E & L:wt	S102A/S103P/S104F A106E	184	wildtype	141
39	H:APF H111S & L:wt	S102A/S103P/S104F H111S	185	wildtype	141
40	H:APFF T28A & L:wt	S102A/S103P/S104F/H111F T28A	186	wildtype	141
41	H:APFF F29A & L:wt	S102A/S103P/S104F/H111F F29A	187	wildtype	141
42	H:APFF T30A & L:wt	S102A/S103P/S104F/H111F T30A	188	wildtype	141
43	H:APFF S31A & L:wt	S102A/S103P/S104F/H111F S31A	189	wildtype	141
44	H:APFF Y33A & L:wt	S102A/S103P/S104F/H111F Y33A	190	wildtype	141
45	H:APFF I50A & L:wt	S102A/S103P/S104F/H111F I50A	191	wildtype	141
46	H:APFF I51A & L:wt	S102A/S103P/S104F/H111F I51A	192	wildtype	141
47	H:APFF N52A & L:wt	S102A/S103P/S104F/H111F N52A	193	wildtype	141
48	H:APFF P53A & L:wt	S102A/S103P/S104F/H111F P53A	194	wildtype	141
49	H:APFF S54A & L:wt	S102A/S103P/S104F/H111F S54A	195	wildtype	141
50	H:APFF G55A & L:wt	S102A/S103P/S104F/H111F G55A	196	wildtype	141
51	H:APFF G56A & L:wt	S102A/S103P/S104F/H111F G56A	197	wildtype	141
52	H:APFF S57A & L:wt	S102A/S103P/S104F/H111F S57A	198	wildtype	141
53	H:APFF T58A & L:wt	S102A/S103P/S104F/H111F T58A	199	wildtype	141
54	H:APFF S59A & L:wt	S102A/S103P/S104F/H111F S59A	200	wildtype	141
55	H:APFF TV & L:wt	S102A/S103P/S104F/H111F I51T/N52V	201	wildtype	141
56	H:APFF N52G & L:wt	S102A/S103P/S104F/H111F N52G	202	wildtype	141
57	H:APFF N52T & L:wt	S102A/S103P/S104F/H111F N52T	203	wildtype	141
58	H:APFF N52P & L:wt	S102A/S103P/S104F/H111F N52P	204	wildtype	141
59	H:APFF N52L & L:wt	S102A/S103P/S104F/H111F N52L	205	wildtype	141
60	H:APFF N52W & L:wt	S102A/S103P/S104F/H111F N52W	206	wildtype	141
61	H:APFF N52Y & L:wt	S102A/S103P/S104F/H111F N52Y	207	wildtype	141
62	H:APFF N52V & L:wt	S102A/S103P/S104F/H111F N52V	208	wildtype	141
63	H:APFF N52S & L:wt	S102A/S103P/S104F/H111F N52S	209	wildtype	141
64	H:APFF N52Q & L:wt	S102A/S103P/S104F/H111F N52Q	210	wildtype	141
65	H:APFF N52K & L:wt	S102A/S103P/S104F/H111F N52K	211	wildtype	141
66	H:APFF G56V & L:wt	S102A/S103P/S104F/H111F G56V	212	wildtype	141

67	H:APFF G56E & L:wt	S102A/S103P/S104F/H111F G56E	213	wildtype	141
68	H:APFF G56S & L:wt	S102A/S103P/S104F/H111F G56S	214	wildtype	141
69	H:APFF G56K & L:wt	S102A/S103P/S104F/H111F G56K	215	wildtype	141
70	H:APFF G56T & L:wt	S102A/S103P/S104F/H111F G56T	216	wildtype	141
71	H:APFF G56L & L:wt	S102A/S103P/S104F/H111F G56L	217	wildtype	141
72	H:APFF G56R & L:wt	S102A/S103P/S104F/H111F G56R	218	wildtype	141
73	H:APFF G56H & L:wt	S102A/S103P/S104F/H111F G56H	219	wildtype	141
74	H:APFF G56I & L:wt	S102A/S103P/S104F/H111F G56I	220	wildtype	141
75	H:APFF G56W & L:wt	S102A/S103P/S104F/H111F G56W	221	wildtype	141
76	H:APFF S54I & L:wt	S102A/S103P/S104F/H111F S54I	222	wildtype	141
77	H:APFF S54E & L:wt	S102A/S103P/S104F/H111F S54E	223	wildtype	141
78	H:APFF S54R & L:wt	S102A/S103P/S104F/H111F S54R	224	wildtype	141
79	H:APFF S54G & L:wt	S102A/S103P/S104F/H111F S54G	225	wildtype	141
80	H:APFF S54T & L:wt	S102A/S103P/S104F/H111F S54T	226	wildtype	141
81	H:APFF S54L & L:wt	S102A/S103P/S104F/H111F S54L	227	wildtype	141
82	H:APFF S54V & L:wt	S102A/S103P/S104F/H111F S54V	228	wildtype	141
83	H:APFF S54N & L:wt	S102A/S103P/S104F/H111F S54N	229	wildtype	141
84	H:APFF S54P & L:wt	S102A/S103P/S104F/H111F S54P	230	wildtype	141
85	H:APFF TP & L:wt	S102A/S103P/S104F/H111F I50T/S54P	231	wildtype	141
86	H:APFF AN & L:wt	S102A/S103P/S104F/H111F S54A/S59N	232	wildtype	141
87	H:APFF LTH & L:wt	S102A/S103P/S104F/H111F N52L/S54T/G56H	233	wildtype	141
88	H:APFF ALTH & L:wt	S102A/S103P/S104F/H111F I51A/N52L/S54T/G56H	234	wildtype	141
89	H:APFF TLTH & L:wt	S102A/S103P/S104F/H111F I51T/N52L/S54T/G56H	235	wildtype	141
90	H:APFF YLTH & L:wt	S102A/S103P/S104F/H111F I51Y/N52L/S54T/G56H	236	wildtype	141
91	H:APFF HLTH & L:wt	S102A/S103P/S104F/H111F I51H/N52L/S54T/G56H	237	wildtype	141
92	H:APFF ELTH & L:wt	S102A/S103P/S104F/H111F I51E/N52L/S54T/G56H	238	wildtype	141
93	H:APFF VLTH & L:wt	S102A/S103P/S104F/H111F I51V/N52L/S54T/G56H	239	wildtype	141
94	H:APFF GLTH & L:wt	S102A/S103P/S104F/H111F I51G/N52L/S54T/G56H	240	wildtype	141

95	H:APFF SLTH & L:wt	S102A/S103P/S104F/H111F I51S/N52L/S54T/G56H	241	wildtype	141
96	H:APFF WLTH & L:wt	S102A/S103P/S104F/H111F I51W/N52L/S54T/G56H	242	wildtype	141
97	H:APFF RLTH & L:wt	S102A/S103P/S104F/H111F I51R/N52L/S54T/G56H	243	wildtype	141
98	H:APFF NLTH & L:wt	S102A/S103P/S104F/H111F I51N/N52L/S54T/G56H	244	wildtype	141
99	H:APFF TLVTH & L:wt	S102A/S103P/S104F/H111F I51T/N52L/P53V/S54T/G56H	245	wildtype	141
100	H:APFF TLGTH & L:wt	S102A/S103P/S104F/H111F I51T/N52L/P53G/S54T/G56H	246	wildtype	141
101	H:APFF TLSTH & L:wt	S102A/S103P/S104F/H111F I51T/N52L/P53S/S54T/G56H	247	wildtype	141
102	H:APFF TLWTH & L:wt	S102A/S103P/S104F/H111F I51T/N52L/P53W/S54T/G56H	248	wildtype	141
103	H:APFF TLRTH & L:wt	S102A/S103P/S104F/H111F I51T/N52L/P53R/S54T/G56H	249	wildtype	141
104	H:APFF TLNTH & L:wt	S102A/S103P/S104F/H111F I51T/N52L/P53N/S54T/G56H	250	wildtype	141
105	H:APFF TLATH & L:wt	S102A/S103P/S104F/H111F I51T/N52L/P53A/S54T/G56H	251	wildtype	141
106	H:APFF TLTTH & L:wt	S102A/S103P/S104F/H111F I51T/N52L/P53T/S54T/G56H	252	wildtype	141
107	H:APFF TLYTH & L:wt	S102A/S103P/S104F/H111F I51T/N52L/P53Y/S54T/G56H	253	wildtype	141
108	H:APFF TLHTH & L:wt	S102A/S103P/S104F/H111F I51T/N52L/P53H/S54T/G56H	254	wildtype	141
109	H:APFF TLETH & L:wt	S102A/S103P/S104F/H111F I51T/N52L/P53E/S54T/G56H	255	wildtype	141
110	H:APFF TLMTH & L:wt	S102A/S103P/S104F/H111F I51T/N52L/P53M/S54T/G56H	256	wildtype	141
111	H:APFF S84G & L:wt	S102A/S103P/S104F/H111F S84G	257	wildtype	141
112	H:APFF S84Q & L:wt	S102A/S103P/S104F/H111F S84Q	258	wildtype	141
113	H:APFF S84N & L:wt	S102A/S103P/S104F/H111F S84N	259	wildtype	141
114	H:APFF S84H & L:wt	S102A/S103P/S104F/H111F S84H	260	wildtype	141
115	H:APFF S84R & L:wt	S102A/S103P/S104F/H111F S84R	261	wildtype	141
116	H:APFF S84K & L:wt	S102A/S103P/S104F/H111F S84K	262	wildtype	141
117	H:APFF S84T & L:wt	S102A/S103P/S104F/H111F S84T	263	wildtype	141
118	H:APF & L:R91P	S102A/S103P/S104F	155	R91P	267
119	H:APF & L:R91L	S102A/S103P/S104F	155	R91L	268
120	H:APF & L: R91G	S102A/S103P/S104F	155	R91G	269
121	H:APF & L: R91Q	S102A/S103P/S104F	155	R91Q	270
122	H:APF & L:S92N	S102A/S103P/S104F	155	S92N	271
123	H:APF & L: S92C	S102A/S103P/S104F	155	S92C	272
124	H:APFF & L:N93Y	S102A/S103P/S104F/H111F	156	N93Y	273
125	H:APFF & L: N93S	S102A/S103P/S104F/H111F	156	N93S	274
126	H:APFF & L: N93H	S102A/S103P/S104F/H111F	156	N93H	275
127	H:APFF & L: N93Q	S102A/S103P/S104F/H111F	156	N93Q	276

128	H:APFF & L:W94R	S102A/S103P/S104F/H111F	156	W94R	277
129	H:APFF & L: W94S	S102A/S103P/S104F/H111F	156	W94S	278
130	H:APFF & L: W94T	S102A/S103P/S104F/H111F	156	W94T	279
131	H:APFF & L: W94L	S102A/S103P/S104F/H111F	156	W94L	280
132	H:APFF & L: W94P	S102A/S103P/S104F/H111F	156	W94P	281
133	II:APFF & L: W94M	S102A/S103P/S104F/H111F	156	W94M	282
134	H:APFF & L:S92P	S102A/S103P/S104F/H111F	156	S92P	283
135	H:APFF & L:S92A	S102A/S103P/S104F/H111F	156	S92A	284
136	H:APFF & L:S92Q	S102A/S103P/S104F/H111F	156	S92Q	285
137	H:APFF & L:S92V	S102A/S103P/S104F/H111F	156	S92V	286
138	H:APFF & L:S92T	S102A/S103P/S104F/H111F	156	S92T	287
139	H:APFF & L:S92C	S102A/S103P/S104F/H111F	156	S92C	272
140	H:APFF & L:S92R	S102A/S103P/S104F/H111F	156	S92R	288
141	H:APFF & L:S92G	S102A/S103P/S104F/H111F	156	S92G	289
142	H:APFF & L:S92V	S102A/S103P/S104F/H111F	156	S92V	290
143	H:APFF & L:S92M	S102A/S103P/S104F/H111F	156	S92M	291
144	H:APFF & L:S92N	S102A/S103P/S104F/H111F	156	S92N	271
145	H:APF & L:S30W	S102A/S103P/S104F	155	S30W	292
146	H:APF & L:S30R	S102A/S103P/S104F	155	S30R	293
147	H:APF & L:S30T	S102A/S103P/S104F	155	S30T	294
148	H:APF & L:S30L	S102A/S103P/S104F	155	S30L	295
149	H:APF & L:GL	S102A/S103P/S104F	155	R24G/Q27L	296
150	H:APF & L:Y32V	S102A/S103P/S104F	155	Y32V	297
151	H:APF & L:Y32S	S102A/S103P/S104F	155	Y32S	298
152	H:APFF & L:S28G	S102A/S103P/S104F/H111F	156	S28G	299
153	H:APFF & L:S28K	S102A/S103P/S104F/H111F	156	S28K	300
154	H:APFF & L:S28V	S102A/S103P/S104F/H111F	156	S28V	301
155	H:APFF & L:S28F	S102A/S103P/S104F/H111F	156	S28F	302
156	H:APFF & L:S28P	S102A/S103P/S104F/H111F	156	S28P	264
157	H:APFF & L:S28T	S102A/S103P/S104F/H111F	156	S28T	303
158	H:APFF & L:S28L	S102A/S103P/S104F/H111F	156	S28L	304
159	H:APFF & L:S28Q	S102A/S103P/S104F/H111F	156	S28Q	305
160	H:APFF & L:S28A	S102A/S103P/S104F/H111F	156	S28A	306
161	H:APFF & L:S28N	S102A/S103P/S104F/H111F	156	S28N	307
162	H:APFF & L:S28H	S102A/S103P/S104F/H111F	156	S28H	308
163	H:APFF & L:S28I	S102A/S103P/S104F/H111F	156	S28I	309
164	H:APFF & L:S28R	S102A/S103P/S104F/H111F	156	S28R	310
165	H:APFF & L:S28W	S102A/S103P/S104F/H111F	156	S28W	311
166	H:APFF & L:S28M	S102A/S103P/S104F/H111F	156	S28M	312
167	H:APFF & L:S28E	S102A/S103P/S104F/H111F	156	S28E	313
168	H:APFF & L:S30C	S102A/S103P/S104F/H111F	156	S30C	314
169	H:APFF & L:S30D	S102A/S103P/S104F/H111F	156	S30D	315
170	H:APFF & L:S30L	S102A/S103P/S104F/H111F	156	S30L	316
171	H:APFF & L:S30T	S102A/S103P/S104F/H111F	156	S30T	317
172	H:APFF & L:S30R	S102A/S103P/S104F/H111F	156	S30R	318
173	H:APFF & L:S30P	S102A/S103P/S104F/H111F	156	S30P	319
174	H:APFF & L:S30W	S102A/S103P/S104F/H111F	156	S30W	320
175	H:APFF & L:S30Y	S102A/S103P/S104F/H111F	156	S30Y	321
176	H:APFF & L:S30Q	S102A/S103P/S104F/H111F	156	S30Q	322
177	H:APFF & L:S30A	S102A/S103P/S104F/H111F	156	S30A	323
178	H:APFF & L:S30G	S102A/S103P/S104F/H111F	156	S30G	324
179	H:APFF & L:S30N	S102A/S103P/S104F/H111F	156	S30N	265
180	H:APFF & L:S30V	S102A/S103P/S104F/H111F	156	S30V	325
181	H:APFF & L:S31T	S102A/S103P/S104F/H111F	156	S31T	326
182	H:APFF & L:S31N	S102A/S103P/S104F/H111F	156	S31N	327

183	H:APFF & L:S31K	S102A/S103P/S104F/H111F	156	S31K	266
184	H:APFF & L:S31L	S102A/S103P/S104F/H111F	156	S31L	328
185	H:APFF & L:S31M	S102A/S103P/S104F/H111F	156	S31M	329
186	H:APFF & L:S31F	S102A/S103P/S104F/H111F	156	S31F	330
187	H:APFF & L:S31I	S102A/S103P/S104F/H111F	156	S31I	331
188	H:APFF & L:S31V	S102A/S103P/S104F/H111F	156	S31V	332
189	H:APFF & L:S31H	S102A/S103P/S104F/H111F	156	S31H	333
190	H:APFF & L:S31A	S102A/S103P/S104F/H111F	156	S31A	334
191	H:APFF & L:S31P	S102A/S103P/S104F/H111F	156	S31P	335
192	H:APFF & L:S31D	S102A/S103P/S104F/H111F	156	S31D	336
193	H:APFF & L:S31R	S102A/S103P/S104F/H111F	156	S31R	337
194	H:APFF & L:S31Y	S102A/S103P/S104F/H111F	156	S31Y	338
195	H:APFF & L:S31Q	S102A/S103P/S104F/H111F	156	S31Q	339
196	H:APFF & L:S31E	S102A/S103P/S104F/H111F	156	S31E	340
197	H:APFF & L:S31G	S102A/S103P/S104F/H111F	156	S31G	341
198	H:APFF & L:PNK	S102A/S103P/S104F/H111F	156	S28P/S30N/S31K	342
199	H:APFF & L:NDH	S102A/S103P/S104F/H111F	156	S28N/S30D/S31H	343
200	H:APFF G56A & L:NDH	S102A/S103P/S104F/H111F G56A	197	S28N/S30D/S31H	343
201	H:APFF S54A & L:NDH	S102A/S103P/S104F/H111F S54A	195	S28N/S30D/S31H	343
202	H:APFF & L:	S102A/S103P/S104F/H111F	156	D50A	344
203	H:APFF & L:D50A	S102A/S103P/S104F/H111F	156	A51T	345
204	H:APFF & L:S52A	S102A/S103P/S104F/H111F	156	S52A	346
205	H:APFF & L:N53A	S102A/S103P/S104F/H111F	156	N53A	347
206	H:APFF & L:R54A	S102A/S103P/S104F/H111F	156	R54A	348
207	H:APFF & L:A55T	S102A/S103P/S104F/H111F	156	A55T	349
208	H:APFF & L:T56A	S102A/S103P/S104F/H111F	156	T56A	350
209	H:APFF & L:NDH S52L	S102A/S103P/S104F/H111F	156	S28N/S30D/S31H S52L	351
210	H:APFF & L:NDH S52T	S102A/S103P/S104F/H111F	156	S28N/S30D/S31H S52T	352
211	H:APFF & L:NDH S52R	S102A/S103P/S104F/H111F	156	S28N/S30D/S31H S52R	353
212	H:APFF & L:NDH S52W	S102A/S103P/S104F/H111F	156	S28N/S30D/S31H S52W	354
213	H:APFF & L:NDH S52N	S102A/S103P/S104F/H111F	156	S28N/S30D/S31H S52N	355
214	H:APFF & L:NDH S52P	S102A/S103P/S104F/H111F	156	S28N/S30D/S31H S52P	356
215	H:APFF & L:NDH S52M	S102A/S103P/S104F/H111F	156	S28N/S30D/S31H S52M	357
216	H:APFF & L:NDH N53E	S102A/S103P/S104F/H111F	156	S28N/S30D/S31H N53E	358
217	H:APFF & L:NDH N53G	S102A/S103P/S104F/H111F	156	S28N/S30D/S31H N53G	359
218	H:APFF & L:NDH N53M	S102A/S103P/S104F/H111F	156	S28N/S30D/S31H N53M	360
219	H:APFF & L:NDH N53C	S102A/S103P/S104F/H111F	156	S28N/S30D/S31H N53C	361
220	H:APFF & L:NDH N53H	S102A/S103P/S104F/H111F	156	S28N/S30D/S31H N53H	362
221	H:APFF & L:NDH N53P	S102A/S103P/S104F/H111F	156	S28N/S30D/S31H N53P	363
222	H:APFF & L:NDH	S102A/S103P/S104F/H111F	156	S28N/S30D/S31H	364

	N53A			N53A	
223	H:APFF & L:NDH A55R	S102A/S103P/S104F/H111F	156	S28N/S30D/S31H A55R	365
224	H:APFF & L:NDH A55C	S102A/S103P/S104F/H111F	156	S28N/S30D/S31H A55C	366
225	H:APFF & L:NDH A55S	S102A/S103P/S104F/H111F	156	S28N/S30D/S31H A55S	367
226	H:APFF & L:NDH A55G	S102A/S103P/S104F/H111F	156	S28N/S30D/S31H A55G	368
227	H:APFF LTH & L:NDH	S102A/S103P/S104F/H111F N52L/S54T/G56H	156	S28N/S30D/S31H	343
228	H:APFF LTH & L:NDH LG	S102A/S103P/S104F/H111F N52L/S54T/G56H	156	S28N/S30D/S31H S52L/A55G	369
229	H:APFF LTH & L:NDH LS	S102A/S103P/S104F/H111F N52L/S54T/G56H	156	S28N/S30D/S31H S52L/A55S	370
230	H:APFF ALTH & L:NDH	S102A/S103P/S104F/H111F I51A/N52L/S54T/G56H	156	S28N/S30D/S31H	343
231	H:APFF ALTH & L:NDH LG	S102A/S103P/S104F/H111F I51A/N52L/S54T/G56H	156	S28N/S30D/S31H S52L/A55G	369
232	H:APFF ALTH & L:NDH LS	S102A/S103P/S104F/H111F I51A/N52L/S54T/G56H	156	S28N/S30D/S31H S52L/A55S	370
233	H:APFF VLTH & L:NDH	S102A/S103P/S104F/H111F I51V/N52L/S54T/G56H	156	S28N/S30D/S31H	343
234	H:APFF VLTH & L:NDH LG	S102A/S103P/S104F/H111F I51V/N52L/S54T/G56H	156	S28N/S30D/S31H S52L/A55G	369
235	H:APFF VLTH & L:NDH LS	S102A/S103P/S104F/H111F I51V/N52L/S54T/G56H	156	S28N/S30D/S31H S52L/A55S	370
236	H:APFF & L:S76L	S102A/S103P/S104F/H111F	156	S76L	371
237	H:APFF & L:S76T	S102A/S103P/S104F/H111F	156	S76T	372
238	H:APFF & L:S76G	S102A/S103P/S104F/H111F	156	S76G	373
239	H:APFF & L:S76A	S102A/S103P/S104F/H111F	156	S76A	374
240	H:APFF & L:S76Y	S102A/S103P/S104F/H111F	156	S76Y	375
241	H:APFF & L:F62L	S102A/S103P/S104F/H111F	156	F62L	376
242	H:APFF & L:S76E	S102A/S103P/S104F/H111F	156	S76E	377
243	H:APFF & L:S76Q	S102A/S103P/S104F/H111F	156	S76Q	378
244	H:APFF & L:S76P	S102A/S103P/S104F/H111F	156	S76P	379
245	H:APFF & L:S76N	S102A/S103P/S104F/H111F	156	S76N	380

Table 31. VH5-51_IGHD5-18*01>3_IGHJ4*01 & V3-4_IGLJ1*01 DLL4 antibodies

	nickname	Heavy Chain	SEQ ID NO	Light Chain	SEQ ID NO
1		wildtype	132	wildtype	142
2	H:G100K & L:wt	G100K	381	wildtype	142
3	H:G100R & L:wt	G100R	382	wildtype	142
4	H:G104T & L:wt	G104T	383	wildtype	142
5	H:KT & L:wt	G100K/G104T	384	wildtype	142
6	H:R99A & L:wt	R99A	385	wildtype	142
7	H:G100A & L:wt	G100A	386	wildtype	142
8	H:Y101A & L:wt	Y101A	387	wildtype	142
9	H:S102A & L:wt	S102A	388	wildtype	142
10	H:Y103A & L:wt	Y103A	389	wildtype	142
11	H:G104A & L:wt	G104A	390	wildtype	142
12	H:Y105A & L:wt	Y105A	391	wildtype	142

13	H:D106A & L:wt	D106A	392	wildtype	142
14	H:G100L & L:wt	G100L	393	wildtype	142
15	II:G100D & L:wt	G100D	394	wildtype	142
16	H:G100T & L:wt	G100T	395	wildtype	142
17	H:G104D & L:wt	G104D	396	wildtype	142
18	H:G104L & L:wt	G104L	397	wildtype	142
19	H:G104P & L:wt	G104P	398	wildtype	142
20	H:G104R & L:wt	G104R	399	wildtype	142
21	H:G104M & L:wt	G104M	400	wildtype	142
22	H:G104K & L:wt	G104K	401	wildtype	142
23	H:G104S & L:wt	G104S	402	wildtype	142
24	H:RY & L:wt	G104R/Y101H	403	wildtype	142
25	H:KT G24A & L:wt	G100K/G104T G24A	404	wildtype	142
26	H:KT I34A & L:wt	G100K/G104T I34A	405	wildtype	142
27	H:KT G35A & L:wt	G100K/G104T G35A	406	wildtype	142
28	H:KT S28A & L:wt	G100K/G104T S28A	407	wildtype	142
29	H:KT F29A & L:wt	G100K/G104T F29A	408	wildtype	142
30	H:KT T30A & L:wt	G100K/G104T T30A	409	wildtype	142
31	H:KT W33A & L:wt	G100K/G104T W33A	410	wildtype	142
32	H:KT G24L & L:wt	G100K/G104T G24L	411	wildtype	142
33	H:KT G24S & L:wt	G100K/G104T G24S	412	wildtype	142
34	H:KT G24R & L:wt	G100K/G104T G24R	413	wildtype	142
35	H:KT S28R & L:wt	G100K/G104T S28R	414	wildtype	142
36	H:KT S28K & L:wt	G100K/G104T S28K	415	wildtype	142
37	H:KT S28N & L:wt	G100K/G104T S28N	416	wildtype	142
38	H:KT G35T & L:wt	G100K/G104T G35T	417	wildtype	142
39	H:KT G35A & L:wt	G100K/G104T G35A	418	wildtype	142
40	H:KT G35V & L:wt	G100K/G104T G35V	419	wildtype	142
41	II:KT Y27A & L:wt	G100K/G104T Y27A	894	wildtype	142
42	H:KT S31A & L:wt	G100K/G104T S31A	895	wildtype	142
43	H:KT S31A & L:wt	G100K/G104T Y32A	896	wildtype	142
44	H:KT LRV & L:wt	G100K/G104T G24L/S28R/G35V	420	wildtype	142
45	H:KT D57A & L:wt	G100K/G104T D57A	421	wildtype	142
46	H:KT I50A & L:wt	G100K/G104T I50A	422	wildtype	142
47	H:KT I51A & L:wt	G100K/G104T I51A	423	wildtype	142
48	H:KT Y52A & L:wt	G100K/G104T Y52A	424	wildtype	142
49	H:KT P53A & L:wt	G100K/G104T P53A	425	wildtype	142
50	II:KT D55A & L:wt	G100K/G104T D55A	426	wildtype	142
51	H:KT T58D & L:wt	G100K/G104T T58D	427	wildtype	142
52	H:KT T58A & L:wt	G100K/G104T T58A	428	wildtype	142
53	H:KT S56G & L:wt	G100K/G104T S56G	429	wildtype	142
54	H:KT S84V & L:wt	G100K/G104T S84V	430	wildtype	142
55	H:KT G54A & L:wt	G100K/G104T G54A	897	wildtype	142
56	H:KT S56A & L:wt	G100K/G104T S56A	898	wildtype	142
57	H:KT S84L & L:wt	G100K/G104T S84L	431	wildtype	142
58	H:KT D109A & L:wt	G100K/G104T D109A	432	wildtype	142
59	H:KT & L:V91A	G100K/G104T	384	V91A	439
60	H:KT & L:L92A	G100K/G104T	384	L92A	440
61	H:KT & L:Y93A	G100K/G104T	384	Y93A	441
62	H:KT & L:M94A	G100K/G104T	384	M94A	442
63	H:KT & L:G95A	G100K/G104T	384	G95A	443
64	H:KT & L:G97A	G100K/G104T	384	G97A	444
65	H:KT & L:S96A	G100K/G104T	384	S96A	445
66	H:KT & L:I98A	G100K/G104T	384	I98A	446

67	H:KT & L:S99A	G100K/G104T	384	S99A	447
68	H:KT & L:V91P	G100K/G104T	384	V91P	448
69	H:KT & L:V91T	G100K/G104T	384	V91T	449
70	H:KT & L:V91S	G100K/G104T	384	V91S	450
71	H:KT & L:V91L	G100K/G104T	384	V91L	451
72	H:KT & L:V91R	G100K/G104T	384	V91R	452
73	H:KT & L:V91C	G100K/G104T	384	V91C	453
74	H:KT & L:V91E	G100K/G104T	384	V91E	454
75	H:KT & L:V91W	G100K/G104T	384	V91W	455
76	H:KT & L:V91N	G100K/G104T	384	V91N	456
77	H:KT & L:V91I	G100K/G104T	384	V91I	457
78	H:KT & L:V91G	G100K/G104T	384	V91G	458
79	H:KT & L:V91H	G100K/G104T	384	V91H	459
80	H:KT & L:M94E	G100K/G104T	384	M94E	460
81	H:KT & L:M94S	G100K/G104T	384	M94S	461
82	H:KT & L:M94G	G100K/G104T	384	M94G	462
83	H:KT & L:M94L	G100K/G104T	384	M94L	463
84	H:KT & L:M94P	G100K/G104T	384	M94P	464
85	H:KT & L:M94V	G100K/G104T	384	M94V	465
86	H:KT & L:M94D	G100K/G104T	384	M94D	466
87	H:KT & L:M94R	G100K/G104T	384	M94R	467
88	H:KT & L:M94N	G100K/G104T	384	M94N	468
89	H:KT & L:M94T	G100K/G104T	384	M94T	469
90	H:KT & L:M94F	G100K/G104T	384	M94F	470
91	H:KT & L:S96W	G100K/G104T	384	S96W	471
92	H:KT & L:S96G	G100K/G104T	384	S96G	472
93	H:KT & L:S96P	G100K/G104T	384	S96P	473
94	H:KT & L:S96R	G100K/G104T	384	S96R	474
95	H:KT & L:S96L	G100K/G104T	384	S96L	475
96	H:KT & L:S96M	G100K/G104T	384	S96M	476
97	H:KT & L:S96E	G100K/G104T	384	S96E	477
98	H:KT & L:S96V	G100K/G104T	384	S96V	478
99	H:KT & L:RM	G100K/G104T	384	M94R/S96M	479
100	H:KT S28R & L:RM	G100K/G104T S28R	414	M94R/S96M	479
101	H:KT LRV & L:RM	G100K/G104T G24L/S28R/G35V	420	M94R/S96M	479
102	H:KT TRV & L:RM	G100K/G104T G24T/S28R/G35V	433	M94R/S96M	479
103	H:KT ARV & L:RM	G100K/G104T G24A/S28R/G35V	434	M94R/S96M	479
104	H:KT TRV & L:wt	G100K/G104T G24T/S28R/G35V	433	wildtype	142
105	H:KT ARV & L:wt	G100K/G104T G24A/S28R/G35V	434	wildtype	142
106	H:KT & L:L24A	G100K/G104T	385	L24A	480
107	H:KT & L:S26A	G100K/G104T	385	S26A	481
108	H:KT & L:G27A	G100K/G104T	385	G27A	482
109	H:KT & L:S28A	G100K/G104T	385	S28A	483
110	H:KT & L:V29A	G100K/G104T	385	V29A	484
111	H:KT & L:S30A	G100K/G104T	385	S30A	485
112	H:KT & L:T31A	G100K/G104T	385	T31A	486
113	H:KT & L:S32A	G100K/G104T	385	S32A	487
114	H:KT & L:Y33A	G100K/G104T	385	Y33A	488
115	H:KT & L:Y34A	G100K/G104T	385	Y34A	489
116	H:KT & L:P35A	G100K/G104T	385	P35A	490

117	H:KT & L:S36A	G100K/G104T	385	S36A	491
118	H:KT & L:G23A	G100K/G104T	385	G23A	492
119	H:KT & L:S25A	G100K/G104T	385	S25A	493
120	H:KT & L:G23R	G100K/G104T	385	G23R	494
121	H:KT & L:G23L	G100K/G104T	385	G23L	495
122	H:KT & L:S52A	G100K/G104T	385	S52A	496
123	H:KT & L:T53A	G100K/G104T	385	T53A	497
124	H:KT & L:N54A	G100K/G104T	385	N54A	498
125	H:KT & L:T55A	G100K/G104T	385	T55A	499
126	H:KT & L:R56A	G100K/G104T	385	R56A	500
127	H:KT & L:S57A	G100K/G104T	385	S57A	501
128	H:KT & L:S58A	G100K/G104T	385	S58A	502
129	H:KT & L:S52G	G100K/G104T	385	S52G	503
130	H:KT & L:S52C	G100K/G104T	385	S52C	504
131	H:KT & L:S52R	G100K/G104T	385	S52R	505
132	H:KT & L:R56I	G100K/G104T	385	R56I	506
133	H:KT & L:R56Y	G100K/G104T	385	R56Y	507
134	H:KT & L:R56D	G100K/G104T	385	R56D	508
135	H:KT & L:R56G	G100K/G104T	385	R56G	509
136	H:KT & L:R56S	G100K/G104T	385	R56S	510
137	H:KT & L:T78S	G100K/G104T	385	T78S	511
138	H:KT & L:T78E	G100K/G104T	385	T78E	512
139	H:KT & L:T78Y	G100K/G104T	385	T78Y	513
140	H:KT & L:T78M	G100K/G104T	385	T78M	514
141	H:KT & L:T78L	G100K/G104T	385	T78L	515
142	H:KT & L:T78K	G100K/G104T	385	T78K	516
143	H:KT & L:T78V	G100K/G104T	385	T78V	517
144	H:KT & L:AK	G100K/G104T	385	G23A/N175K	518
145	H:KT & L:AT	G100K/G104T	385	S25A/A116T	519
146	H:KT TRV & L:V91A	G100K/G104T G24T/S28R/G35V	433	V91A	439
147	H:KT TRV & L:L92A	G100K/G104T G24T/S28R/G35V	433	L92A	440
148	H:KT TRV & L:Y93A	G100K/G104T G24T/S28R/G35V	433	Y93A	441
149	H:KT TRV & L:M94A	G100K/G104T G24T/S28R/G35V	433	M94A	442
150	H:KT TRV & L:G95A	G100K/G104T G24T/S28R/G35V	433	G95A	443
151	H:KT TRV & L:S96A	G100K/G104T G24T/S28R/G35V	433	S96A	444
152	H:KT TRV & L:G67A	G100K/G104T G24T/S28R/G35V	433	G97A	445
153	H:KT TRV & L:I98A	G100K/G104T G24T/S28R/G35V	433	I98A	446
154	H:KT TRV & L:S99A	G100K/G104T G24T/S28R/G35V	433	S99A	447
155	H:KT TRV & L:T78S	G100K/G104T G24T/S28R/G35V	433	T78S	511
156	H:KT TRV & L:T78E	G100K/G104T G24T/S28R/G35V	433	T78E	512
157	H:KT TRV & L:T78L	G100K/G104T G24T/S28R/G35V	433	T78L	515
158	H:KT TRV & L:T78K	G100K/G104T G24T/S28R/G35V	433	T78K	516

159	H:KT TRV & L:T78V	G100K/G104T G24T/S28R/G35V	433	T78V	517
160	H:KT TRV & L:G23A	G100K/G104T G24T/S28R/G35V	433	G23A	492
161	H:KT TRV & L:L24A	G100K/G104T G24T/S28R/G35V	433	L24A	480
162	H:KT TRV & L:S25A	G100K/G104T G24T/S28R/G35V	433	S25A	493
163	H:KT TRV & L:S26A	G100K/G104T G24T/S28R/G35V	433	S26A	481
164	H:KT TRV & L:G27A	G100K/G104T G24T/S28R/G35V	433	G27A	482
165	H:KT TRV & L:S28A	G100K/G104T G24T/S28R/G35V	433	S28A	483
166	H:KT TRV & L:V29A	G100K/G104T G24T/S28R/G35V	433	V29A	484
167	H:KT TRV & L:S30A	G100K/G104T G24T/S28R/G35V	433	S30A	485
168	H:KT TRV & L:T31A	G100K/G104T G24T/S28R/G35V	433	T31A	486
169	H:KT TRV & L:S32A	G100K/G104T G24T/S28R/G35V	433	S32A	487
170	H:KT TRV & L:Y33A	G100K/G104T G24T/S28R/G35V	433	Y33A	488
171	H:KT TRV & L:Y34A	G100K/G104T G24T/S28R/G35V	433	Y34A	489
172	H:KT TRV & L:P35A	G100K/G104T G24T/S28R/G35V	433	P35A	490
173	H:KT TRV & L:S36A	G100K/G104T G24T/S28R/G35V	433	S36A	491
174	H:KT TRV & L:S52A	G100K/G104T G24T/S28R/G35V	433	S52A	496
175	H:KT TRV & L:T53A	G100K/G104T G24T/S28R/G35V	433	T53A	497
176	H:KT TRV & L:N54A	G100K/G104T G24T/S28R/G35V	433	N54A	498
177	H:KT TRV & L:T55A	G100K/G104T G24T/S28R/G35V	433	T55A	499
178	H:KT TRV & L:R56A	G100K/G104T G24T/S28R/G35V	433	R56A	500
179	H:KT TRV & L:S57A	G100K/G104T G24T/S28R/G35V	433	S57A	501
180	H:KT TRV & L:S58A	G100K/G104T G24T/S28R/G35V	433	S58A	502
181	H:KT TRV & L:V91L	G100K/G104T G24T/S28R/G35V	433	V91L	451
182	H:KT TRV & L:V91P	G100K/G104T G24T/S28R/G35V	433	V91P	447
183	H:KT TRV & L:V91T	G100K/G104T G24T/S28R/G35V	433	V91T	449
184	H:KT TRV & L:V91S	G100K/G104T G24T/S28R/G35V	433	V91S	450
185	H:KT TRV & L:V91R	G100K/G104T G24T/S28R/G35V	433	V91R	452
186	H:KT TRV & L:V91C	G100K/G104T G24T/S28R/G35V	433	V91C	453

187	H:KT TRV & L:V91E	G100K/G104T G24T/S28R/G35V	433	V91E	454
188	H:KT TRV & L:V91W	G100K/G104T G24T/S28R/G35V	433	V91W	455
189	H:KT TRV & L:V91N	G100K/G104T G24T/S28R/G35V	433	V91N	456
190	H:KT TRV & L:V91I	G100K/G104T G24T/S28R/G35V	433	V91I	457
191	H:KT TRV & L:V91G	G100K/G104T G24T/S28R/G35V	433	V91G	458
192	H:KT TRV & L:V91H	G100K/G104T G24T/S28R/G35V	433	V91H	459
193	H:KT TRV & L:M94T	G100K/G104T G24T/S28R/G35V	433	M94T	469
194	H:KT TRV & L:M94E	G100K/G104T G24T/S28R/G35V	433	M94E	460
195	H:KT TRV & L:M94S	G100K/G104T G24T/S28R/G35V	433	M94S	461
196	H:KT TRV & L:M94G	G100K/G104T G24T/S28R/G35V	433	M94G	462
197	H:KT TRV & L:M94L	G100K/G104T G24T/S28R/G35V	433	M94L	463
198	H:KT TRV & L:M94P	G100K/G104T G24T/S28R/G35V	433	M94P	464
199	H:KT TRV & L:M94V	G100K/G104T G24T/S28R/G35V	433	M94V	465
200	H:KT TRV & L:M94D	G100K/G104T G24T/S28R/G35V	433	M94D	466
201	H:KT TRV & L:M94R	G100K/G104T G24T/S28R/G35V	433	M94R	467
202	H:KT TRV & L:M94N	G100K/G104T G24T/S28R/G35V	433	M94N	468
203	H:KT TRV & L:M94F	G100K/G104T G24T/S28R/G35V	433	M94F	470
204	H:KT TRV & L:S96W	G100K/G104T G24T/S28R/G35V	433	S96W	471
205	H:KT TRV & L:S96G	G100K/G104T G24T/S28R/G35V	433	S96G	472
206	H:KT TRV & L:S96P	G100K/G104T G24T/S28R/G35V	433	S96P	473
207	H:KT TRV & L:S96R	G100K/G104T G24T/S28R/G35V	433	S96R	474
208	H:KT TRV & L:S96L	G100K/G104T G24T/S28R/G35V	433	S96L	475
209	H:KT TRV & L:S96M	G100K/G104T G24T/S28R/G35V	433	S96M	476
210	H:KT TRV & L:S96E	G100K/G104T G24T/S28R/G35V	433	S96E	477
211	H:KT TRV & L:S96V	G100K/G104T G24T/S28R/G35V	433	S96V	478
212	H:KT TRV & L:LP S52F	G100K/G104T G24T/S28R/G35V	433	V91L/S96P S52F	520
213	H:KT TRV & L:LP S52L	G100K/G104T G24T/S28R/G35V	433	V91L/S96P S52L	521
214	H:KT TRV & L:LP S52I	G100K/G104T G24T/S28R/G35V	433	V91L/S96P S52I	522

215	H:KT TRV & L:LP S52M	G100K/G104T G24T/S28R/G35V	433	V91L/S96P S52M	523
216	H:KT TRV & L:LP S52V	G100K/G104T G24T/S28R/G35V	433	V91L/S96P S52V	524
217	H:KT TRV & L:LP S52P	G100K/G104T G24T/S28R/G35V	433	V91L/S96P S52P	525
218	H:KT TRV & L:LP S52T	G100K/G104T G24T/S28R/G35V	433	V91L/S96P S52T	526
219	H:KT TRV & L:LP S52Y	G100K/G104T G24T/S28R/G35V	433	V91L/S96P S52Y	527
220	H:KT TRV & L:LP S52H	G100K/G104T G24T/S28R/G35V	433	V91L/S96P S52H	528
221	H:KT TRV & L:LP S52Q	G100K/G104T G24T/S28R/G35V	433	V91L/S96P S52Q	529
222	H:KT TRV & L:LP S52N	G100K/G104T G24T/S28R/G35V	433	V91L/S96P S52N	530
223	H:KT TRV & L:LP S52K	G100K/G104T G24T/S28R/G35V	433	V91L/S96P S52K	531
224	H:KT TRV & L:LP S52D	G100K/G104T G24T/S28R/G35V	433	V91L/S96P S52D	532
225	H:KT TRV & L:LP S52E	G100K/G104T G24T/S28R/G35V	433	V91L/S96P S52E	533
226	H:KT TRV & L:LP S52W	G100K/G104T G24T/S28R/G35V	433	V91L/S96P S52W	534
227	H:KT TRV & L:LP S52R	G100K/G104T G24T/S28R/G35V	433	V91L/S96P S52R	535
228	H:KT TRV & L:LP S52G	G100K/G104T G24T/S28R/G35V	433	V91L/S96P S52G	536
229	H:KT TRV & L:LP	G100K/G104T G24T/S28R/G35V	433	V91L/S96P	537
230	H:KT TRV & L:LP T53F	G100K/G104T G24T/S28R/G35V	433	V91L/S96P T53F	538
231	H:KT TRV & L:LP T53L	G100K/G104T G24T/S28R/G35V	433	V91L/S96P T53L	539
232	H:KT TRV & L:LP T53I	G100K/G104T G24T/S28R/G35V	433	V91L/S96P T53I	540
233	H:KT TRV & L:LP T53M	G100K/G104T G24T/S28R/G35V	433	V91L/S96P T53M	541
234	H:KT TRV & L:LP T53V	G100K/G104T G24T/S28R/G35V	433	V91L/S96P T53V	542
235	H:KT TRV & L:LP T53S	G100K/G104T G24T/S28R/G35V	433	V91L/S96P T53S	543
236	H:KT TRV & L:LP T53P	G100K/G104T G24T/S28R/G35V	433	V91L/S96P T53P	544
237	H:KT TRV & L:LP T53Y	G100K/G104T G24T/S28R/G35V	433	V91L/S96P T53Y	545
238	H:KT TRV & L:LP T53H	G100K/G104T G24T/S28R/G35V	433	V91L/S96P T53H	546
239	H:KT TRV & L:LP T53Q	G100K/G104T G24T/S28R/G35V	433	V91L/S96P T53Q	547
240	H:KT TRV & L:LP T53N	G100K/G104T G24T/S28R/G35V	433	V91L/S96P T53N	548
241	H:KT TRV & L:LP T53K	G100K/G104T G24T/S28R/G35V	433	V91L/S96P T53K	549
242	H:KT TRV & L:LP T53D	G100K/G104T G24T/S28R/G35V	433	V91L/S96P T53D	550

243	H:KT TRV & L:LP T53E	G100K/G104T G24T/S28R/G35V	433	V91L/S96P T53E	551
244	H:KT TRV & L:LP T53W	G100K/G104T G24T/S28R/G35V	433	V91L/S96P T53W	552
245	H:KT TRV & L:LP T53R	G100K/G104T G24T/S28R/G35V	433	V91L/S96P T53R	553
246	H:KT TRV & L:LP T53G	G100K/G104T G24T/S28R/G35V	433	V91L/S96P T53G	554
247	H:KT TRV & L:LP S57F	G100K/G104T G24T/S28R/G35V	433	V91L/S96P S57F	555
248	H:KT TRV & L:LP S57L	G100K/G104T G24T/S28R/G35V	433	V91L/S96P S57L	556
249	H:KT TRV & L:LP S57I	G100K/G104T G24T/S28R/G35V	433	V91L/S96P S57I	557
250	H:KT TRV & L:LP S57M	G100K/G104T G24T/S28R/G35V	433	V91L/S96P S57M	558
251	H:KT TRV & L:LP S57V	G100K/G104T G24T/S28R/G35V	433	V91L/S96P S57V	559
252	H:KT TRV & L:LP S57P	G100K/G104T G24T/S28R/G35V	433	V91L/S96P S57P	560
253	H:KT TRV & L:LP S57T	G100K/G104T G24T/S28R/G35V	433	V91L/S96P S57T	561
254	H:KT TRV & L:LP S57Y	G100K/G104T G24T/S28R/G35V	433	V91L/S96P S57Y	562
255	H:KT TRV & L:LP S57H	G100K/G104T G24T/S28R/G35V	433	V91L/S96P S57H	563
256	H:KT TRV & L:LP S57Q	G100K/G104T G24T/S28R/G35V	433	V91L/S96P S57Q	564
257	H:KT TRV & L:LP S57N	G100K/G104T G24T/S28R/G35V	433	V91L/S96P S57N	565
258	H:KT TRV & L:LP S57K	G100K/G104T G24T/S28R/G35V	433	V91L/S96P S57K	566
259	H:KT TRV & L:LP S57D	G100K/G104T G24T/S28R/G35V	433	V91L/S96P S57D	567
260	H:KT TRV & L:LP S57E	G100K/G104T G24T/S28R/G35V	433	V91L/S96P S57E	568
261	H:KT TRV & L:LP S57W	G100K/G104T G24T/S28R/G35V	433	V91L/S96P S57W	569
262	H:KT TRV & L:LP S57R	G100K/G104T G24T/S28R/G35V	433	V91L/S96P S57R	570
263	H:KT TRV & L:LP S57G	G100K/G104T G24T/S28R/G35V	433	V91L/S96P S57G	571
264	H:KT TRV Y105H & L:wt	G100K/G104T G24T/S28R/G35V Y105H	435	wildtype	142
265	H:KT TRV Y105N & L:wt	G100K/G104T G24T/S28R/G35V Y105N	436	wildtype	142
266	H:KT TRV Y107F & L:wt	G100K/G104T G24T/S28R/G35V Y107F	437	wildtype	142
267	H:KT TRV D109Q & L:wt	G100K/G104T G24T/S28R/G35V D109Q	438	wildtype	142

EXAMPLE 6

Surface Plasmon Resonance

In this example, the binding affinities of selected anti-DLL4 Fabs to recombinant human DLL4 (hDLL4, Cat# 1506-D4/CF, R&D Systems) were analyzed using Surface Plasmon Resonance (SPR) (Biosensor Tools, Salt Lake City, UT). The Fabs analyzed include germline-derived antibodies and germline-modified DLL4 antibodies. Recombinant hDLL4 was immobilized on a SPR chip using amine coupling at three different surface densities. The Fabs were serially diluted 3-fold, with an initial concentration of 1 μM. Binding studies were run on a ProteOn system using a GLM sensor chip in 10 mM HEPES, pH 7.4, 150 mM NaCl, 0.01% Tween-20, and 0.1 mg/ml BSA at 25 °C. The response data from each surface was globally fit to determine the binding constants.

The results are shown in Table 32 below. Tables 32 sets forth the Fab, the k_a ($M^{-1}s^{-1}$), the k_d (s^{-1}), and the K_D (nM) and standard deviation.

Table 32. Binding affinity of DLL4 Fabs

Heavy Chain	Light Chain	k_a ($x10^5$) ($M^{-1}s^{-1}$)	k_d (s^{-1})	K_D (nM)
VH5-51_IGHD5-18*01>3_IGHJ4*01	V3-4_IGLJ1*01	n/a	n/a	4800 (±200)
VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T (H:KT)	V3-4_IGLJ1*01	0.645 (±0.92)	0.023 (±0.004)	355 (±7)
VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T S28R (H:KT S28R)	V3-4_IGLJ1*01	7.4 (±0.6)	0.0845 (±0.0050)	114 (±6)
VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T G24T/S28R/G35V (H:KT TRV)	V3-4_IGLJ1*01	20.90 (±6.24)	0.0717 (±0.00351)	36.2 (±8.5)
VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T G24T/S28R/G35V (H:KT TRV)	V3-4_IGLJ1*01 M94R/S96M (L:RM)	25.30 (±4.16)	0.101 (±0.0153)	40.3 (±9.3)
VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T G24T/S28R/G35V (KT TRV)	V3-4_IGLJ1*01 V91L/S96P (LP)	110	0.036	3.3
VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T G24T/S28R/G35V (KT TRV)	V3-4_IGLJ1*01 V91L/S96P S52G (LP S52G)	29.6	0.0147	5.0
VH1-46_IGHD6-6*01_IGHJ1*01	L6_IGKJ1*01	1.63 (±3)	0.101 (±2)	730 (±130)
VH1-46_IGHD6-6*01_IGHJ1*01 S104F	L6_IGKJ1*01	5.0 (±0.8)	0.19 (±0.01)	380 (±60)
VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F (H:APF)	L6_IGKJ1*01	4.05 (±0.05)	0.0492 (±0.0004)	122 (±1)
VH1-46_IGHD6-6*01_IGHJ1*01	L6_IGKJ1*01	4.25	0.0300	70.6

S102A/S103P/S104F/H111F (H:APFF)		(±0.04)	(±0.0002)	(±0.7)
VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111Y (H:APFY)	L6_IGKJ1*01	3.40 (±0.03)	0.0317 (±0.0002)	93.1 (±0.9)
VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F (APF)	L6_IGKJ1*01 S31K	3.50 (±0.05)	0.0392 (0.0004)	112 (±2)
VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F G56H (H:APFF G56H)	L6_IGKJ1*01	3.51 (±1.84)	0.0101 (±0.000716)	32.7 (±11.6)
VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F (APFF)	L6_IGKJ1*01 S28N/S30D/S31H (NDH)	4.44	0.0689	*155.2 and 14
VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F I51V/N52L/S54T/G56H (H:APFF VLTH)	L6_IGKJ1*01 S28N/S30D/S31H (L:NDH)	4.30 (±1.45)	0.00113 (±0.000138)	2.7 (±0.6)
VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F I51V/N52L/S54T/G56H (H:APFF VLTH)	L6_IGKJ1*01 S28N/S30D/S31H S52L/A55S (L:NDH LS)	6.84 (±2.51)	0.00109 (±0.000106)	1.7 (±0.5)
VH6-1_IGHD3-3*01_IGHJ4*01	V4-3_IGLJ4*01	n/a	n/a	38000 (±4000)
VH1-46_IGHD3-10*01_IGHJ4*01	L12_IGKJ1*01	5 (±1)	0.29 (±2)	500 (±100)

$K_D=k_d/k_a$; *Fab Fab VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F & L6_IGKJ1*01 S28N/S30D/S31H displays 2-site binding: 89% with Kd of 155.2 nM and 10% with Kd of 14 nM.

Binding affinity of anti-DLL4 Fab H:KT TRV & L:RM and anti-DLL4 Fab H:APFF VLTH & L:NDH LS to recombinant mouse DLL4 (mDLL4, Cat# 1389-D4-050/CF, R&D Systems) were analyzed using SPR as described above for human DLL4. The results (see Table 33 below) showed that no binding could be detected on mouse surfaces for anti-DLL4 Fab H:KT TRV & L:RM. In contrast, anti-DLL4 Fab H:APFF VLTH & L:NDH LS showed binding to mouse DLL4 with an affinity of 9.7 (±2.0). Fab H:APFF VLTH & L:NDH LS, however, binds hDLL4 with 5-fold greater affinity as compared to mouse DLL4 (see Table 32 above).

Table 33. Fab VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F I51V/N52L/S54T/G56H (H:APFF VLTH) & L6_IGKJ1*01 S28N/S30D/S31H S52L/A55S (L:NDH LS) binding to mDLL4

mDLL4	k_a ($M^{-1}s^{-1}$)	k_d (s^{-1})	K_D (nM)
Surface 1	2.87E+05	2.10E-03	7.3
Surface 1	1.65E+05	0.00178	10.8
Surface 1	1.73E+05	1.88E-03	10.9
Average	**2.08E+05**	**1.92E-03**	**9.7**
Standard Deviation	6.81E+04	1.63E-04	2.0

EXAMPLE 7

ELISA Binding Assay

In this example, an ELISA binding assay was used to assess the dose-dependent binding of Fab antibodies to recombinant human DLL4 and recombinant mouse DLL4.

A. Assay

Briefly, 50µl of a 0.5 µg/ml solution of hDLL4 or mDLL4 in 100 mM $NaHCO_3$, pH 9 was added to each well of a 96-well Costar plate (Cat # 3370, Corning Inc.) and allowed to incubate for 1 hour at room temperature. The plate was blocked by adding 1% BSA in Tris-buffered Saline Tween (TBST) and incubating for 1 hour at room temperature followed by washing 2 times with 150 µl TBST. A Fab antibody was serially diluted in 1% BSA in PBS. A 50 µl aliquot of each serial dilution was added, in triplicate, to each well and the plate was incubated for 1 hour at room temperature followed by washing 2 times with TBST. 50 µl of either goat anti-human kappa HRP conjugated secondary antibody (Cat # A7164-1mL, Sigma-Aldrich) or goat anti-human lambda HRP conjugated secondary antibody (Cat # L1645-1ml, Sigma-Aldrich), diluted 1:1000 in 1% BSA in PBS, was added to each well and the plate was incubated for 30 minutes at room temperature followed by washing 3 times with 200 µl TBST. Finally, 50 µl TMB one-component reagent (Cat # TMBW-1000-01, BioFax) was added and allowed to develop for 2 minutes at room temperature. The reaction was immediately halted by the addition of 50 µl 0.5 M H_2S0_4 and the absorbance at 450 nm was measured using an ELISA plate reader.

B. Results

Tables 34-43 below set forth dose dependent binding of various Fabs for binding to DLL4.

Table 34 sets forth the binding of heavy chain mutant Fab H:AFP & L:wt (SEQ ID NOS:155 and 141) as compared to parent Fab VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01 (SEQ ID NOS:131 and 141), at Fab concentrations of 125 nm to 1000 nm. At the tested concentrations, the parent Fab antibody did not show a detectable signal for binding to DLL4. In contrast, the H:APF & L:wt triple mutant had a detectable signal evidencing DLL4 binding in a concentration dependent manner.

Table 34. Binding affinity of triple mutant Fab VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F (H:APF) & L6_IGKJ1*01 as compared to parent Fab VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01				
Fab [nM]	**Parent**	**Blank**	**S102A, S103P, S104F**	**Blank**
1000	0.071	0.060	0.463	0.080
500	0.070	0.069	0.307	0.074
250	0.069	0.064	0.231	0.071
125	0.070	0.066	0.173	0.075

Table 35 sets forth the binding of heavy chain mutants H:APFF LTH, H:APPF ELTH, H:APFF VLTH, H:APFF NLTH, H:APFF TLATH, and H:APFF TV paired with light chain L6_IGKJ1*01 (SEQ ID NO:141), at Fab concentrations of 0.16 nM to 20 nM. Fabs containing heavy chain mutants H:APFF LTH (SEQ ID NO:233), H:APFF ELTH (SEQ ID NO: 238), H:APPF VLTH (SEQ ID NO: 239) and H:APFF NLTH (SEQ ID NO: 244) bind DLL4 with a Kd of approximately between 1 nM and 10 nM. Fabs containing heavy chain mutants H:APFF TLATH (SEQ ID NO: 251) and H:APFF TV (SEQ ID NO: 201) have lower affinity for DLL4 as compared to the other tested Fabs. Heavy chain mutant H:APFF TLATH has an approximate Kd greater than 100 nM and heavy chain mutant H:APFF TV has a Kd between 10 and 100 nM.

Table 35. Heavy chain Fab mutants of VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01 (SEQ ID NO:141) binding to DLL4 by ELISA							
Fab [nM]	**Heavy Chain**	**APFF LTH**	**APFF ELTH**	**APFF VLTH**	**APFF NLTH**	**APFF TLATH**	**APFF I51T/N52V**
	Light Chain	**L6_IGKJ1*01**	**L6_IGKJ1*01**	**L6_IGKJ1*01**	**L6_IGKJ1*01**	**L6_IGKJ1*01**	**L6_IGKJ1*01**
20		2.402	2.290	2.052	1.627	1.109	0.648
10		2.345	2.168	1.854	1.362	0.875	0.506
5		2.477	2.333	2.198	1.751	1.272	0.724
2.5		2.151	1.982	1.656	1.165	0.592	0.358
1.3		0.653	0.402	0.252	0.143	0.078	0.055
0.63		1.367	1.010	0.785	0.419	0.227	0.115
0.31		2.402	2.290	2.052	1.627	1.109	0.648
0.16		2.345	2.168	1.854	1.362	0.875	0.506

Table 36 sets for the binding of heavy chain mutants H:APFF (SEQ ID NO:156), H:APFF G56A (SEQ ID NO:197) and H:APFF S54A (SEQ ID NO:195) paired with light chain L6_IGKJ1*01 (SEQ ID NO:141) and light chain mutant

L:NDH (SEQ ID NO:343), at Fab concentrations of 50 to 100 nM. Fab mutant H:APFF & L:NDH binds DLL4 with 4-fold increased affinity as compared to Fab mutant APFF. The antibody Fab H:APFF G56A & L:NDH resulted in 8-fold greater affinity for binding to DLL4 as compared to the H:APFF & L:wt antibody mutant, and also exhibited increased binding affinity compared to the other antibodies tested. The antibody Fab H:APFF S54A & L:NDH resulted in a slight decrease in binding affinity compared to the H:APFF & L:NDH antibody mutant.

Table 36. Binding affinity of VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01 Fab mutants

Fab [nM]	Heavy Chain	APFF	APFF	APFF G56A	APFF G56A	APFF S54A
	Light Chain	Parent	NDH	Parent	NDH	NDH
100 nM		0.072	0.259	0.338	0.453	0.213
75 nM		0.072	0.268	0.399	0.543	0.212
50 nM		0.060	0.202	0.301	0.366	0.154
0		0.006	0.002	0.002	0.002	0.000

Table 37 sets forth the binding of heavy chain mutant H:APFF (SEQ ID NO:156) paired with light chain mutants L:NDH (SEQ ID NO:343), L:NDH S52L (SEQ ID NO:351), L:NDH S52T (SEQ ID NO:352), L:NDH N53H (SEQ ID NO:363), L:NDH A55S (SEQ ID NO:367) and L:NDH A55G (SEQ ID NO:368), at Fab concentrations of 3.125 nM to 100 nM. Fabs H:APFF& L:NDH S52L, H:APFF & L:NDH A55S and H:APFF & L:NDH A55G had a slightly increased affinity for binding to DLL4 as compared to Fab H:APFF & L:NDH mutant. All of the Fab light chain mutants bind DLL4 within the same range of affinity as Fab H:APFF & L:NDH mutant.

Table 37. Fab VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F (APFF) (SEQ ID NO:156) & L6_IGKJ1*01 S28N/S30D/S31H (NDH) light chain S52, N53 and A55 mutant binding to DLL4 by ELISA

Fab [nM]	H	APFF	APFF	APFF	APFF	APFF	APFF
	L	NDH S52L	NDH S52T	NDH N53H	NDH A55S	NDH A55G	NDH
100		0.791	0.653	0.608	0.858	0.814	0.686
50		0.546	0.490	0.416	0.588	0.510	0.507
25		0.335	0.323	0.238	0.407	0.316	0.310
12.5		0.215	0.215	0.167	0.258	0.198	0.192
6.25		0.142	0.130	0.109	0.154	0.125	0.125
3.125		0.095	0.099	0.089	0.108	0.093	0.096

Table 38 sets forth the binding of heavy chain mutants H:APFF LTH (SEQ ID NO:233), H:APFF ALTH (SEQ ID NO:234), and H:APFF VLTH (SEQ ID NO:239) paired with light chain mutants L:NDH (SEQ ID NO:343), L:NDH LG (SEQ ID NO:369), and L:NDH LS (SEQ ID NO:370), at Fab concentrations of 0.74 nM to 20 nM. Antibodies containing the H:APFF LTH and H:APFF VLTH heavy chain mutations had approximately 10-fold increased binding affinity to DLL4 compared to the antibody mutants containing the heavy chain mutant H:APFF ALTH.

Table 38. Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 & V3-4_IGLJ*01 mutant binding to DLL4 by ELISA

Heavy Chain VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F (APFF)	Light Chain L6_IGKJ1*01 S28N/S30D/S31H (NDH)	Fab [nM]			
		20	6.67	2.22	0.74
N52L/S54T/G56H (LTH)	(NDH)	0.863	0.739	0.463	0.270
N52L/S54T/G56H (LTH)	S52L/A55G (NDH LG)	1.008	0.880	0.594	0.368
N52L/S54T/G56H (LTH)	S52L/A55S (NDH LS)	1.054	0.916	0.557	0.398
I51A/N52L/S54T/G56H (ALTH)	(NDH)	0.391	0.232	0.069	0.024
I51A/N52L/S54T/G56H (ALTH)	S52L/A55G (NDH LG)	0.390	0.212	0.069	0.028
I51A/N52L/S54T/G56H (ALTH)	S52L/A55S (NDH LS)	0.458	0.282	0.040	0.046
I51V/N52L/S54T/G56H (VLTH)	(NDH)	0.979	0.776	0.608	0.288
I51V/N52L/S54T/G56H (VLTH)	S52L/A55G (NDH LG)	1.057	0.916	0.755	0.397
I51V/N52L/S54T/G56H (VLTH)	S52L/A55S (NDH LS)	0.910	0.747	0.523	0.263

Table 39 sets forth the binding of heavy chain mutants H:KT (SEQ ID NO:384), H:KT S28R (SEQ ID NO:414), H:KT LRV (SEQ ID NO:420), H:KT TRV (SEQ ID NO:433) and H:KT ARV (SEQ ID NO:434) paired with light chain L:wt (SEQ ID NO:142) and light chain mutant L:RM (SEQ ID NO:479), at Fab concentrations of 0.74 nM to 20 nM. Fab KT TRV-V3-4 RM had the greatest binding affinity for DLL4.

Table 39. Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 & V3-4_IGLJ*01 mutant binding to DLL4 by ELISA

Heavy Chain VH5-51_IGHD5-18*01>3_IGHJ4*01	Light Chain V3-4_IGLJ*01	Fab [nM]			
		20	6.67	2.22	0.74
G100K/G104T	parent	0.018	0.042	0.014	0.019
G100K/G104T S28R	parent	0.009	0.003	0.000	0.000
G100K/G104T G24L/S28R/G35V	parent	0.027	0.005	0.000	0.006
G100K/G104T G24T/S28R/G35V	parent	0.054	0.023	0.000	0.002
G100K/G104T G24A/S28R/G35V	parent	0.054	0.025	0.002	0.008
G100K/G104T	M94R/S96M	0.087	0.023	0.007	0.000

G100K/G104T S28R	M94R/S96M	0.011	0.001	0.003	0.000
G100K/G104T G24L/S28R/G35V	M94R/S96M	0.003	0.000	0.000	0.000
G100K/G104T G24T/S28R/G35V	M94R/S96M	0.122	0.062	0.028	0.006
G100K/G104T G24A/S28R/G35V	M94R/S96M	0.006	0.034	0.000	0.000

Table 40 sets forth the binding of heavy chain mutant H:KT TRV (SEQ ID NO:433) paired with light chain mutants L:wt (SEQ ID NO:142), L:LP (SEQ ID NO:537), L:LP S52M (SEQ ID NO:523) and L:LP S52G (SEQ ID NO:536), at Fab concentrations of 100 nM to 0.05 nM. Fab H:KT TRV & L:LP S52G had the greatest binding affinity for DLL4.

Table 40: Bindign affinity of Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T/G24T/S28R/G35V (KT TRV) & V3-4_IGLJ1*01 light chain mutants

Fab [nM]	Heavy Chain	KT TRV	KT TRV	KT TRV	KT TRV
	Light Chain	Wildtype	V91L/S96P	V91L/S96P S52M	V91L/S96P S52G
100		0.16	0.34	0.24	0.69
33.33		0.08	0.19	0.12	0.35
11.11		0.04	0.07	0.06	0.17
3.70		0.03	0.03	0.03	0.06
1.23		0.01	0.03	0.03	0.03
0.41		0.01	0.02	0.03	0.01
0.14		0.00	0.03	0.02	0.02
0.05		0.01	0.02	0.02	0.02

Table 41 sets forth the binding affinity of heavy chain mutants of VH5-51_IGHD5-18*01>3_IGHJ4*01, including H:G100K (SEQ ID NO:381), H:G104T (SEQ ID NO:383), H:KT (SEQ ID NO:384), H:KT S28R (SEQ ID NO:414), H:KT TRV (SEQ ID NO:433), H:KT TRV Y105H (SEQ ID NO:435), H:KT TRV Y105N (SEQ ID NO:436), H:KT TRV Y107F (SEQ ID NO:437), and H:KT TRV D109Q (SEQ ID NO:438) with light chain mutants L:wt (SEQ ID NO:142), L:LP (SEQ ID NO:537) and various L:LP S52 mutants (SEQ ID NOS:520-531 and 536), at Fab concentrations of 100 nM to 12.5 nM. FabH:KT TRV & L:LP S52G (SEQ ID NOS:433 and 536) had the greatest affinity for binding to DLL4.

Table 41. Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 & V3-4_IGLJ*01 mutant binding to DLL4 by ELISA

Heavy Chain VH5-51_IGHD5-18*01>3_IGHJ4*01	Light Chain V3-4_IGLJ*01	Fab [nM]			
		100	**50**	**25**	**12.5**
G100K/G104T G24L/S28R/G35V Y105H	Wildtype	0.23	0.20	0.19	0.21

G100K/G104T G24T/S28R/G35V Y105N	Wildtype	0.25	0.18	0.19	0.21
G100K/G104T G24A/S28R/G35V Y107F	Wildtype	0.28	0.24	0.20	0.21
G100K/G104T G24L/S28R/G35V D109Q	Wildtype	0.30	0.25	0.22	0.24
G100K/G104T G24T/S28R/G35V	V91L/S96P	1.00	0.81	0.58	0.45
G100K	Wildtype	0.20	0.19	0.18	0.19
Wildtype	Wildtype	0.17	0.16	0.18	0.17
G104T	Wildtype	0.17	0.17	0.18	0.19
G100K/G104T	Wildtype	0.18	0.18	0.16	0.18
G100K/G104T G24T/S28R/G35V	Wildtype	0.45	0.32	0.26	0.23
G100K/G104T S28R	Wildtype	0.26	0.23	0.20	0.18
G100K/G104T G24A/S28R/G35V	V91L/S96P S52V	0.95	0.74	0.60	0.43
G100K/G104T G24L/S28R/G35V	V91L/S96P S52F	0.99	0.69	0.49	0.42
G100K/G104T G24T/S28R/G35V	V91L/S96P S52L	1.02	0.78	0.58	0.43
G100K/G104T G24A/S28R/G35V	V91L/S96P S52I	1.04	0.82	0.60	0.40
G100K/G104T G24L/S28R/G35V	V91L/S96P S52M	1.01	0.80	0.59	0.41
G100K/G104T G24T/S28R/G35V	**V91L/S96P S52G**	**1.14**	**1.02**	**0.90**	**0.63**
G100K/G104T G24A/S28R/G35V	V91L/S96P S52P	1.00	0.79	0.59	0.43
G100K/G104T G24L/S28R/G35V	V91L/S96P S52T	0.99	0.79	0.62	0.41
G100K/G104T G24T/S28R/G35V	V91L/S96P S52Y	0.90	0.72	0.56	0.41
G100K/G104T G24A/S28R/G35V	**V91L/S96P S52H**	**1.09**	**0.91**	**0.73**	**0.50**
G100K/G104T G24L/S28R/G35V	V91L/S96P S52Q	0.96	0.81	0.67	0.47
G100K/G104T G24T/S28R/G35V	**V91L/S96P S52N**	**1.05**	**0.90**	**0.86**	**0.65**
G100K/G104T G24T/S28R/G35V	**V91L/S96P S52K**	**1.23**	**1.03**	**0.79**	**0.56**

Tables 42-43 set forth the ELISA signals for binding to human and mouse DLL4. All tested Fabs show a preference for binding to hDLL4 as compared to mDLL4. Fabs H:APFF VLTH & L:NDH LS (SEQ ID NOS:239 and 370) and H:APFF VLTH & L:NDH (SEQ ID NOS:239 and 343) bind hDLL4 with approximately the same affinity, approximately 1 nM. Additionally, Fab H:APFF VLTH & L:NDH LS binds mDLL4 with 10-fold decrease affinity as compared to binding to hDLL4. Fab H:KT TRV & L:wt (SEQ ID NOS:433 and 142) binds hDLL4 with an affinity of approximately 50 nM. None of the tested VH5-51_IGHD5-18*01>3_IGHJ4*01 & V3-4_IGLJ1*01 mutant Fabs showed appreciable binding to mDLL4 at the tested concentrations.

TABLE 42. Fab VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01 mutant binding to human and mouse DLL4 by ELISA

		0.5 ng/µl h DLL4			0.5 ng/µl mDLL4		
	Heavy	APFF G56H	APFF VLTH	APFF VLTH	APFF G56H	APFF VLTH	APFF VLTH
Fab [nM]	Light	L6_IGKJ1*01	NDH	NDH LS	L6_IGKJ1*01	NDH	NDH LS
10.00		1.199	2.253	2.246	0.088	1.215	1.555
5.00		0.882	1.918	2.060	0.070	0.833	1.284
2.50		0.535	1.831	1.964	0.061	0.583	0.983
1.25		0.264	1.396	1.651	0.054	0.317	0.604

0.63		0.168	1.089	1.403	0.052	0.206	0.404
0.31		0.103	0.683	0.850	0.049	0.105	0.205
0.16		0.079	0.407	0.593	0.048	0.081	0.142
0.08		0.071	0.189	0.259	0.048	0.063	0.078

TABLE 43. Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 & V3-4_IGLJ*01 mutant binding to human and mouse DLL4 by ELISA

		0.5 ng/µl h DLL4			0.5 ng/µl mDLL4		
	Heavy	KT S28R	KT TRV	KT TRV	KT S28R	KT TRV	KT TRV
Fab [nM]	Light	V3-4 _IGLJ1*01	V3-4 _IGLJ1*01	RM	V3-4 _IGLJ1*01	V3-4 _IGLJ1*01	RM
100.00		0.670	1.447	1.067	0.158	0.305	0.457
50.00		0.524	0.976	0.661	0.145	0.234	0.331
25.00		0.333	0.600	0.421	0.138	0.178	0.232
12.50		0.226	0.389	0.294	0.126	0.153	0.186
6.25		0.203	0.310	0.229	0.123	0.133	0.148
3.13		0.164	0.187	0.167	0.117	0.125	0.131
1.56		0.148	0.183	0.148	0.116	0.120	0.131
0.78		0.138	0.143	0.145	0.118	0.115	0.130

Example 8

Binding to DLL4 expressed on the surface of CHO cells

In this example, Fabs H:APFF VLTH & L:NDH LS (SEQ ID NOS:239 and 371) and H:KT TRV & L:LP S52G (SEQ ID NOS:433 and 536) were tested for their ability to bind to DLL4 expressed on the surface of CHO cells as detected by flow cytometry.

To generate a DLL4 expression construct, human DLL4 cDNA (SEQ ID NO:113, Accession No. BC106950; and encoding amino acids set forth in SEQ ID NO:114, Accession No. AAI06951) in pCR-BluntII-TOPO (SEQ ID NO:116) as a glycerol stock was obtained from Open Biosystems (Clone ID# 40034887). The stock was streaked on kanamycin agar plates and a colony picked for purification of the DNA. DNA was obtained with Purelink™ Quick Plasmid Miniprep Kit (Invitrogen, Catalog # K210010).

Full-length DLL4 was digested out from the OpenBiosystems vector and ligated into pCDNA5/FRT (SEQ ID NO:117; Invitrogen Catalog # K601001) between NheI and NotI. Ligation was performed with Rapid DNA Ligation Kit (Roche, Catalog # 11 635 379 001) and cells transformed using heat shock into One Shot® Max Efficiency® DH5α™-T1^R Competent Cells (Invitrogen, Catalog # 12297016). Cells were selected on carbenicillin plates. Colonies were picked and

inoculated overnight in luria broth (LB) containing 1:1000 100 mg/mL carbenicillin. Plasmid DNA was extracted by miniprep (Invitrogen; Catalog # K210011).

Using Invitrogen's LipofectamineTM Transfection Reagent, pcDNA5/FRT containing full-length DLL4 and pOG44 recombinase vector (SEQ ID NO:118; Invitrogen Catalog # K601001) were transfected into Invitrogen's Flp-InTM-CHO Cell Line (Cat. No. R75807) according to Flp-InTM System protocol. Cells were approximately 90% confluent in a 12-well plate. Transfected cells were selected with 400μg/ml Hygromycin after a couple days. Colonies were picked about 5 days after and transferred into a 10 cm^2 tissue culture dish. These cell lines were maintained with hygromycin selection

CHO cells expressing full-length DLL4 and control CHO cells were detached from tissue culture plates (BD Falcon 10 cm^2) using Accutase™ Enzyme Cell Detachment Medium (Cat# 00-4555-56, eBioscience). After washing the cells in 2% Bovine Serum Albumin in Phosphate Buffered Saline (2% BSA/PBS), 10 nM Fab in 2% BSA/PBS was added and incubated at on ice for 30 minutes. The cells were washed one time with 2% BSA/PBS and mouse anti-human kappa-PE antibody (diluted 1:100, Cat# MH10514, Invitrogen) or mouse anti-human lambda-PE antibody (diluted 1:100, Cat# MH10614, Invitrogen) was added and incubated on ice for 10 minutes. Secondary antibody mouse anti-human kappa-PE alone (without Fab) was used as a control for DLL4-expressing CHO cells. The cells were then washed twice in 2% BSA/PBS and analyzed by flow cytometry on a BD FACSAria. The results show that the tested Fabs bind DLL4 expressed on the surface of CHO cells.

Example 9

Epitope Mapping of DLL4

In this example, the binding epitopes of the VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01 and VH5-51_IGHD5-18*01>3_IGHJ4*01 & V3-4_IGLJ1*01 Fabs for DLL4 were mapped using two different assays. In the first experiment, a competition assay was performed to determine whether Fabs VH1-46_IGHD6-6*01_IGHJ1*01 H:APFF G56H & L6_IGKJ1*01 (SEQ ID NOS:219 and 141) and VH5-51_IGHD5-18*01>3_IGHJ4*01 H:KT TRV & V3-4_IGLJ1*01 (SEQ ID NOS:433 and 142) compete for the same binding site on DLL4. In the second

experiment, the epitopes on DLL4 recognized by Fabs VH1-46_IGHD6-6*01_IGHJ1*01 H:APFF VLTH & L6_IGKJ1*01 L:NDH LS (SEQ ID NOS:239 and 370) and VH5-51_IGHD5-18*01>3_IGHJ4*01 H:KT TRV & V3-4_IGLJ1*01 L:LP S52G (SEQ ID NOS:433 and 536) were mapped by Western Blot using various truncated forms of DLL4.

A. Competition Assay for binding to DLL4

In this assay, two Fabs, H:APFF G56H & L:wt and H:KT TRV & L:wt, that contain different heavy and light chains but have similar binding affinities to DLL4 (K_Ds of 32.7 ± 11.6, 36.2 ± 8.5 nM, respectively), were used in a competition assay for binding to DLL4 with ruthenium labeled Fab H:APF & L:wt.

Briefly, single spot 96-well standard plates (MSD) were coated overnight with 5 µl per well of 10 µg/ml DLL4 (R&D systems) in PBS with 0.03% Triton X-100. Some wells were left uncoated as blank. The next day, an 150 µl aliquot of 3% BSA in TBST was added to each well and allowed to incubate for 60 min at 20 °C to block the plate. After washing twice with 150 µl TBST and tap drying, 50 µl aliquots of 100 nM Ru-labeled Fab H:APF & L:wt plus serial dilutions of either Fab H:APFF G56H & L:wt or Fab H:KT TRV & L:wt, in duplicates, were added. After incubating the plate at 20 °C with shaking for 1 hour, the ECL signal was measured using a Sector Imager 2400. After subtracting the signals from the blank wells, percent (%) Ru-labeled Fab H:APF & L:wt binding was calculated by dividing the average ECL signal for the tested Fabs with the ECL signal for Ru-labeled Fab H:APF & L:wt binding.

The results show that at equilibrium Fab H:APFF G56H & L:wt competes efficiently with Fab H:APF & L:wt for binding on DLL4, with a competition K_D of about 30 nM. In contrast, Fab H:KT TRV & L:wt shows much weaker competition. At a concentration of 400 nM, Fab H:KT TRV & L:wt only competes off 33% of Ru-labeled Fab H:APF & L:wt. Thus Fabs H:APFF G56H & L:wt and H:KT TRV & L:wt have either minimal overlapping or different epitopes on DLL4.

B. Epitope Mapping

In this example, a series of recombinant DLL4 extracellular domain truncation mutants were generated, expressed and purified in order to allow for mapping of the binding epitopes of the Fabs on DLL4 by Western Blot.

1. Generation and Transfection of DLL4-Expression Constructs

CHO cells expressing the extracellular domain (ECD) of DLL4 were generated using pcDNA5/FRT vector from Invitrogen's Flp-In™ System. In this example, human DLL4 cDNA (SEQ ID NO:113, Accession No. BC106950, start codon for DLL4 at nucleotide position 137; and encoding amino acids set forth in SEQ ID NO:114, Accession No. AAI06951) in pCR-BluntII-TOPO (SEQ ID NO:116) as a glycerol stock was obtained from Open Biosystems (Clone ID# 40034887). The stock was streaked on kanamycin agar plates. and a colony picked for purification of the DNA. DNA was obtained with Purelink™ Quick Plasmid Miniprep Kit (Invitrogen, Catalog # K210010).

To obtain the ECD of of DLL4 (corresponding to nucleotides 137-1708 of SEQ ID NO:113, and encoding amino acids 1-524 of SEQ ID NO:14), primers were generated for PCR as set forth in Table 44. The primers also were used to generate other truncated fragments of DLL4 (see Table 45). An extra 8 nucleotides and an NheI restriction site (SEQ ID NO:109) were added to the beginning of the ECD with the DLL4 ECD forward primer. A myc tag, his tag, NotI restriction site (SEQ ID NO:112) and 8 extra nucleotides were added to the end of the ECD using DLL4 ECD reverse2 primer. PCR was conducted with Pfu Ultra™ HF polymerase (Stratagene, La Jolla, CA; Catalog No. 600385) as described by the manufacturer. Seven different DLL4 constructs were amplified as described in Table 45 using different combinations of the PCR primers.

Table 44: Primers for DLL4 ECD and for DLL4 truncation PCR

Primer Name	Primer	SEQ ID NO
DLL4 ECD forward	tgacctaggctagcatggcggcagcgtcccg	119
DLL4 ECD reverse1	cagatcctcttctgagatgagtttttgttcggcaagcccacgggga	120
DLL4 ECD reverse2	ttactgacgcggccgctcatcaatggtgatggtgatgatgcagatcctcttctgagatg	121
DLL4 pre-DSL reverse 1	ttactgacgcggccgctcatcacagatcctcttctgagatgagtttttgttcccggtaagagtagcgcagc	122
DLL4 DSL reverse 1	ttactgacgcggccgctcatcacagatcctcttctgagatgagtttttgttcgcaatattccccagtccaacc	123
DLL4 Egf1 reverse1	ttactgacgcggccgctcatcacagatcctcttctgagatgagtttttgttcgttacacagccggccctgc	124
DLL4 Egf2 reverse1	CAGATCCTCTTCTGAGATGAGTTTTTGTTCGTTGAGATCTTGGT CACAAAAC	901
DLL4 Egf4 reverse 1	ttactgacgcggccgctcatcacagatcctcttctgagatgagtttttgttcttcacaatgcaggccatagta	125
DLL4 Egf7 reverse 1	ttactgacgcggccgctcatcacagatcctcttctgagatgagtttttgttcctcacagcgtcggccagag	126

Table 45: DLL4 Constructs	
Construct	PCR Primers for Amplification
DLL4 ECD (amino acids 1-524)	primers DLL4 ECD forward and DLL4 ECD reverse1 and reverse2
DLL4 pre-DSL (amino acid: 1-172)	primers DLL4 ECD forward and DLL4 pre-DSL reverse1 then DLL4 ECD reverse2
DLL4 DSL (amino acid: 1-217)	primers DLL4 ECD forward and DLL4 DSL reverse1 then DLL4 ECD reverse2
DLL4 Egf1 (amino acid: 1-251)	primers DLL4 ECD forward and DLL4 EGF1 reverse1 then DLL4 ECD reverse2
DLL4 Egf2 (amino acid: 1-282)	primers DLL4 ECD forward and DLL4 EGF2 reverse1 then DLL4 ECD reverse2
DLL4 Egf4 (amino acid: 1-360)	primers DLL4 ECD forward and DLL4 EGF4 reverse1 then DLL4 ECD reverse2
DLL4 Egf7 (amino acid: 1-476)	primers DLL4 ECD forward and DLL4 EGF7 reverse1 then DLL4 ECD reverse2

The respective PCR product and pcDNA5/FRT (SEQ ID NO:117; Invitrogen, Carlsbad, CA, Catalog # K601001) were digested with NheI and NotI (SEQ ID NOS:109 and 112; New England Biosystem) and gel purified using Purelink™ Quick Gel Extraction and PCR Purification Kit (Invitrogen, Catalog # K220001). The gel purified products were ligated with Rapid DNA Ligation Kit (Roche, Catalog # 11 635 379 001) and transformed using heat shock into One Shot® Max Efficiency® DH5α™-T1^R Competent Cells (Invitrogen, Catalog # 12297016). Cells were selected on carbenicillin plates. Colonies were picked and inoculated overnight in luria broth (LB) containing 1:1000 100 mg/mL carbenicillin. Plasmid DNA was extracted by miniprep (Invitrogen; Catalog # K210011).

Using Invitrogen's LipofectamineTM Transfection Reagent, pcDNA5/FRT containing DLL4 ECD or constructs and pOG44 recombinase vector (SEQ ID NO:118; Invitrogen Catalog # K601001) were transfected into Invitrogen's Flp-InTM-CHO Cell Line (Cat. No. R75807) according to Flp-InTM System protocol (Invitrogen; Flp-In System Complete Kit Cat. No. K601001). Cells were approximately 90% confluent in a 12-well plate. Transfected cells were selected with 400μg/ml Hygromycin after a couple days. Colonies were picked about 5 days after and transferred into a 10 cm^2 tissue culture dish. These cell lines were maintained with hygromycin selection

2. Epitope Mapping by Western Blot

Media from transfected CHO cells was collected after 7 days. To enrich for the DLL4 protein, 1 ml aliquots of each sample were batch bound with 50 μl of Talon

Resin for 30 minutes. To confirm protein production media samples were tested with mouse anti-c-myc mAb (Genescript; Catalog # A00704). Samples were washed and then boiled with loading dye in the presence or absence of DTT. A gel was run on each of the 2 samples for each condition: with DTT and without DTT. The gel was transferred to PVDF membrane and probed with either 0.5 μg/ml anti-c-myc, 20nM Fab VH1-46_IGHD6-6*01_IGHJ1*01 H:APFF VLTH & L6_IGKJ1*01 L:NDH LS (SEQ ID NOS:239 and 370) or 20 nM Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 H:KT TRV & V3-4_IGLJ1*01 L:LP S52G (SEQ ID NOS:433 and 536). For detection goat anti-mouse HRP, goat anti-kappa HRP, and goat anti-lambda HRP were used, respectively.

Using the anti-myc antibody, the results show detection of all expressed proteins, except for the protein expressed from the pre-DSL construct, under reducing conditions. Under non-reducing conditions, only truncated proteins expressed from the DLL4 ECD and EGF4 constructs were detected using the anti-myc antibody. Binding of Fab H:APFF VLTH & L:NDH LS was detected by Western Blot under non-reducing conditions to the truncated protein expressed from the EGF7 construct, the EGF4 construct, EGF2 construct and the DLL4 ECD construct, but not to the proteins expressed from the other constructs tested. Binding of Fab H:KT TRV & L:LP S52G was detected by Western Blot under non-reducing conditions to the truncated protein expressed from the EGF7 construct, the EGF4 construct,and the DLL4 ECD construct, but not to the proteins expressed from the other constructs tested. This suggests that the DLL4 epitope recognized by the H:APFF VLTH & L:NDH LS antibody is within amino acid residues 252 to 280 of DLL4 in the EGF2 region while the epitope recognized by the H:KT TRV & L:LP S52G antibody is within amino acid residues 283 to 360 of DLL4 in the EGF3 to EGF4 region. Both anti-DLL4 Fabs appear to recognize conformational epitopes formed in the presence of disulfide bonds because their binding was abolished when the DLL4 protein was first treated with a reducing reagent.

Example 10

Inhibition of DLL4-Notch interaction by ELISA

In this example, four Fabs previously identified as binding to DLL4 were functionally screened for their ability to block the binding of Notch-Fc to DLL4.

In this ELISA assay, recombinant human DLL4 was bound to the plate followed by the addition of both the Fab and Notch-Fc. An anti-human FC-HRP conjugated antibody was used as a detection molecule therefore if Notch-Fc binds to DLL4, a strong signal will be observed at A_{450}. Alternatively, if the Fab is capable of blocking the binding of Notch-Fc to DLL4, no signal should be observed. The DLL4 Fabs that were assayed included Fab H:APF & L6_IGKJ1*01 (SEQ ID NOS:155 and 141), Fab H:APFF & L6_IGKJ1*01 (SEQ ID NOS:156 and 141), Fab H:KT & V3-4_IGLJ1*01 (SEQ ID NOS:385 and 142) and Fab VH1-46_IGHD3-10*01_IGHJ4*01 & L12_IGKJ1*01 (SEQ ID NOS:134 and 147).

In short, Maxisorp Nunc 96-well plates were coated with 0.5 μg/ml recombinant human DLL4 extracellular domain (Cat# 1506-D4-050/CF, R&D Systems) for at least 2 hours. The wells were washed and then blocked with 4% BSA. Following blocking, Fabs H:APF & L6_IGKJ1*01, Fab H:APFF & L6_IGKJ1*01, H:KT & V3-4_IGLJ1*01 and VH1-46_IGHD3-10*01_IGHJ4*01 & L12_IGKJ1*01 at concentrations from 0.004 and 5 μM were added together with recombinant human Fc-Notch extracellular domain (R&D Systems) at a concentration of 10 nM. After incubation for one to two hours, the wells were washed and Notch binding was measured using a mouse anti-human FC-HRP conjugated antibody (Southern Biotech) at an 1:1000 dilution. HRP activity was detected using TMB substrate (Pierce) followed by acid neutralization. The A_{450} was measured on a SpectraMax Plus 384.

Results show that the addition of Fabs H:APF & L6_IGKJ1*01, Fab H:APFF & L6_IGKJ1*01 or H:KT & V3-4_IGLJ1*01 resulted in a decreased signal therefore indicating their ability to block the binding of Notch-Fc to DLL4. The addition of Fab VH1-46_IGHD3-10*01_IGHJ4*01 & L12_IGKJ1*01 did not result an any loss of activity, indicating that Fab VH1-46_IGHD3-10*01_IGHJ4*01 & L12_IGKJ1*01 does not block the Notch-DLL4 interaction. This result also indicates that Fabs H:APF & L6_IGKJ1*01, Fab H:APFF & L6_IGKJ1*01 and H:KT & V3-

4_IGLJ1*01 bind different epitopes of DLL4 than Fab VH1-46_IGHD3-10*01_IGHJ4*01 & L12_IGKJ1*01.

Example 11

Inhibition of DLL4-Notch interaction by Flow Cytometry

In this example, three DLL4 binding Fabs were functionally screened for their ability to block the binding of Notch-Fc to DLL4. In this assay, DLL4-expressing CHO cells were incubated in the presence of both Fab and biotinylated-Notch-Fc. Streptavidin-PE was used as a detection molecule. If Notch-Fc binds to DLL4-expressing CHO cells, these cells will be detected by a PE signal at 578 nm. Alternatively, if the Fab blocks the binding of Notch-Fc to DLL4, the DLL4-expressing CHO cells will not be labeled or detected. The tested Fabs included H:APFF VLTH & L:NDH LS (SEQ ID NOS:239 and 370), H:KT TRV & V3-4_IGLJ1*01 (SEQ ID NOS:433 and 142) and H:KT TRV & L:LP S52G (SEQ ID NOS:433 and 536).

In short, CHO cells expressing full-length DLL4 (CHO-DLL4) as described in Example 8 were detached from tissue culture plates using Accutase™ Enzyme Cell Detachment Medium (Cat# 00-4555-56, eBioscience). Fab was 5-fold serially diluted in 2% BSA/PBS from a starting concentration of 50 nM. Notch-FC (cat# 3647-TK-050, R&D Systems) was biotinylated following using EZ-Link NHS-Biotin Reagent (cat# 20217. Pierce) according to the manufacturers instructions. Detached cells were treated with 250 nM biotinylated Notch-FC in 2% BSA/PBS and 30 μL Fab for 30 minutes on ice. PE-labeled streptavidin (Cat# 21627, Pierce-Thermo Scientific) was then added to a final dilution of 1:5 followed by incubation for 10 minutes at room temperature. The cells were then washed twice in 2% BSA/PBS and analyzed by flow cytometry on a BD FACSAria.

The results are set forth in Table 46 below. All three Fabs effectively block Notch-Fc binding to CHO-DLL4. Fab H:APFF VLTH & L:NDH LS completely blocks the binding of Notch to DLL4 by 80% at a Fab concentration of 2 nM. Fab H:KT TRV & V3-4_IGLJ1*01 blocks the binding of Notch to DLL4 by 50% at a concentration of 50 nM Fab. Fab H:KT TRV & L:LP S52G blocks the binding of Notch to DLL4 by 80% at a concentration of 50 nM Fab.

Table 46. Inhibition of DLL4-Notch interaction			
Fab [nM]	H:APFF VLTH & L:NDH LS	H:KT TRV & L:wt	H:KT TRV & L:LP S52G
50	30	141	105
10	30	244	190
2	117	448	250
0.4	277	Not tested	324
0	531	531	531

Example 12

IgG Cloning and Expression

In this example, Fab antibodies that bind to DLL4 were converted into IgGs by cloning into the pFUSE vectors. Briefly, sequences encoding heavy and light chains were cloned separately into the pFUSE family of vectors (pFUSE-hIgG2-Fc2, Cat# pfuse-hfc2, InvivoGen) behind the included IL-2 signal sequence. These two vectors were then co-transformed into 293F cells and the protein was expressed and purified.

Light Chain: The Sequence encoding the Fab light chain (excluding the N-terminal *E. coli* sorting signal Met Ala) was amplified by PCR with primers containing EcoRI and NheI ends. The amplified Fab light chain was subcloned into pFUSE-hIgG2-Fc2, previously digested with EcoRI and NheI. The Fab light chain immediately follows the IL-2 signal sequence, and completely replaces the Fc sequence in pFUSE-hIgG2-Fc2.

Heavy Chain: A full-length IgG1 heavy chain sequence with a NheI site between VH and CH1-CH2-CH3 was synthesized by Genscript, amplified by PCR with primers containing EcoRI and XbaI ends, and subcloned into pFUSE-hIgG2-Fc2, previously digested with EcoRI and NheI. Ligation of the XbaI and NheI compatible cohesive ends eliminates both sties at this position, making the NheI site between VH and CH1-CH2-CH3 of the IgG1 heavy chain sequence unique. The sequence encoding Fab heavy chain (excluding the N-terminal *E. coli* sorting signal Met Ala) was amplified by PCR with EcoRI and NheI ends. The vector containing the full length IgG1 heavy chain was then digested with EcoRI and NheI, which removed the VH sequence, and the amplified Fab heavy chain was subcloned into the digested vector. Thus the Fab Heavy chain was subcloned between IL-2 and the IgGI heavy chain.

Protein Expression and Purification: To produce IgG, the heavy and light chain plasmids were co-transfected into 293F cells (Cat# R790-07, Invitrogen) using 293fectin (Cat# 12347, Invitrogen) per manufacturer's instructions. Cells grown in serum-free 293Freestyle media (Cat# 12338026, Invitrogen) were transfected at 1×106 cells/ml in 50 ml spinner flask. Cell culture media were harvested 3 and 6 days after transfection and pooled together for purification by column chromatography using Protein-G Sepharose (GE Healthcare). IgG elution fractions were pooled and dialysed into PBS.

Example 13

Inhibition of DLL4-Notch interaction by a Reporter Assay

In this example, two DLL4 binding antibodies were assayed for their ability to inhibit DLL4-dependent Notch 1 signaling using a luciferase reporter assay. Reporter cells were generated by stably transfecting human glioma T98G cells, known for the presence of Notch 1 on their cell surface (see Purow et al. (2005) Cancer Res., 65:2353-63), with a Notch reporter plasmid (p6xCBF) containing six C promoter binding factor-1 (CBF-1) responsive elements (set forth in SEQ ID NO:129; see Nefedova et al. (2004), Blood. 103(9):3503-10). Subsequent addition of DLL4-CHO cells (see Example 8 above) to the reporter T98G cells results in expression of firefly luciferase due to the Notch1-DLL4 interaction. Disruption of the Notch1-DLL4 by a DLL4 binding antibody therefore causes a decrease in luciferase expression.

A. Notch reporter plasmids

A reporter construct containing six C promoter binding factor-1 (CBF-1) response elements (set forth in SEQ ID NO:129; CBF Notch-response elements are indicated by bold;

ggtacctgagctcgctagcgatctggtgtaaacacgcc**gtgggaa**aaaatttatggatctggtgtaaacacgcc**gtggga**
aaaaatttatggagctcgctagcgatctggtgtaaacacgcc**gtgggaa**aaaatttatggatctggtgtaaacacgcc**gtg**
ggaaaaatttatgctcgaggatctggtgtaaacacgcc**gtgggaa**aaaatttatggatctggtgtaaacacgcc**gtggga**
aaaaatttatgaagctt;)

was digested with KpnI and HindIII. The digested product was then cloned into two different luciferase reporter vectors (pGL4.23 (SEQ ID NO:128; Promega, Catalog # E8411) and pGL4.26 (SEQ ID NO:902; Promega, Catalog # E8441)) at the KpnI and

HindIII sites. The pGL4.23 vector requires co-transformation of a Renilla luciferase for normalization (see Section B.1 below). The pGL4.26 vector allows for hygromycin selection, which facilitates the production of a cell line with a stably-integrated copy of the reporter (see section B.2 below). Both reporter vectors are suitable for the assay. The use of pGL4.26 elminates the need need to transiently transfect the reporter and normalize for variable transfection efficiency, as described in Section B.1. below.

B. Assay

T98G cells from ATCC (No. CRL-1690™) were plated onto a 96-well tissue culture plate at 20,000 cells per well in Eagle's Minimum Essential Media (EMEM, Invitrogen) supplemented with 10% Fetal Bovine Serum (BSA, Invitrogen) and 1X penicillin/streptomycin/glutamine (P/S/G, Invitrogen).

1. pGL4.23 p6xCBF Reporter Plasmid

The following day, T98G cells were transfected with the Notch reporter construct expressing Firefly luciferase (p6xCBF) and an internal control construct expressing *Renilla* luciferase (pGL4.75, SEQ ID NO:130; Promega, Catalog # E6931). The transfection was carried out using 0.16 μg of p6xCBF with 0.04 μg of pGL4.75 and 0.5 μl of Lipofectamine 2000 (Invitrogen; Catalog # 11668-027) per well in accordance with manufacturers instructions.

Twenty four hours after transfection, Notch-expressing T98G cells were stimulated by DLL4-expressing CHO cells (as described in Example 8) or control CHO cells. Briefly, media on T98G cells was replaced by 100 μl of serum free F12 media supplemented with P/S/G containing 1 x 10^6 cells/ml of the respective CHO cells. Inhibitory Fabs H:APFF VLTH & L:NDH LS (SEQ ID NOS:239 and 370) and H:KT TRV & L:LP S52G (SEQ ID NOS:433 and 536) and control Fab VH1-69_IGHD1-1*01_IGHJ6*01 & A17_IGKJ1*01 (SEQ ID NOS:572 and 573) were added at 100, 20, 4 and 0.8 nM to the cells.

After 24 hours, the reporter readout was assessed using Dual-Glo (Catalog # E2920; Promega, Madison WI). The assay system permits a quantitation of both reporters, firefly luciferase and renilla luciferase, thereby allowing for normalization of the expression of an experimental reporter to the expression of a control reporter to differentiate between specific and nonspecific cellular responses. Briefly, media was

replaced with a mixture of 75 µl Dual-Glo luciferase buffer and 25 µl PBS per well. After 15 minutes of incubation, firefly luminenscence of the plate was read on a Wallac Victor II model 1420. Next, 25 µl of Dual-Glo Stop & Glo buffer containing 1:100 dilution of Dual-Glo Stop & Glo substrate was added to each well. The plate was incubated for 15 minutes and then *Renilla* luciferase was readout on the Wallac Victor II model 1420 plate reader. Each condition was performed in quadruplicate and data normalized by dividing firefly luminenscence in counts per second (CPS) by *Renilla* luminenscence in CPS.

The results show that cells stimulated just with CHO cells showed a baseline luminescence signal at all doses of Fab antibody tested. Upon stimulation with CHO-DLL4 expressing cells, a high luminescence signal was observed, which remained at a constant high level in the presence of the VH1-69_IGHD1-1*01_IGHJ6*01 & A17_IGKJ1*01 Fab antibody at all concentrations tested. In the presence of the H:APFF VLTH & L:NDH LS Fab, the level of luminescence signal at the 4 nM and 0.8 nM Fab concentrations was similar to that observed in the presence of the VH1-69_IGHD1-1*01_IGHJ6*01 & A17_IGKJ1*01 Fab antibody. In contrast, the luminescence signal observed upon stimulation with CHO-DLL4 cells in the presence of the H:APFF VLTH & L:NDH LS antibody at higher Fab concentrations of 20 nM and 100 nM was decreased, approaching the baseline signal at the 100 nM Fab concentration.

2. pGL4.26 p6xCBF Reporter Plasmid

The following day, T98G cells were transfected with the Notch reporter construct expressing Firefly luciferase (p6xCBF) and stable integrants were selected with 200ug/ml Hygromycin B (Invitrogen). CHO cells expressing DLL4 or control CHO cells were propagated in F12 media (Invitrogen) supplemented with 10% FBS and P/S/G. Separately, T98G Notch reporter cells (2×10^5 cells/well) in EMEM with 10% FBS and P/S/G were plated onto 96-well tissue culture plates. Notch-expressing T98G cells were stimulated by CHO-DLL4 or control CHO cells (1×10^5 cells/well). Media on T98G cells was replaced by 100 µl of serum free F12 media supplemented with P/S/G. Fabs H:APFF VLTH & L:NDH LS and H:KT TRV & L:LP S52G and their corresponding IgGs, and control Fab (that does not bind DLL4) were added at 100, 20, 4 and 0.8 nM. After 24 hours, luciferase-reporter expression was measured

with Bright-Glo luciferase assay reagent (Cat# E2620, Promega). Luminenscence was read using a Wallac Victor II model 1420 plate reader. Each condition was performed in quadruplicate.

The results show that CHO cells (not expressing DLL4) did not activate Notch reporter alone or in combination with any antibody. Incubation of the T98G reporter cells with CHO-DLL4 resulted in 8- to 9-fold increase in Notch reporter levels compared to those incubated with CHO cells alone. Notch-activation remained constant in the presence of a control Fab that does not bind DLL4. Activation was reduced in the presence of increasing concentrations of anti-DLL4 Fabs H:APFF VLTH & L:NDH LS and H:KT TRV & L:LP S52G. IgG H:APFF VLTH & L:NDH LS (IC50 ~ 6 nM), was 30-fold more efficient at disrupting Notch1 binding to DLL4 as compared to Fab H:APFF VLTH & L:NDH LS. IgG H:KT TRV & L:LP S52G was also more efficient at disrupting Notch1 binding to DLL4 as compared to Fab H:KT TRV & L:LP S52G, displaying about 30% reduction in Notch-activation at 0.8 nM. At higher concentrations IgG H:KT TRV & L:LP S52G did not show complete suppression of Notch-activation.

Example 14

Inhibition of DLL4/Jag1

In this example, a cellular assay is described in which activation of the Notch pathway prevents C2C12 myoblast cell differentiation (see e.g., Jarriault et al., 1998 Molecular and Cellular Biology, 18:7423-7431). In order to activate the Notch pathway, Notch ligands, such as DLL4 or Jag1, must be expressed as full-length proteins on the cell surface. To achieve this Notch activation, non-adherent cells naturally or ectopically expressing Notch ligands DLL4 or Jag1 are co-cultured with C2C12 cells and selected Fabs. Functional inhibition of DLL4 or Jag1 is assessed by the ability of the Fab to promote differentiation, indicating Notch pathway inactivation. The differentiation into tube-like structures is easily discernible morphologically and additionally can be detected with an antibody against troponin t (Sigma-Aldrich).

In short, C2C12 mouse myoblast cells are cultured in the presence and absence of Jag1-expressing IM9 cells (a human lymphoblast cell line) and Fabs. The

cells are plated onto glass coverslips in 12 well dishes in DMEM containing 10% FBS (fetal bovine serum). The next day attached C2C12 cells are transferred into DMEM containing 1% FBS to induce differentiation. Following incubation, the cells are visualized to observe whether differentiation into myotubes occurred. Low serum conditions will induce the differentiation of myotubes while Jag1-expressing IM9 cells maintain C2C12 cells in an undifferentiated state in low serum conditions.

Since modifications will be apparent to those of skill in this art, it is intended that this invention be limited only by the scope of the appended claims.

2009313551 23 Nov 2015

CLAIMS

1. An isolated antibody that specifically binds to human DLL4 or an isolated antigen-binding fragment thereof that specifically binds to human DLL4, wherein the antibody comprises at least one heavy chain variable domain and at least one light chain variable domain, wherein each heavy chain variable domain comprises three complementarity determining regions (CDRs), CDRH1, CDRH2, and CDRH3, and each light chain variable domain comprises three CDRs, CDRL1, CDRL2, and CDRL3, wherein:

a) CDRH3 comprises an amino acid sequence of EEYSSSSAEYKQH (SEQ ID NO:851), wherein CDRH3 contains modifications of CDRH3 set forth in SEQ ID NO:851 and wherein the modifications are S98A/S99P/S100F/H102F, based on kabat numbering;

b) CDRH2 comprises an amino acid sequence of IINPSGGSTSYAQKFQG (SEQ ID NO:844), wherein CDRH2 contains modifications of CDRH2 set forth in SEQ ID NO: 844 and wherein the modifications are I51V/N52L/S53T/G55H, based on kabat numbering;

c) CDRH1 comprises an amino acid sequence of GYTFTSYYMH (SEQ ID NO: 830);

d) CDRL3 comprises an amino acid sequence of QQRSNWPPWT (SEQ ID NO:881);

e) CDRL2 comprises an amino acid sequence of DASNRAT (SEQ ID NO:871), wherein CDRL2 contains modifications of CDRL2 set forth in SEQ ID NO: 871 and wherein the modifications are S52L/A55S or S52L/A55G, based on kabat numbering; and

f) CDRL1 comprises an amino acid sequence of RASQSVSSYLA (SEQ ID NO: 861), wherein CDRL1 contains modifications of CDRL1 set forth in SEQ ID NO: 861 and wherein the modifications are S28N/S30D/S31H, based on kabat numbering.

2. An antibody or antigen-binding fragment according to claim 1, wherein the antibody is a full-length IgG antibody.

3. An antibody or antigen-binding fragment according to claim 1, wherein the antigen-binding fragment is selected from the group consisting of a Fab, Fab', $F(ab')_2$, single-chain Fv (scFv), Fv, dsFv, diabody, Fd and Fd' fragment, Fab fragment, Fd fragment, scFv fragment, and a scFab fragment.

2009313551 23 Nov 2015

4. An antibody or antigen-binding fragment according to claim 1, wherein the CDRL2 contains modifications of CDRL2 set forth in SEQ ID NO: 871 and wherein the modifications are S52L/A55S, based on kabat numbering.

5. An antibody or antigen-binding fragment according to claim 1, wherein the CDRL2 contains modifications of CDRL2 set forth in SEQ ID NO: 871 and wherein the modifications are S52L/A55G, based on kabat numbering.

6. An antibody or antigen-binding fragment according to any one of claims 1 to 5 that exhibits at least a binding affinity that is 10^{-6} M or lower as measured by surface plasmon resonance (SPR).

7. An antibody or antigen-binding fragment according to any one of claims 1 to 6 that is germline-derived, wherein the antibody or antigen-binding fragment comprises:

A: a heavy chain variable domain comprising V_H, D_H, and J_H germline segments wherein

a) the V_H germline segment is an IGHV1, an IGHV4, an IGHV5 or an IGHV6;

b) the D_H germline segment is an IGHD6, an IGHD5, an IGHD4, an IGHD2, an IGHD3, or an IGHD7; and

c) the J_H germline segment is an IGHJ1, an IGHJ2, an IGHJ4, or an IGHJ6; and

a light chain variable domain comprising V_κ and J_κ or V_λ and J_λ germline segments, wherein

a) the V_κ germline segment is an IGKV1, an IGKV2, or an IGKV3 and the J_κ is a IGKJ1; or

b) the V_λ germline segment is an IGLV2, an IGLV8, an IGLV11 or an IGLV5 and the J_λ germline segment is an IGLJ1 or an IGLJ4;

B: a heavy chain variable domain comprising V_H, D_H, and J_H germline segments and a light chain variable domain comprising V_κ and J_κ or V_λ and J_λ germline segments, wherein:

a) the V_H germline segment is an IGHV1-3*01, an IGHV1-3*02, an IGHV1-8*01, an IGHV1-46*01, an IGHV1-46*02, an IGHV1-46*03, an IGHV4-31*01, an IGHV4-31*02, an IGHV4-31*03, an IGHV4-31*04, an IGHV4-31*05, an IGHV4-31*06, an IGHV4-31*07, an IGHV4-31*08, an IGHV4-31*09, an IGHV4-31*10, an IGHV4-34*01, an IGHV4-34*02, an IGHV4-34*03, an IGHV4-34*04, an IGHV4-34*05, an IGHV4-34*06, an IGHV4-34*07, an IGHV4-34*08, an IGHV4-34*09, an IGHV4-34*10, an IGHV4-34*11, an IGHV4-

2009313551 23 Nov 2015

34*12, an IGHV4-34*13, an IGHV5-51*01, an IGHV5-51*02, an IGHV5-51*03, an IGHV5-51*04, an IGHV5-51*05, an IGHV6-1*01, or an IGHV6-1*02 germline segment; and

b) the D_H germline segment is an IGHD2-2*01, an IGHD2-2*02, an IGHD2-15*01, an IGHD4-23*01, an IGHD6-6*01, an IGHD6-13*01, IGHD5-18*01, IGHD3-3*01, an IGHD3-3*02, an IGHD3-10*01, an IGHD3-10*02, or an IGHD7-27*01 germline segment; and

c) the J_H germline segment is an IGHJ1*01, an IGHJ2*01, an IGHJ4*01, an IGHJ4*02, an IGHJ4*03, an IGHJ6*01, an IGHJ6*02, an IGHJ6*03, or an IGHJ6*04 germline segment; and

d) the V_κ germline segment is an IGKV1-5*01, an IGKV1-5*02, an IGKV1-5*03, an IGKV1-12*01, an IGKV1-12*02, an IGKV2-D-40*01, an IGKV3-11*01, an IGKV3-11*02, an IGKV3-15*01, an IGKV3-20*01, or an IGKV3-20*02 germline segment and the J_κ germine segment is an IGKJ1*01 germline segment; or

e) the V_λ germline segment is an IGLV2-14*01, an IGLV2-14*02, an IGLV2-14*03, an IGLV2-14*04, an IGLV8-61*01, an IGLV8-61*02, an IGLV8-61*03, an IGLV5-48*01, or an IGLV11-55*01 germline segment and the J_κ germline segment is an IGLJ1*01 or IGLJ4*01 germline segment; and/or

C: a heavy chain variable domain comprising V_H, D_H, and J_H germline segments and a light chain variable domain comprising V_κ and J_κ or V_λ and J_λ germline segments, wherein:

a) the heavy chain variable domain comprises IGHV1-46*01, an IGHD6-6*01, and an IGHJ1*01 germline segments and the light chain variable domain comprises IGKV3-11*01 and IGKJ1*01 germline segments; or

b) the heavy chain variable domain comprises IGHV5-51*03, IGHD5-18*01, and IGHJ4*01 germline segments and the light chain variable domain comprises IGLV8-61*01 and IGLJ1*01 germline segments; or

c) the heavy chain variable domain comprises IGHV6-1*01, IGHD3-3*01, and IGHJ4*01 germline segments and the light chain variable domain comprises IGLV5-48*01 and IGLJ4*01 germline segments; or

d) the heavy chain variable domain comprises IGHV1-46*01, IGHD6-13*01, and IGHJ4*01 germline segments and the light chain variable domain comprises IGKV3-15*01 and IGKJ1*01 germline segments; or

e) the heavy chain variable domain comprises IGHV4-34*01, IGHD7-27*01, and IGHJ4*01 germline segments and the light chain variable domain comprises IGKV1-12*01 and IGKJ1*01 germline segments; or

2009313551 26 Nov 2015

f) the heavy chain variable domain comprises IGHV1-46*01, IGHD6-13*01, and IGHJ4*01 germline segments and the light chain variable domain comprises IGKV3-20*01 and IGKJ1*01 germline segments; or

g) the heavy chain variable domain comprises IGHV1-3*02, IGHD4-23*01, and IGHJ4*01 germline segments and the light chain variable domain comprises IGKV1-5*01 and IGKJ1*01 germline segments; or

h) the heavy chain variable domain comprises IGHV1-46*01, IGHD2-15*01, and IGHJ2*01 germline segments and the light chain variable domain comprises IGKV1-5*01 and IGKJ1*01 germline segments; or

i) the heavy chain variable domain comprises IGHV1-46*01, IGHD3-10*01, and IGHJ4*01 germline segments and the light chain variable domain comprises IGKV1-5*01 and IGKJ1*01 germline segments; or

j) the heavy chain variable domain comprises IGHV1-8*01, IGHD2-2*01, and IGHJ6*01 germline segments and the light chain variable domain comprises IGKV1-5*01 and IGKJ1*01 germline segments; or

k) the heavy chain variable domain comprises IGHV1-46*01, IGHD6-13*01, and IGHJ4*01 germline segments and the light chain variable domain comprises IGKV2D-40*01 and IGKJ1*01 germline segments; or

l) the heavy chain variable domain comprises IGHV4-34*01, IGHD7-27*01, and IGHJ4*01 germline segments and the light chain variable domain comprises IGLV2-14*01 and IGLJ4*01 germline segments; or

m) the heavy chain variable domain comprises IGHV4-31*02, IGHD2-15*01, and IGHJ2*01 germline segments and the light chain variable domain comprises IGLV2-14*01 and IGLJ4*01 germline segments; or

n) the heavy chain variable domain comprises IGHV4-34*01, IGHD7-27*01, and IGHJ4*01 germline segments and the light chain variable domain comprises IGLV11-55*01 and IGLJ4*01 germline segments.

8. An antibody or antigen-binding fragment according to claim 1, wherein the antibody or antigen-binding fragment (i) exhibits affinity for human DLL4 expressed on the surface of a cell, and/or (ii) modulates an activity of human DLL4.

2009313551 26 Nov 2015

9. A composition comprising a carrier and an isolated antibody or antigen-binding fragment according to any one of claims 1 to 8, wherein the composition is formulated into a formulation for single dose administration or as a sustained release formulation.

10. The composition of claim 9, wherein the formulation is a gel, ointment, cream, paste, suppository, flush, liquid, suspension, aerosol, tablet, pill, or powder.

11. The composition of claim 9, wherein formulation is suitable for systemic, parenteral, topical, oral, mucosal, intranasal, subcutaneous, aerosolized, intravenous, bronchial, pulmonary, vaginal, vulvovaginal, or esophageal administration.

12. The composition of claim 9, wherein the composition is further combined with anti-angiogenic agent.

13. The composition of claim 9, wherein the composition is further combined with an antagonist of vascular endothelial growth factor (VEGF), wherein the VEGF antagonist is an anti-VEGF antibody or antigen-binding fragment thereof.

14. A method of making an anti-DLL4 antibody or antigen-binding fragment, comprising expressing the anti-DLL4 antibody or antigen-binding fragment using a composition comprising a first isolated or recombinant polynucleotide that comprises a coding sequence for a heavy chain variable domain of the antibody or antigen-binding fragment of any one of claims 1 to 8 and a second isolated or recombinant polynucleotide that comprises a coding sequence for a light chain variable domain of the antibody or antigen-binding fragment of any one of claims 1 to 8, wherein the composition comprises at least one of the following:

a) a first vector that contains the first polynucleotide;

b) a second vector that contains the second polynucleotide;

c) a vector that contains the first and second polynucleotides;

d) a host cell stably transfected with the first polynucleotide, wherein the host cell expresses the first polynucleotide to produce a polypeptide that comprises the heavy chain variable domain of an antibody or antigen-binding fragment encoded by the first polynucleotide;

e) a host cell stably transfected with the second polynucleotide, wherein the host cell expresses the second polynucleotide to produce a polypeptide that comprises the light chain

2009313551 26 Nov 2015

variable domain of an antibody or antigen-binding fragment encoded by the second polynucleotide; and

f) a host cell stably transfected with the first and second polynucleotides, wherein the host cell expresses the first and second polynucleotides to produce a first polypeptide that comprises the heavy chain variable domain of an antibody or antigen-binding fragment encoded by the first polynucleotide and a second polypeptide that comprises the light chain variable domain of an antibody or antigen-binding fragment encoded by the second polynucleotide, and wherein the first and second polypeptides assemble to form an antibody or antigen-binding fragment,

and recovering the antibody or antigen-binding fragment.

15. A method of inhibiting Notch activation, comprising delivering an antibody or antigen-binding fragment according to any one of claims 1 to 8 in an amount that inhibits Notch activation.

16. Use of the antibody or antigen-binding fragment according to any one of claims 1 to 8 in the preparation of a medicament for the treatment of a disease or disorder associated with expression and/or activity of DLL4, wherein the disease or disorder is selected from the group consisting of a tumor, cancer, prostate cancer, pancreatic cancer, colon cancer, lung cancer, breast cancer, atherosclerosis, arthritis, ocular neovascularization, endometriosis, uterine fibroids, pre-eclampsia, and a cell proliferative disorder.

17. The use of claim 16, wherein said use further comprises in conjunction at least one of the following:

(i) use of an anti-angiogenic agent to prepare a medicament for use in treating said disease or disorder; and/or

(ii) use of a chemotherapeutic agent to prepare a medicament for use in treating said disease or disorder.

18. The use of claim 17, wherein said anti-angiogenic agent is an antagonist of vascular endothelial growth factor (VEGF), wherein the VEGF antagonist is an anti-VEGF antibody or antigen-binding fragment thereof.

19. An anti-DLL4 antibody or antigen-binding fragment thereof when produced by the method according to claim 14.

2009313551 26 Nov 2015

20. A method of treating a disease or disorder associated with expression and/or activity of DLL4, said method comprising administering the antibody or antigen-binding fragment according to any one of claims 1 to 8, wherein the disease or disorder is selected from the group consisting of a tumor, cancer, prostate cancer, pancreatic cancer, colon cancer, lung cancer, breast cancer, atherosclerosis, arthritis, ocular neovascularization, endometriosis, uterine fibroids, pre-eclampsia, and a cell proliferative disorder.

21. The isolated antibody or antigen-binding fragment thereof according to any one of claims 1 to 8; the composition according to any one of claims 9 to 13; the method according to any one of claims 14, 15 or 20; the use according to any one of claims 16 to 18; or the anti-DLL4 antibody or antigen-binding fragment according to claim 19 substantially as herein described with reference to any one or more of the examples but excluding comparative examples.

Heavy Chain VH1-46_IGHD6-6*01_IGHJ1*01

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
FW1	**Q**	**V**	**Q**	**L**	**V**	**Q**	**S**	**G**	**A**	**E**	**V**	**K**	**K**	**P**	**G**	**A**	**S**	**V**	**K**	**V**	**S**	**C**	**K**	**A**	**S**
Kabat	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Chothia	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25

	26	27	28	29	30	31	32	33	34	35
CDRH1	**G**	**Y**	**T**	**F**	**T**	**S**	**Y**	**Y**	**M**	**H**
Kabat	26	27	28	29	30	31	32	33	34	35
Chothia	26	27	28	29	30	31	32	33	34	35

	36	37	38	39	40	41	42	43	44	45	46	47	48	49	
FW2	**W**	**V**	**R**	**Q**	**A**	**P**	**G**	**Q**	**G**	**L**	**E**	**W**	**M**	**G**	
Kabat	36	37	38	39	40	41	42	43	44	45	46	47	48	49	
Chothia	36	37	38	39	40	41	42	43	44	45	46	47	48	49	

	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66
CDRH2	**I**	**I**	**N**	**P**	**S**	**G**	**G**	**S**	**T**	**S**	**Y**	**A**	**Q**	**K**	**F**	**Q**	**G**
Kabat	50	51	52	a	53	54	55	56	57	58	59	60	61	62	63	64	65
Chothia	50	51	52	a	53	54	55	56	57	58	59	60	61	62	63	64	65

	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98
FW3	**R**	**V**	**T**	**M**	**T**	**R**	**D**	**T**	**S**	**T**	**S**	**T**	**V**	**Y**	**M**	**E**	**L**	**S**	**S**	**L**	**R**	**S**	**E**	**D**	**T**	**A**	**V**	**Y**	**Y**	**C**	**A**	**R**
Kabat	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	a	b	c	83	84	85	86	87	88	89	90	91	92	93	94
Chothia	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	a	b	c	83	84	85	86	87	88	89	90	91	92	93	94

	99	100	101	102	103	104	105	106	107	108	109	110	111	
CDRH3	**E**	**E**	**Y**	**S**	**S**	**S**	**S**	**A**	**E**	**Y**	**F**	**Q**	**H**	
Kabat	95	96	97	98	99	100	a	b	c	d	e	101	102	
Chothia	95	96	97	98	99	100	a	b	c	d	e	101	102	

	112	113	114	115	116	117	118	119	120	121	122	123	124	
FW4	**W**	**G**	**Q**	**G**	**T**	**L**	**V**	**T**	**V**	**S**	**S**	**A**	**S**	
Kabat	103	104	105	106	107	108	109	110	111	112	113			
Chothia	103	104	105	106	107	108	109	110	111	112	113			

FIGURE 1A

Light Chain L6_IGKJ1*01

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	
FW1	**E**	**I**	**V**	**L**	**T**	**Q**	**S**	**P**	**A**	**T**	**L**	**S**	**L**	**S**	**P**	**G**	**E**	**R**	**A**	**T**	**L**	**S**	**C**	
Kabat	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	
Chothia	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	

	24	25	26	27	28	29	30	31	32	33	34	
CDRL1	**R**	**A**	**S**	**Q**	**S**	**V**	**S**	**S**	**Y**	**L**	**A**	
Kabat	24	25	26	27	28	29	30	31	32	33	34	
Chothia	24	25	26	27	28	29	30	31	32	33	34	

	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	
FW2	**W**	**Y**	**Q**	**Q**	**K**	**P**	**G**	**Q**	**A**	**P**	**R**	**L**	**L**	**I**	**Y**	
Kabat	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	
Chothia	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	

	50	51	52	53	54	55	56	
CDRL2	**D**	**A**	**S**	**N**	**R**	**A**	**T**	
Kabat	50	51	52	53	54	55	56	
Chothia	50	51	52	53	54	55	56	

	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88
FW3	**G**	**I**	**P**	**A**	**R**	**F**	**S**	**G**	**S**	**G**	**S**	**G**	**T**	**D**	**F**	**T**	**L**	**T**	**I**	**S**	**S**	**L**	**E**	**P**	**E**	**D**	**F**	**A**	**V**	**Y**	**Y**	**C**
Kabat	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88
Chothia	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88

	89	90	91	92	93	94	95	96	97	98	
CDRL3	**Q**	**Q**	**R**	**S**	**N**	**W**	**P**	**P**	**W**	**T**	
Kabat	89	90	91	92	93	94	95	a	96	97	
Chothia	89	90	91	92	93	94	95	a	96	97	

	99	100	101	102	103	104	105	106	107	108	109	110	
FW4	**F**	**G**	**Q**	**G**	**T**	**K**	**V**	**E**	**I**	**K**	**R**	**T**	
Kabat	98	99	100	101	102	103	104	105	106	107	108	109	
Chothia	98	99	100	101	102	103	104	105	106	107	108	109	

FIGURE 1B

Heavy Chain VH5-51_IGHD5-18*01>3_IGHJ4*01

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
FW1	**E**	**V**	**Q**	**L**	**V**	**Q**	**S**	**G**	**A**	**E**	**V**	**K**	**K**	**P**	**G**	**E**	**S**	**L**	**K**	**I**	**S**	**C**	**K**	**G**	**S**
Kabat	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Chothia	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25

	26	27	28	29	30	31	32	33	34	35
CDRH1	**G**	**Y**	**S**	**F**	**T**	**S**	**Y**	**W**	**I**	**G**
Kabat	26	27	28	29	30	31	32	33	34	35
Chothia	26	27	28	29	30	31	32	33	34	35

	36	37	38	39	40	41	42	43	44	45	46	47	48	49
FW2	**W**	**V**	**R**	**Q**	**M**	**P**	**G**	**K**	**G**	**L**	**E**	**W**	**M**	**G**
Kabat	36	37	38	39	40	41	42	43	44	45	46	47	48	49
Chothia	36	37	38	39	40	41	42	43	44	45	46	47	48	49

	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66
CDRH2	**I**	**I**	**Y**	**P**	**G**	**D**	**S**	**D**	**T**	**R**	**Y**	**S**	**P**	**S**	**F**	**Q**	**G**
Kabat	50	51	52	a	53	54	55	56	57	58	59	60	61	62	63	64	65
Chothia	50	51	52	a	53	54	55	56	57	58	59	60	61	62	63	64	65

	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98
FW3	**Q**	**V**	**T**	**I**	**S**	**A**	**D**	**K**	**S**	**I**	**S**	**T**	**A**	**Y**	**L**	**Q**	**W**	**S**	**S**	**L**	**K**	**A**	**S**	**D**	**T**	**A**	**M**	**Y**	**Y**	**C**	**A**	**R**
Kabat	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	a	b	c	83	84	85	86	87	88	89	90	91	92	93	94
Chothia	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	a	b	c	83	84	85	86	87	88	89	90	91	92	93	94

	99	100	101	102	103	104	105	106	107	108	109	110
CDRH3	**R**	**G**	**Y**	**S**	**Y**	**G**	**Y**	**D**	**Y**	**F**	**D**	**Y**
Kabat	95	96	97	98	99	100	a	b	c	d	101	102
Chothia	95	96	97	98	99	100	a	b	c	d	101	102

	111	112	113	114	115	116	117	118	119	120	121	122	123
FW4	**W**	**G**	**Q**	**G**	**T**	**L**	**V**	**T**	**V**	**S**	**S**	**A**	**S**
Kabat	103	104	105	106	107	108	109	110	111	112	113		
Chothia	103	104	105	106	107	108	109	110	111	112	113		

FIGURE 2A

Light Chain V3-4_IGLJ1*01

	1	2	3	4	5	6	7	8	9		10	11	12	13	14	15	16	17	18	19	20	21	22
FW1	**Q**	**T**	**V**	**V**	**T**	**Q**	**E**	**P**	**S**	**-**	**F**	**S**	**V**	**S**	**P**	**G**	**G**	**T**	**V**	**T**	**L**	**T**	**C**
Kabat	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Chothia	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23

	23	24	25	26	27	28	29	30	31	32	33	34	35
CDRL1	**G**	**L**	**S**	**S**	**G**	**S**	**V**	**S**	**T**	**S**	**Y**	**Y**	**P**
Kabat	24	25	26	27	a	b	c	28	29	30	31	32	33
Chothia	24	25	26	27	28	29	30	a	b	c	31	32	33

	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51
FW2	**S**	**W**	**Y**	**Q**	**Q**	**T**	**P**	**G**	**Q**	**A**	**P**	**R**	**T**	**L**	**I**	**Y**
Kabat	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49
Chothia	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49

	52	53	54	55	56	57	58
CDRL2	**S**	**T**	**N**	**T**	**R**	**S**	**S**
Kabat	50	51	52	53	54	55	56
Chothia	50	51	52	53	54	55	56

	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90
FW3	**G**	**V**	**P**	**D**	**R**	**F**	**S**	**G**	**S**	**I**	**L**	**G**	**N**	**K**	**A**	**A**	**L**	**T**	**I**	**T**	**G**	**A**	**Q**	**A**	**D**	**D**	**E**	**S**	**D**	**Y**	**Y**	**C**
Kabat	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88
Chothia	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88

	91	92	93	94	95	96	97	98	99	100	101
CDRL3	**V**	**L**	**Y**	**M**	**G**	**S**	**G**	**I**	**S**	**Y**	**V**
Kabat	89	90	91	92	93	94	95	a	b	96	97
Chothia	89	90	91	92	93	94	95	a	b	96	97

	101	102	103	104	105	106	107	108	109	110
FW4	**F**	**G**	**T**	**G**	**T**	**K**	**V**	**T**	**V**	**L**
Kabat	98	99	100	101	102	103	104	105	106	a
Chothia	98	99	100	101	102	103	104	105	106	a

FIGURE 2B

SEQUENCE LISTING

<110> Fabrus LLC
Snider, Vaughn
Mao, Helen Hongyuan
Bentley, Cornelia A.
Chase, Tyson

<120> Anti-DLL4 Antibodies and Uses Thereof

<130> 3800016.00087/703PC

<140> Not yet assigned
<141> Herewith

<150> 61/198,764
<151> 2008-11-07

<150> 61/211,204
<151> 2009-03-25

<160> 904

<170> FastSEQ for Windows Version 4.0

<210> 1
<211> 45
<212> DNA
<213> Artificial Sequence

<220>
<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 R99A_F

<400> 1

gccatgtatt actgtgcgag agccggatac agctatggtt acgac 45

<210> 2

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 R99A_R

<400> 2

gtcgtaacca tagctgtatc cggctctcgc acagtaatac atggc 45

<210> 3

<211> 43

<212> DNA

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 E100A_F

<400> 3

gtgtattact gtgcgagaga ggcctatagc agctcgtccg ctg 43

<210> 4

<211> 43

<212> DNA

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 E100A_R

<400> 4

cagcggacga gctgctatag gcctctctcg cacagtaata cac 43

<210> 5

<211> 33

<212> DNA

<213> Artificial Sequence

<220>

<223> EcoRI_F

<400> 5

ttgggcgaat tccctagata attaattagg agg 33

<210> 6

<211> 28

<212> DNA

<213> Artificial Sequence

<220>

<223> FLXhoI_R

<400> 6

ttaaacctcg agccgcggtt cattaaag 28

<210> 7

<211> 40

<212> DNA

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100_NNK_F

<220>

<221> unsure

<222> (20)...(21)

<223> n = a or g or c or t

<400> 7

gtattactgt gcgagacgtn nktacagcta tggttacgac 40

<210> 8

<211> 40

<212> DNA

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100_NNK_R

<220>

<221> unsure

<222> (20)...(21)

<223> n = a or g or c or t

<400> 8

gtcgtaacca tagctgtamm nacgtctcgc acagtaatac 40

<210> 9

<211> 35

<212> DNA

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102_NNK_F

<220>

<221> unsure

<222> (17)...(18)

<223> n = a or g or c or t

<400> 9

tgcgagagag gggtatnnka gcagctggta cgact 35

<210> 10

<211> 35

<212> DNA

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102_NNK_R

<220>

<221> unsure

<222> (18)...(19)

<223> n = a or g or c or t

<400> 10

agtcgtacca gctgctmnna taccctctc tcgca 35

<210> 11

<211> 39

<212> DNA

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 CDR1_F

<400> 11

gagacctact atggttcggg tctctgggtg cgacaggcc 39

<210> 12

<211> 44

<212> DNA

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 CDR2_F

<400> 12

gagacctact atggttcggg tctcaagttc cagggcagag tcac 44

<210> 13

<211> 38

<212> DNA

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 CDR3_F

<400> 13

gagacctact atggttcggg tctctggggc cagggcac 38

<210> 14

<211> 39

<212> DNA

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 CDR1_F

<400> 14

gagacctact atggttcggg tctctgggtg cgccagatg 39

<210> 15

<211> 43

<212> DNA

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 CDR2_F

<400> 15

gagacctact atggttcggg tctccaggtc accatctcag ccg 43

<210> 16

<211> 40

<212> DNA

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 CDR3_F

<400> 16

gagacctact atggttcggg tctctggggc caaggaaccc 40

<210> 17

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 CDR1_F

<400> 17

gagacctact atggttcggg tctctggtac caacagaaac ctggc 45

<210> 18

<211> 39

<212> DNA

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 CDR2_F

<400> 18

gagacctact atggttcggg tctcggcatc ccagccagg 39

<210> 19

<211> 40

<212> DNA

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 CDR3_F

<400> 19

gagacctact atggttcggg tctcttcggc caagggacca 40

<210> 20

<211> 42

<212> DNA

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 CDR1_F

<400> 20

gagacctact atggttcggg tctctggtac cagcagaccc ca 42

<210> 21

<211> 42

<212> DNA

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 CDR2_F

<400> 21

gagacctact atggttcggg tctcggggtc cctgatcgct tc 42

<210> 22

<211> 42

<212> DNA

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 CDR3_F

<400> 22

gagacctact atggttcggg tctcttcgga actgggacca ag 42

<210> 23

<211> 20

<212> DNA

<213> Artificial Sequence

<220>

<223> Lambda_BSA_F

<400> 23

gagtggagac gaccacaccc 20

<210> 24

<211> 43

<212> DNA

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 CDR1_R

<400> 24
gagacccgaa ccatagtagg tctcagatgc cttgcaggaa acc 43

<210> 25
<211> 42
<212> DNA
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 CDR2_R

<400> 25
gagacccgaa ccatagtagg tctctcccat ccactcaagc cc 42

<210> 26
<211> 45
<212> DNA
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 CDR3_R

<400> 26
gagacccgaa ccatagtagg tctctctcgc acagtaatac acggc 45

<210> 27
<211> 47
<212> DNA
<213> Artificial Sequence

<220>
<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 CDR1_R

<400> 27
gagacccgaa ccatagtagg tctcagaacc cttacaggag atcttca 47

<210> 28
<211> 41
<212> DNA
<213> Artificial Sequence

<220>
<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 CDR2_R

<400> 28
gagacccgaa ccatagtagg tctcccccat ccactccagg c 41

<210> 29
<211> 45
<212> DNA
<213> Artificial Sequence

<220>
<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 CDR3_R

<400> 29
gagacccgaa ccatagtagg tctctctcgc acagtaatac atggc 45

<210> 30
<211> 41
<212> DNA
<213> Artificial Sequence

<220>
<223> L6_IGKJ1*01 CDR1_R

<400> 30

gagacccgaa ccatagtagg tctcgcagga gagggtggct c 41

<210> 31

<211> 44

<212> DNA

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 CDR2_R

<400> 31

gagacccgaa ccatagtagg tctcatagat gaggagcctg ggag 44

<210> 32

<211> 50

<212> DNA

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 CDR3_R

<400> 32

gagacccgaa ccatagtagg tctcacagta ataaactgca aaatcttcag 50

<210> 33

<211> 46

<212> DNA

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 CDR1_R

<400> 33

gagacccgaa ccatagtagg tctcacaagt gagtgtgact gtccct 46

<210> 34
<211> 42
<212> DNA
<213> Artificial Sequence

<220>
<223> V3-4_IGLJ1*01 CDR2_R

<400> 34
gagacccgaa ccatagtagg tctcgtagat gagcgtgcgt gg 42

<210> 35
<211> 51
<212> DNA
<213> Artificial Sequence

<220>
<223> V3-4_IGLJ1*01 CDR3_R

<400> 35
gagacccgaa ccatagtagg tctcacagta ataatcagat tcatcatctg c 51

<210> 36
<211> 45
<212> DNA
<213> Artificial Sequence

<220>
<223> A_ILPTH_F

<400> 36
tgggaataat tctccctact ggtcatagca caagctacgc acaga 45

<210> 37

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> A_VLPTH_F

<400> 37

tgggaatagt gctccctact ggtcatagca caagctacgc acaga 45

<210> 38

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> A_ALPTH_F

<400> 38

tgggaatagc tctccctact ggtcatagca caagctacgc acaga 45

<210> 39

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> A_GLPTH_F

<400> 39

tgggaatagg cctccctact ggtcatagca caagctacgc acaga 45

<210> 40

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> A_TLPTH_F

<400> 40

tgggaataac cctccctact ggtcatagca caagctacgc acaga 45

<210> 41

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> A_SLPTH_F

<400> 41

tgggaatatc cctccctact ggtcatagca caagctacgc acaga 45

<210> 42

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> A_YLPTH_F

<400> 42

tgggaatata cctccctact ggtcatagca caagctacgc acaga 45

<210> 43

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> A_WLPTH_F

<400> 43

tgggaatatg gctccctact ggtcatagca caagctacgc acaga 45

<210> 44

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> A_HLPTH_F

<400> 44

tgggaataca cctccctact ggtcatagca caagctacgc acaga 45

<210> 45

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> A_RLPTH_F

<400> 45

tgggaatacg cctccctact ggtcatagca caagctacgc acaga 45

<210> 46

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> A_ELPTH_F

<400> 46

tgggaataga actccctact ggtcatagca caagctacgc acaga 45

<210> 47

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> A_NLPTH_F

<400> 47

tgggaataaa cctccctact ggtcatagca caagctacgc acaga 45

<210> 48

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> A_TLVTH_F

<400> 48

tgggaataac cctcgtgact ggtcatagca caagctacgc acaga 45

<210> 49

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> A_TLATH_F

<400> 49

tgggaataac cctcgctact ggtcatagca caagctacgc acaga 45

<210> 50

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> A_TLGTH_F

<400> 50

tgggaataac cctcggcact ggtcatagca caagctacgc acaga 45

<210> 51

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> A_TLTTH_F

<400> 51

tgggaataac cctcaccact ggtcatagca caagctacgc acaga 45

<210> 52

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> A_TLSTH_F

<400> 52

tgggaataac cctctccact ggtcatagca caagctacgc acaga 45

<210> 53

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> A_TLYTH_F

<400> 53

tgggaataac cctctacact ggtcatagca caagctacgc acaga 45

<210> 54

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> A_TLWTH_F

<400> 54

tgggaataac cctctggact ggtcatagca caagctacgc acaga 45

<210> 55

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> A_TLHTH_F

<400> 55

tgggaataac cctccacact ggtcatagca caagctacgc acaga 45

<210> 56

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> A_TLRTH_F

<400> 56

tgggaataac cctccgcact ggtcatagca caagctacgc acaga 45

<210> 57

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> A_TLETH_F

<400> 57

tgggaataac cctcgaaact ggtcatagca caagctacgc acaga 45

<210> 58

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> A_TLNTH_F

<400> 58

tgggaataac cctcggcact ggtcatagca caagctacgc acaga 45

<210> 59

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> A_TLMTH_F

<400> 59

tgggaataac cctcatgact ggtcatagca caagctacgc acaga 45

<210> 60

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> A_ILPTH_R

<400> 60

aacttctgtg cgtagcttgt gctatgacca gtagggagaa ttatt 45

<210> 61

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> A_VLPTH_R

<400> 61

aacttctgtg cgtagcttgt gctatgacca gtagggagca ctatt 45

<210> 62

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> A_ALPTH_R

<400> 62

aacttctgtg cgtagcttgt gctatgacca gtagggagag ctatt 45

<210> 63

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> A_GLPTH_R

<400> 63

aacttctgtg cgtagcttgt gctatgacca gtagggaggc ctatt 45

<210> 64

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> A_TLPTH_R

<400> 64

aacttctgtg cgtagcttgt gctatgacca gtagggaggg ttatt 45

<210> 65

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> A_SLPTH_R

<400> 65

aacttctgtg cgtagcttgt gctatgacca gtagggaggg atatt 45

<210> 66

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> A_YLPTH_R

<400> 66

aacttctgtg cgtagcttgt gctatgacca gtagggaggt atatt 45

<210> 67

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> A_WLPTH_R

<400> 67

aacttctgtg cgtagcttgt gctatgacca gtagggagcc atatt 45

<210> 68
<211> 45
<212> DNA
<213> Artificial Sequence

<220>
<223> A_HLPTH_R

<400> 68
aacttctgtg cgtagcttgt gctatgacca gtagggaggt gtatt 45

<210> 69
<211> 45
<212> DNA
<213> Artificial Sequence

<220>
<223> A_RLPTH_R

<400> 69
aacttctgtg cgtagcttgt gctatgacca gtagggaggc gtatt 45

<210> 70
<211> 45
<212> DNA
<213> Artificial Sequence

<220>
<223> A_ELPTH_R

<400> 70
aacttctgtg cgtagcttgt gctatgacca gtagggagtt ctatt 45

<210> 71

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> A_NLPTH_R

<400> 71

aacttctgtg cgtagcttgt gctatgacca gtagggaggt ttatt 45

<210> 72

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> A_TLVTH_R

<400> 72

aacttctgtg cgtagcttgt gctatgacca gtcacgaggg ttatt 45

<210> 73

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> A_TLATH_R

<400> 73

aacttctgtg cgtagcttgt gctatgacca gtagcgaggg ttatt 45

<210> 74

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> A_TLGTH_R

<400> 74

aacttctgtg cgtagcttgt gctatgacca gtgccgaggg ttatt 45

<210> 75

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> A_TLTTH_R

<400> 75

aacttctgtg cgtagcttgt gctatgacca gtggtgaggg ttatt 45

<210> 76

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> A_TLSTH_R

<400> 76

aacttctgtg cgtagcttgt gctatgacca gtggagaggg ttatt 45

<210> 77

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> A_TLYTH_R

<400> 77

aacttctgtg cgtagcttgt gctatgacca gtgtagaggg ttatt 45

<210> 78

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> A_TLWTH_R

<400> 78

aacttctgtg cgtagcttgt gctatgacca gtccagaggg ttatt 45

<210> 79

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> A_TLHTH_R

<400> 79

aacttctgtg cgtagcttgt gctatgacca gtgtggaggg ttatt 45

<210> 80

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> A_TLRTH_R

<400> 80

aacttctgtg cgtagcttgt gctatgacca gtgcggaggg ttatt 45

<210> 81

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> A_TLETH_R

<400> 81

aacttctgtg cgtagcttgt gctatgacca gtttcgaggg ttatt 45

<210> 82

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> A_TLNTH_R

<400> 82

aacttctgtg cgtagcttgt gctatgacca gtgccgaggg ttatt 45

<210> 83

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> A_TLMTH_R

<400> 83

aacttctgtg cgtagcttgt gctatgacca gtcatgaggg ttatt 45

<210> 84

<211> 5476

<212> DNA

<213> Artificial Sequence

<220>

<223> Plasmid A (heavy chain with Flag-H6 tag)

<400> 84

catgaccaaa atcccttaac gtgagttttc gttccactga gcgtcagacc ccgtagaaaa 60

gatcaaagga tcttcttgag atcctttttt tctgcgcgta atctgctgct tgcaaacaaa 120

aaaaccaccg ctaccagcgg tggtttgttt gccggatcaa gagctaccaa ctcttttcc 180

gaaggtaact ggcttcagca gagcgcagat accaaatact gttcttctag tgtagccgta 240

gttaggccac cacttcaaga actctgtagc accgcctaca tacctcgctc tgctaatcct 300

gttaccagtg gctgctgcca gtggcgataa gtcgtgtctt accgggttgg actcaagacg 360

atagttaccg gataaggcgc agcggtcggg ctgaacgggg ggttcgtgca cacagcccag 420

cttggagcga acgacctaca ccgaactgag atacctacag cgtgagctat gagaaagcgc 480

cacgcttccc gaagggagaa aggcggacag gtatccggta agcggcaggg tcggaacagg 540

agagcgcacg agggagcttc cagggggaaa cgcctggtat ctttatagtc ctgtcgggtt 600

tcgccacctc tgacttgagc gtcgatttt gtgatgctcg tcaggggggc ggagcctatg 660

gaaaaacgcc agcaacgcgg cctttttacg gttcctggcc ttttgctggc cttttgctca 720

catgtcccgg gtctttcctg cgttatcccc tgattctgtg gataaccgta ttaccgcctt 780

tgagtgagct gataccgctc gccgcagccg aacgaccgag cgcagcgagt cagtgagcga 840

ggaagcggaa gagcgcctga tgcggtattt tctccttacg catctgtgcg gtatttcaca 900

ccgcatatgg tgcactctca gtacaatctg ctctgatgcc gcatagttaa gccagtatac 960

actccgctat cgctacgtga ctgggtcatg gctgcgcccc gacacccgcc aacacccgct 1020

gacgcgccct gacgggct t g t ct gct cccg gcat ccgct t acagacaagc t gt gaccgt c 1080

t ccgggagct gcat gt gt ca gaggt t t t ca ccgt cat cac cgaaacgcgc gaggcagcag 1140

at caat t cgc gcgcgaaggc gaagcggcat gcat aat gt g cct gt caaat ggacgaagca 1200

gggat t ct gc aaaccct at g ct act ccgt c aagccgt caa t t gt ct gat t cgt t accaat 1260

t at gacaact t gacggct ac at cat t cact t t t t ct t cac aaccggcacg gaact cgct c 1320

gggct ggccc cggt gcat t t t t t aaat acc cgcgagaaat agagt t gat c gt caaaacca 1380

acat t gcgac cgacggt ggc gat aggcat c cgggt ggt gc t caaaagcag ct t cgcct gg 1440

ct gat acgt t ggt cct cgcg ccagct t aag acgct aat cc ct aact gct g gcggaaaaga 1500

t gt gacagac gcgacggcga caagcaaaca t gct gt gcga cgct ggcgat at caaaat t g 1560

ct gt ct gcca ggt gat cgct gat gt act ga caagcct cgc gt acccgat t at ccat cggt 1620

ggat ggagcg act cgt t aat cgct t ccat g cgccgcagt a acaat t gct c aagcagat t t 1680

at cgccagca gct ccgaat a gcgccct t cc cct t gcccgg cgt t aat gat t t gcccaaac 1740

aggt cgct ga aat gcggct g gt gcgct t ca t ccgggcgaa agaaccccgt at t ggcaaat 1800

at t gacggcc agt t aagcca t t cat gccag t aggcgcgcg gacgaaagt a aacccact gg 1860

t gat accat t cgcgagcct c cggat gacga ccgt agt gat gaat ct ct cc t ggcgggaac 1920

agcaaaat at cacccggt cg gcaaacaaat t ct cgt ccct gat t t t t cac cacccct ga 1980

ccgcgaat gg t gagat t gag aat at aacct t t cat t ccca gcggt cggt c gat aaaaaaa 2040

t cgagat aac cgt t ggcct c aat cggcgt t aaacccgcca ccagat gggc at t aaacgag 2100

t at cccggca gcaggggat c at t t t gcgct t cagccat ac t t t t cat act cccgccat t c 2160

agagaagaaa ccaat t gt cc at at t gcat c agacat t gcc gt cact gcgt ct t t t act gg 2220

ct ct t ct cgc t aaccaaacc ggt aaccccg ct t at t aaaa gcat t ct gt a acaaagcggg 2280

accaaagcca t gacaaaaac gcgt aacaaa agt gt ct at a at cacggcag aaaagt ccac 2340

at t gat t at t t gcacggcgt cacact t t gc t at gccat ag cat t t t t at c cat aagat t a 2400

gcggat cct a cct gacgct t t t t at cgcaa ct ct ct act g t t t ct ccat a cccgt t t t t t 2460

gggcgaat t c cct aggt aat t aat t aggag gaat t t aaaa t gaaaaagaa t at cgcat t t 2520

ct t ct t gcat ct at gt t cgt t t t t t caat t gct acgaacg ccat ggcaga ggt gcagct g 2580

t t ggagt ct g ggggaggct t ggt acagcct gggggt ccc t gagact ct c ct gt gcagcc 2640

t ct ggat t ca cct t t agcag ct at gccat g agct gggt cc gccaggct cc agggaagggg 2700

ct ggagt ggg t ct cagct at t agt ggt agt ggt ggt agca cat act acgc agact ccgt g 2760

aagggccggt t caccat ct c cagagacaat t ccaagaaca cgct gt at ct gcaaat gaac 2820

agcct gagag ccgaggacac ggccgt at at t act gt gcga aagagt at t a ct at ggt t cg 2880

gggagt t at t at aacgact a ct t t gact ac t ggggccaag gaaccct ggt caccgt ct cc 2940

t cagct agca ccaagggccc at cggt ct t c cccct ggcac cct cct ccaa gagcacct ct 3000

gggggcacag cggccct ggg ct gcct ggt c aaggact act t ccccgaacc ggt gacggt g 3060

t cgt ggaact caggcgccct gaccagcggc gt gcacacct t cccggct gt cct acagt cc 3120

t caggact ct act ccct cag cagcgt ggt g accgt gccct ccagcagct t gggcacccag 3180

acct acat ct gcaacgt gaa t cacaagccc agcaacacca aggt ggacaa gaaagt t gag 3240

cccaaat ct t gt gacaaaga cgt cgat t ac aaggat gacg acgat aagca t cat caccat 3300

caccat t aat t aat t aagcg gccgct ccca cagccgccag t t ccgct ggc ggcat t t t aa 3360

ct t t ct t t aa t gaaccgcgg ct cgagcat g cat ct agagg gcccaat t cg ccct at agt g 3420

agt cgt at t a caat t cact g gccgt cgt t t t acaacgt cg t gact gggaa aaccct ggcg 3480

t t acccaact t aat cgcct t gcagcacat c cccct t t cgc cagct ggcgt aat agcgaag 3540

aggcccgcac cgat cgccct t cccaacagt t gcgcagcct at acgt acgg cagt t t aagg 3600

t t t acacct a t aaaagagag agccgt t at c gt ct gt t t gt ggat gt acag agt gat at t a 3660

t t gacacgcc ggggcgacgg at ggt gat cc ccct ggccag t gcacgt ct g ct gt cagat a 3720

aagt ct cccg t gaact t t ac ccggt ggt gc at at cgggga t gaaagct gg cgcat gat ga 3780

ccaccgat at ggccagt gt g ccggt ct ccg t t at cgggga agaagt ggct gat ct cagcc 3840

accgcgaaaa t gacat caaa aacgccat t a acct gat gt t ct ggggaat a t aaat gt cag 3900

gcct gaat gg cgaat ggacg cgccct gt ag cggcgcat t a agcgcggcgg gt gt ggt ggt 3960

t acgcgcagc gt gaccgct a cact t gccag cgccct agcg cccgct cct t t cgct t t ct t 4020

ccct t cct t t ct cgccacgt t cgccggct t t ccccgt caa gct ct aaat c gggggct ccc 4080

t t t agggt t c cgat t t agt g ct t t acggca cct cgacccc aaaaaact t g at t agggt ga 4140

t ggt t cacgt agt gggccat cgccct gat a gacggt t t t t cgccct t t ga cgt t ggagt c 4200

cacgt t ct t t aat agt ggac t ct t gt t cca aact ggaaca acact caacc ct at ct cggt 4260

ct at t ct t t t gat t t at aag ggat t t t gcc gat t t cggcc t at t ggt t aa aaaat gagct 4320

gat t t aacaa aaat t t t aac aaaat t caga agaact cgt c aagaaggcga t agaaggcga 4380

t gcgct gcga at cgggagcg gcgat accgt aaagcacgag gaagcggt ca gcccat t cgc 4440

cgccaagct c t t cagcaat a t cacgggt ag ccaacgct at gt cct gat ag cggt ccgcca 4500

cacccagccg gccacagt cg at gaat ccag aaaagcggcc at t t t ccacc at gat at t cg 4560

gcaagcaggc at cgccat ga gt cacgacga gat cct cgcc gt cgggcat g ct cgcct t ga 4620

gcct ggcgaa cagt t cggct ggcgcgagcc cct gat gct c t t cgt ccaga t cat cct gat 4680

cgacaagacc ggct t ccat c cgagt acgt g ct cgct cgat gcgat gt t t c gct t ggt ggt 4740

cgaat gggca ggt agccgga t caagcgt at gcagccgccg cat t gcat ca gccat gat gg 4800

at act t t ct c ggcaggagca aggt gagat g acaggagat c ct gccccggc act t cgccca 4860

at agcagcca gt ccct t ccc gct t cagt ga caacgt cgag cacagct gcg caaggaacgc 4920

ccgt cgt ggc cagccacgat agccgcgct g cct cgt ct t g cagt t cat t c agggcaccgg 4980

acaggt cggt ct t gacaaaa agaaccgggc gcccct gcgc t gacagccgg aacacggcgg 5040

cat cagagca gccgat t gt c t gt t gt gccc agt cat agcc gaat agcct c t ccacccaag 5100

cggccggaga acctgcgtgc aatccatctt gttcaatcat gcgaaacgat cctcatcctg 5160
tctcttgatc agagcttgat cccctgcgcc atcagatcct tggcggcgag aaagccatcc 5220
agtttacttt gcagggcttc ccaaccttac cagagggcgc cccagctggc aattccggtt 5280
cgcttgctgt ccataaaacc gcccagtcta gctatcgcca tgtaagccca ctgcaagcta 5340
cctgctttct ctttgcgctt gcgttttccc ttgtccagat agcccagtag ctgacattca 5400
tccggggtca gcaccgtttc tgcggactgg ctttctacgt gaaaaggatc taggtgaaga 5460
tcctttttga taatct 5476

<210> 85
<211> 5491
<212> DNA
<213> Plasmid D (heavy chain with Flag-LPETG-H6 tag) Arti

<220>
<223> Plasmid D (heavy chain with Flag-LPETG-H6 tag)

<400> 85
catgaccaaa atcccttaac gtgagttttc gttccactga gcgtcagacc ccgtagaaaa 60
gatcaaagga tcttcttgag atcctttttt tctgcgcgta atctgctgct tgcaaacaaa 120
aaaaccaccg ctaccagcgg tggtttgttt gccggatcaa gagctaccaa ctcttttcc 180
gaaggtaact ggcttcagca gagcgcagat accaaatact gttcttctag tgtagccgta 240
gttaggccac cacttcaaga actctgtagc accgcctaca tacctcgctc tgctaatcct 300
gttaccagtg gctgctgcca gtggcgataa gtcgtgtctt accgggttgg actcaagacg 360
atagttaccg gataaggcgc agcggtcggg ctgaacgggg ggttcgtgca cacagcccag 420
cttggagcga acgacctaca ccgaactgag atacctacag cgtgagctat gagaaagcgc 480
cacgcttccc gaagggagaa aggcggacag gtatccggta agcggcaggg tcggaacagg 540
agagcgcacg agggagcttc cagggggaaa cgcctggtat ctttatagtc ctgtcgggtt 600
tcgccacctc tgacttgagc gtcgatttt gtgatgctcg tcaggggggc ggagcctatg 660
gaaaaacgcc agcaacgcgg cctttttacg gttcctggcc ttttgctggc ctttgctca 720
catgtcccgg gtctttcctg cgttatcccc tgattctgtg gataaccgta ttaccgcctt 780
tgagtgagct gataccgctc gccgcagccg aacgaccgag cgcagcgagt cagtgagcga 840
ggaagcggaa gagcgcctga tgcggtattt tctccttacg catctgtgcg gtatttcaca 900
ccgcatatgg tgcactctca gtacaatctg ctctgatgcc gcatagttaa gccagtatac 960

act ccgct at cgct acgt ga ct gggt cat g gct gcgcccc gacacccgcc aacacccgct 1020

gacgcgccct gacgggct t g t ct gct cccg gcat ccgct t acagacaagc t gt gaccgt c 1080

t ccgggagct gcat gt gt ca gaggt t t t ca ccgt cat cac cgaaacgcgc gaggcagcag 1140

at caat t cgc gcgcgaaggc gaagcggcat gcat aat gt g cct gt caaat ggacgaagca 1200

gggat t ct gc aaaccct at g ct act ccgt c aagccgt caa t t gt ct gat t cgt t accaat 1260

t at gacaact t gacggct ac at cat t cact t t t t ct t cac aaccggcacg gaact cgct c 1320

gggct ggccc cggt gcat t t t t t aaat acc cgcgagaaat agagt t gat c gt caaaacca 1380

acat t gcgac cgacggt ggc gat aggcat c cgggt ggt gc t caaaagcag ct t cgcct gg 1440

ct gat acgt t ggt cct cgcg ccagct t aag acgct aat cc ct aact gct g gcggaaaaga 1500

t gt gacagac gcgacggcga caagcaaaca t gct gt gcga cgct ggcgat at caaaat t g 1560

ct gt ct gcca ggt gat cgct gat gt act ga caagcct cgc gt acccgat t at ccat cggt 1620

ggat ggagcg act cgt t aat cgct t ccat g cgccgcagt a acaat t gct c aagcagat t t 1680

at cgccagca gct ccgaat a gcgccct t cc cct t gcccgg cgt t aat gat t t gcccaaac 1740

aggt cgct ga aat gcggct g gt gcgct t ca t ccgggcgaa agaaccccgt at t ggcaaat 1800

at t gacggcc agt t aagcca t t cat gccag t aggcgcgcg gacgaaagt a aacccact gg 1860

t gat accat t cgcgagcct c cggat gacga ccgt agt gat gaat ct ct cc t ggcgggaac 1920

agcaaaat at cacccggt cg gcaaacaaat t ct cgt ccct gat t t t t cac caccccct ga 1980

ccgcgaat gg t gagat t gag aat at aacct t t cat t ccca gcggt cggt c gat aaaaaaa 2040

t cgagat aac cgt t ggcct c aat cggcgt t aaacccgcca ccagat gggc at t aaacgag 2100

t at cccggca gcaggggat c at t t t gcgct t cagccat ac t t t t cat act cccgccat t c 2160

agagaagaaa ccaat t gt cc at at t gcat c agacat t gcc gt cact gcgt ct t t t act gg 2220

ct ct t ct cgc t aaccaaacc ggt aaccccg ct t at t aaaa gcat t ct gt a acaaagcggg 2280

accaaagcca t gacaaaaac gcgt aacaaa agt gt ct at a at cacggcag aaaagt ccac 2340

at t gat t at t t gcacggcgt cacact t t gc t at gccat ag cat t t t t at c cat aagat t a 2400

gcggat cct a cct gacgct t t t t at cgcaa ct ct ct act g t t t ct ccat a cccgt t t t t t 2460

gggcgaat t c cct aggt aat t aat t aggag gaat t t aaaa t gaaaaagaa t at cgcat t t 2520

ct t ct t gcat ct at gt t cgt t t t t t caat t gct acgaacg ccat ggcaga ggt gcagct g 2580

t t ggagt ct g ggggaggct t ggt acagcct ggggggt ccc t gagact ct c ct gt gcagcc 2640

t ct ggat t ca cct t t agcag ct at gccat g agct gggt cc gccaggct cc agggaagggg 2700

ct ggagt ggg t ct cagct at t agt ggt agt ggt ggt agca cat act acgc agact ccgt g 2760

aagggccggt t caccat ct c cagagacaat t ccaagaaca cgct gt at ct gcaaat gaac 2820

agcct gagag ccgaggacac ggccgt at at t act gt gcga aagagt at t a ct at ggt t cg 2880

gggagt t at t at aacgact a ct t t gact ac t ggggccaag gaaccct ggt caccgt ct cc 2940

t cagct agca ccaagggccc at cggt ct t c cccct ggcac cct cct ccaa gagcacct ct 3000

ggggg cacag cggccct ggg ct gcct ggt c aaggact act t ccccgaacc ggt gacggt g 3060

t cgt ggaact caggcgccct gaccagcggc gt gcacacct t cccggct gt cct acagt cc 3120

t caggact ct act ccct cag cagcgt ggt g accgt gccct ccagcagct t gggcacccag 3180

acct acat ct gcaacgt gaa t cacaagccc agcaacacca aggt ggacaa gaaagt t gag 3240

cccaaat ct t gt gacaaaga cgt cgat t ac aaggat gacg acgat aagct t ccggaaacc 3300

ggt cat cat c accat cacca t t aat t aat t aagcggccgc t cccacagcc gccagt t ccg 3360

ct ggcggcat t t t aact t t c t t t aat gaac cgcggct cga gcat gcat ct agagggccca 3420

at t cgccct a t agt gagt cg t at t acaat t cact ggccgt cgt t t t acaa cgt cgt gact 3480

gggaaaaccc t ggcgt t acc caact t aat c gcct t gcagc acat ccccct t t cgccagct 3540

ggcgt aat ag cgaagaggcc cgcaccgat c gccct t ccca acagt t gcgc agcct at acg 3600

t acggcagt t t aaggt t t ac acct at aaaa gagagagccg t t at cgt ct g t t t gt ggat g 3660

t acagagt ga t at t at t gac acgccggggc gacggat ggt gat ccccct g gccagt gcac 3720

gt ct gct gt c agat aaagt c t cccgt gaac t t t acccggt ggt gcat at c ggggat gaaa 3780

gct ggcgcat gat gaccacc gat at ggcca gt gt gccggt ct ccgt t at c ggggaagaag 3840

t ggct gat ct cagccaccgc gaaaat gaca t caaaaacgc cat t aacct g at gt t ct ggg 3900

gaat at aaat gt caggcct g aat ggcgaat ggacgcgccc t gt agcggcg cat t aagcgc 3960

ggcgggt gt g gt ggt t acgc gcagcgt gac cgct acact t gccagcgccc t agcgcccgc 4020

t cct t t cgct t t ct t ccct t cct t t ct cgc cacgt t cgcc ggct t t cccc gt caagct ct 4080

aaat cggggg ct ccct t t ag ggt t ccgat t t agt gct t t a cggcacct cg accccaaaaa 4140

act t gat t ag ggt gat ggt t cacgt agt gg gccat cgccc t gat agacgg t t t t t cgccc 4200

t t t gacgt t g gagt ccacgt t ct t t aat ag t ggact ct t g t t ccaaact g gaacaacact 4260

caaccct at c t cggt ct at t ct t t t gat t t at aagggat t t t gccgat t t cggcct at t g 4320

gt t aaaaaat gagct gat t t aacaaaaat t t t aacaaaat t cagaagaac t cgt caagaa 4380

ggcgat agaa ggcgat gcgc t gcgaat cgg gagcggcgat accgt aaagc acgaggaagc 4440

ggt cagccca t t cgccgcca agct ct t cag caat at cacg ggt agccaac gct at gt cct 4500

gat agcggt c cgccacaccc agccggccac agt cgat gaa t ccagaaaag cggccat t t t 4560

ccaccat gat at t cggcaag caggcat cgc cat gagt cac gacgagat cc t cgccgt cgg 4620

gcat gct cgc ct t gagcct g gcgaacagt t cggct ggcgc gagcccct ga t gct ct t cgt 4680

ccagat cat c ct gat cgaca agaccggct t ccat ccgagt acgt gct cgc t cgat gcgat 4740

gt t t cgct t g gt ggt cgaat gggcaggt ag ccggat caag cgt at gcagc cgccgcat t g 4800

cat cagccat gat ggat act t t ct cggcag gagcaaggt g agat gacagg agat cct gcc 4860

ccggcact t c gcccaat agc agccagt ccc t t cccgct t c agt gacaacg t cgagcacag 4920

ct gcgcaagg aacgcccgt c gt ggccagcc acgat agccg cgct gcct cg t ct t gcagt t 4980

cat t cagggc accggacagg t cggt ct t ga caaaaagaac cgggcgcccc t gcgct gaca 5040

gccggaacac ggcggcatca gagcagccga ttgtctgttg tgcccagtca tagccgaata 5100
gcctctccac ccaagcggcc ggagaacctg cgtgcaatcc atcttgttca atcatgcgaa 5160
acgatcctca tcctgtctct tgatcagagc ttgatccccct gcgccatcag atccttggcg 5220
gcgagaaagc catccagttt actttgcagg gcttcccaac cttaccagag ggcgccccag 5280
ctggcaattc cggttcgctt gctgtccata aaaccgccca gtctagctat cgccatgtaa 5340
gcccactgca agctacctgc tttctctttg cgcttgcgtt ttccctgtc cagatagccc 5400
agtagctgac attcatccgg ggtcagcacc gtttctgcgg actggctttc tacgtgaaaa 5460
ggatctaggt gaagatcctt tttgataatc t 5491

<210> 86
<211> 4980
<212> DNA
<213> Artificial Sequence

<220>
<223> Plasmid C (for kappa light chain)

<400> 86
catgaccaaa atcccttaac gtgagttttc gttccactga gcgtcagacc ccgtagaaaa 60
gatcaaagga tcttcttgag atcctttttt tctgcgcgta atctgctgct tgcaaacaaa 120
aaaaccaccg ctaccagcgg tggtttgttt gccggatcaa gagctaccaa ctctttttcc 180
gaaggtaact ggcttcagag cgcagatacc aaatactgtt cttctagtgt agccgtagtt 240
aggccaccac ttcaagaact ctgtagcacc gcctacatac ctcgctctgc taatcctgtt 300
accagtggct gctgccagtg gcgataagtc gtgtcttacc gggttggact caagacgata 360
gttaccggat aaggcgcagc ggtcgggctg aacgggggggt tcgtgcacac agcccagctt 420
ggagcgaacg acctacaccg aactgagata cctacagcgt gagctatgag aaagcgccac 480
gcttcccgaa gggagaaagg cggacaggta tccggtaagc ggcagggtcg gaacaggaga 540
gcgcacgagg gagcttccag ggggaaacgc ctggtatctt tatagtcctg tcgggtttcg 600
ccacctctga cttgagcgtc gatttttgtg atgctcgtca ggggggcgga gcctatggaa 660
aaacgccagc aacgcggcct ttttacggtt cctggccttt tgctggcctt ttgctcacat 720
gtccgggtct ttcctgcgtt atcccctgat tctgtggata accgtattac cgcctttgag 780
tgagctgata ccgctcgccg cagccgaacg accgagcgca gcgagtcagt gagcgaggaa 840

gcggaagagc gcct gat gcg gt at t t t ct c ct t acgcat c t gt gcggt at t t cacaccgc 900

at at ggt gca ct ct cagt ac aat ct gct ct gat gccgcat agt t aagcca gt at acact c 960

cgct at cgct acgt gact gg gt cat ggct g cgccccgaca cccgccaaca cccgct gacg 1020

cgccct gacg ggct t gt ct g ct cccggcat ccgct t acag acaagct gt g accgt ct ccg 1080

ggagct gcat gt gt cagagg t t t t caccgt cat caccgaa acgcgcgagg cagcagat ca 1140

at t cgcgcgc gaaggcgaag cggcat gcat aat gt gcct g t caaat ggac gaagcaggga 1200

t t ct gcaaac cct at gct ac t ccgt caagc cgt caat t gt ct gat t cgt t accaat t at g 1260

acaact t gac ggct acat ca t t cact t t t t ct t cacaacc ggcacggaac t cgct cgggc 1320

t ggccccggt gcat t t t t t a aat acccgcg agaaat agag t t gat cgt ca aaaccaacat 1380

t gcgaccgac ggt ggcgat a ggcat ccggg t ggt gct caa aagcagct t c gcct ggct ga 1440

t acgt t ggt c ct cgcgccag ct t aagacgc t aat ccct aa ct gct ggcgg aaaagat gt g 1500

acagacgcga cggcgacaag caaacat gct gt gcgacgct ggcgat at ca aaat t gct gt 1560

ct gccaggt g at cgct gat g t act gacaag cct cgcgt ac ccgat t at cc at cggt ggat 1620

ggagcgact c gt t aat cgct t ccat gcgcc gcagt aacaa t t gct caagc agat t t at cg 1680

ccagcagct c cgaat agcgc cct t cccct t gcccggcgt t aat gat t t gc ccaaacaggt 1740

cgct gaaat g cggct ggt gc gct t cat ccg ggcgaaagaa ccccgt at t g gcaaat at t g 1800

acggccagt t aagccat t ca t gccagt agg cgcgcggacg aaagt aaacc cact ggt gat 1860

accat t cgcg agcct ccgga t gacgaccgt agt gat gaat ct ct cct ggc gggaacagca 1920

aaat at cacc cggt cggcaa acaaat t ct c gt ccct gat t t t t caccacc ccct gaccgc 1980

gaat ggt gag at t gagaat a t aacct t t ca t t cccagcgg t cggt cgat a aaaaaat cga 2040

gat aaccgt t ggcct caat c ggcgt t aaac ccgccaccag at gggcat t a aacgagt at c 2100

ccggcagcag gggat cat t t t gcgct t cag ccat act t t t cat act cccg ccat t cagag 2160

aagaaaccaa t t gt ccat at t gcat cagac at t gccgt ca ct gcgt ct t t t act ggct ct 2220

t ct cgct aac caaaccggt a accccgct t a t t aaaagcat t ct gt aacaa agcgggacca 2280

aagccat gac aaaaacgcgt aacaaaagt g t ct at aat ca cggcagaaaa gt ccacat t g 2340

at t at t t gca cggcgt caca ct t t gct at g ccat agcat t t t t at ccat a agat t agcgg 2400

at cct acct g acgct t t t t a t cgcaact ct ct act gt t t c t ccat acccg t t t t t t gggc 2460

gaat t ccct a ggt aat t aat t aggaggaat t t aaaat gaa gaaaaacat c gcct t t ct gc 2520

t t gcat cgat gt t cgt gt t t t cgat cgcga ccaacgccat ggcggaaat t gt gt t gacgc 2580

agt ct ccagg caccct gt ct t t gt ct ccag gggaaagagc caccct ct cc t gcagggcca 2640

gt cagagt gt t agcagcagc t act t agcct ggt accagca gaaacct ggc caggct ccca 2700

ggct cct cat ct at ggt gca t ccagcaggg ccact ggcat cccagacagg t t cagt ggca 2760

gt gggt ct gg gacagact t c act ct cacca t cagcagact ggagcct gaa gat t t t gcag 2820

t gt at t act g t cagcagt at ggt agct cac ct ccgt ggac gt t cggccaa gggaccaagg 2880

t ggaaat caa acgt acggt g gct gcaccat ct gt ct t cat ct t cccgcca t ct gat gagc 2940

agt t gaaat c t ggaact gcc t ct gt t gt gt gcct gct gaa t aact t ct at cccagagagg 3000

ccaaagt aca gt ggaaggt g gat aacgccc t ccaat cggg t aact cccag gagagt gt ca 3060

cagagcagga cagcaaggac agcacct aca gcct cagcag caccct gacg ct gagcaaag 3120

cagact acga gaaacacaaa gt ct acgcct gcgaagt cac ccat cagggc ct gagct cgc 3180

ccgt cacaaa gagct t caac aggggagagt gt t aagcggc cgct cccaca gccgccagt t 3240

ccgct ggcgg cat t t t aact t t ct t t aat g aaccgcggct cgagcat gca t ct agagggc 3300

ccaat t cgcc ct at agt gag t cgt at t aca at t cact ggc cgt cgt t t t a caacgt cgt g 3360

act gggaaaa ccct ggcgt t acccaact t a at cgcct t gc agcacat ccc cct t t cgcca 3420

gct ggcgt aa t agcgaagag gcccgcaccg at cgccct t c ccaacagt t g cgcagcct at 3480

acgt acaagg cct at t ggcg aat gggacgc gccct gt agc ggcgcat t aa gcgcggcggg 3540

t gt ggt ggt t acgcgcagcg t gaccgct ac act t gccagc gccct agcgc ccgct cct t t 3600

cgct t t ct t c cct t cct t t c t cgccacgt t cgccggct t t ccccgt caag ct ct aaat cg 3660

ggggct ccct t t agggt t cc gat t t agt gc t t t acggcac ct cgacccca aaaaact t ga 3720

t t agggt gat ggt t cacgt a gt gggccat c gccct gat ag acggt t t t t c gccct t t gac 3780

gt t ggagt cc acgt t ct t t a at agt ggact ct t gt t ccaa act ggaacaa cact caaccc 3840

t at ct cggt c t at t ct t t t g at t t at aagg gat t t t gccg at t t cggcct at t ggt t aaa 3900

aaat gagct g at t t aacaaa aat t t aacgc gaat t t t aac aaaat at t aa cgct t acaat 3960

t t aggt ggca ct t t t cgggg aaat gt gcgc ggaacccct a t t t gt t t at t t t t ct aaat a 4020

cat t caaat a t gt at ccgct cat gact agt gct t ggat t c t caccaat aa aaaacgcccg 4080

gcggcaaccg agcgt t ct ga acaaat ccag at ggagt t ct gaggt cat t a ct ggat ct at 4140

caacaggagt ccaagcgagc t cgat at caa at t acgcccc gccct gccac t cat cgcagt 4200

act gt t gt aa t t cat t aagc at t ct gccga cat ggaagcc at cacagacg gcat gat gaa 4260

cct gaat cgc cagcggcat c agcacct t gt cgcct t gcgt at aat at t t g cccat agt ga 4320

aaacgggggc gaagaagt t g t ccat at t gg ccacgt t t aa at caaaact g gt gaaact ca 4380

cccagggat t ggct gagacg aaaaacat at t ct caat aaa ccct t t aggg aaat aggcca 4440

ggt t t t cacc gt aacacgcc acat ct t gcg aat at at gt g t agaaact gc cggaaat cgt 4500

cgt ggt at t c act ccagagc gat gaaaacg t t t cagt t t g ct cat ggaaa acggt gt aac 4560

aagggt gaac act at cccat at caccagct caccgt ct t t cat t gccat a cgaaat t ccg 4620

gat gagcat t cat caggcgg gcaagaat gt gaat aaaggc cggat aaaac t t gt gct t at 4680

t t t t ct t t ac ggt ct t t aaa aaggccgt aa t at ccagct g aacggt ct gg t t at aggt ac 4740

at t gagcaac t gact gaaat gcct caaaat gt t ct t t acg at gccat t gg gat at at caa 4800

cggt ggt at a t ccagt gat t t t t t ct cca t t t t agct t c ct t agct cct gaaaat ct cg 4860

at aact caaa aaat acgccc ggt agt gat c t t at t t cat t at ggt gaaag t t ggaacct c 4920

ttacgtgccg atcaacgtct catttttcgcc agatatcgac gtctaagaaa ccattattat 4980

<210> 87

<211> 4986

<212> DNA

<213> Artificial Sequence

<220>

<223> Plasmid E (for lambda light chain)

<400> 87

catgaccaaa atccctt aac gtgagtttt c gttccactga gcgtcagacc ccgtagaaaa 60

gatcaaagga tcttctt gag atccttttt t tctgcgcgta atctgctgct tgcaaacaaa 120

aaaaccaccg ctaccagcgg tggtttgttt gccggatcaa gagctaccaa ctcttttcc 180

gaaggtaact ggcttcagag cgcagatacc aaatactgtt cttctagtgt agccgtagtt 240

aggccaccac ttcaagaact ctgtagcacc gcctacatac ctcgctctgc taatcctgtt 300

accagtggct gctgccagtg gcgataagtc gtgtcttacc gggttggact caagacgata 360

gttaccggat aaggcgcagc ggtcgggctg aacgggggggt tcgtgcacac agcccagctt 420

ggagcgaacg acctacaccg aactgagata cctacagcgt gagctatgag aaagcgccac 480

gcttcccgaa gggagaaagg cggacaggta tccggtaagc ggcagggtcg gaacaggaga 540

gcgcacgagg gagcttccag ggggaaacgc ctggtatctt tatagtcctg tcgggtttcg 600

ccacctctga cttgagcgtc gatttttgtg atgctcgtca ggggggcgga gcctatggaa 660

aaacgccagc aacgcggcct ttttacggtt cctggccttt tgctggcctt ttgctcacat 720

gtccgggtct ttcctgcgtt atcccctgat tctgtggata accgtattac cgcctttgag 780

tgagctgata ccgctcgccg cagccgaacg accgagcgca gcgagtcagt gagcgaggaa 840

gcggaagagc gcctgatgcg gtattttctc cttacgcatc tgtgcggtat ttcacaccgc 900

atatggtgca ctctcagtac aatctgctct gatgccgcat agttaagcca gtatacactc 960

cgctatcgct acgtgactgg gtcatggctg cgccccgaca cccgccaaca cccgctgacg 1020

cgccctgacg ggcttgtctg ctcccggcat ccgcttacag acaagctgtg accgtctccg 1080

ggagctgcat gtgtcagagg ttttcaccgt catcaccgaa acgcgcgagg cagcagatca 1140

attcgcgcgc gaaggcgaag cggcatgcat aatgtgcctg tcaaatggac gaagcaggga 1200

ttctgcaaac cctatgctac tccgtcaagc cgtcaattgt ctgattcgtt accaattatg 1260

acaacttgac ggctacatca ttcactttt t ctcacaacc ggcacggaac tcgctcgggc 1320

t ggccccggt gcat t t t t t a aat acccgcg agaaat agag t t gat cgt ca aaaccaacat 1380

t gcgaccgac ggt ggcgat a ggcat ccggg t ggt gct caa aagcagct t c gcct ggct ga 1440

t acgt t ggt c ct cgcgccag ct t aagacgc t aat ccct aa ct gct ggcgg aaaagat gt g 1500

acagacgcga cggcgacaag caaacat gct gt gcgacgct ggcgat at ca aaat t gct gt 1560

ct gccaggt g at cgct gat g t act gacaag cct cgcgt ac ccgat t at cc at cggt ggat 1620

ggagcgact c gt t aat cgct t ccat gcgcc gcagt aacaa t t gct caagc agat t t at cg 1680

ccagcagct c cgaat agcgc cct t cccct t gcccggcgt t aat gat t t gc ccaaacaggt 1740

cgct gaaat g cggct ggt gc gct t cat ccg ggcgaaagaa ccccgt at t g gcaaat at t g 1800

acggccagt t aagccat t ca t gccagt agg cgcgcggacg aaagt aaacc cact ggt gat 1860

accat t cgcg agcct ccgga t gacgaccgt agt gat gaat ct ct cct ggc gggaacagca 1920

aaat at cacc cggt cggcaa acaaat t ct c gt ccct gat t t t t caccacc ccct gaccgc 1980

gaat ggt gag at t gagaat a t aacct t t ca t t cccagcgg t cggt cgat a aaaaaat cga 2040

gat aaccgt t ggcct caat c ggcgt t aaac ccgccaccag at gggcat t a aacgagt at c 2100

ccggcagcag gggat cat t t t gcgct t cag ccat act t t t cat act cccg ccat t cagag 2160

aagaaaccaa t t gt ccat at t gcat cagac at t gccgt ca ct gcgt ct t t t act ggct ct 2220

t ct cgct aac caaaccggt a accccgct t a t t aaaagcat t ct gt aacaa agcgggacca 2280

aagccat gac aaaaacgcgt aacaaaagt g t ct at aat ca cggcagaaaa gt ccacat t g 2340

at t at t t gca cggcgt caca ct t t gct at g ccat agcat t t t t at ccat a agat t agcgg 2400

at cct acct g acgct t t t t a t cgcaact ct ct act gt t t c t ccat acccg t t t t t t gggc 2460

gaat t ccct a gat aat t aat t aggaggaat t t aaaat gaa gaaaaacat c gcct t t ct gc 2520

t t gcat cgat gt t cgt gt t t t cgat cgcga ccaacgccat ggcgcagct t gt gct gact c 2580

aat cgccct c t gcct ct gcc t ccct gggag cct cggt caa gct cacct gc act ct gagca 2640

gt gggcacag cagct acgcc at cgcat ggc at cagcagca gccagagaag ggccct cggt 2700

act t gat gaa gct t aacagt gat ggcagcc acagcaaggg ggacggcat c cct gat cgct 2760

t ct caggct c cagct ct ggg gct gagcgct acct caccat ct ccagcct c cagt ct gagg 2820

at gaggct ga ct at t act gt cagacct ggg gcact ggcat t cat t at gt c t t cggaact g 2880

ggaccaaggt caccgt cct a ggt cagccca aggct gcccc ct cggt cact ct gt t cccgc 2940

cct cct ct ga ggagct t caa gccaacaagg ccacact ggt gt gt ct cat a agt gact t ct 3000

acccgggagc cgt gacagt g gcct ggaagg cagat agcag ccccgt caag gcgggagt gg 3060

agaccaccac accct ccaaa caaagcaaca acaagt acgc ggccagcagc t at ct gagcc 3120

t gacgcct ga gcagt ggaag t cccacagaa gct acagct g ccaggt cacg cat gaaggga 3180

gcaccgt gga gaagacagt g gcccct acag aat gt t cat a agcggccgct cccacagccg 3240

ccagt t ccgc t ggcggcat t t t aact t t ct t t aat gaacc gcggct cgag cat gcat ct a 3300

gagggcccaa t t cgccct at agt gagt cgt at t acaat t c act ggccgt c gt t t t acaac 3360

gtcgtgactg ggaaaaccct ggcgttaccc aacttaatcg ccttgcagca catccccctt 3420
tcgccagctg gcgtaatagc gaagaggccc gcaccgatcg ccctt cccaa cagttgcgca 3480
gcctatacgt acaaggccta ttggcgaatg ggacgcgccc tgtagcggcg cattaagcgc 3540
ggcgggtgtg gtggttacgc gcagcgtgac cgctacactt gccagcgccc tagcgcccgc 3600
tcctttcgct ttcttcccct cctttctcgc cacgttcgcc ggctttcccc gtcaagctct 3660
aaatcggggg ctccctttag ggttccgatt tagtgcttta cggcacctcg accccaaaaa 3720
acttgattag ggtgatggtt cacgtagtgg gccatcgccc tgatagacgg ttttt cgccc 3780
tttgacgttg gagtccacgt tctttaatag tggactcttg ttccaaactg gaacaacact 3840
caaccctatc tcggtctatt cttttgattt ataagggatt ttgccgattt cggcctattg 3900
gttaaaaaat gagctgattt aacaaaaatt taacgcgaat tttaacaaaa tattaacgct 3960
tacaatttag gtggcacttt tcggggaaat gtgcgcggaa ccccta tttg tttatttttc 4020
taaatacatt caaatatgta tccgctcatg actagtgctt ggattctcac caataaaaaa 4080
cgcccggcgg caaccgagcg ttctgaacaa atccagatgg agttctgagg tcattactgg 4140
atctatcaac aggagtccaa gcgagctcga tatcaaatta cgccccgccc tgccactcat 4200
cgcagtactg ttgtaattca ttaagcattc tgccgacatg gaagccatca cagacggcat 4260
gatgaacctg aatcgccagc ggcatcagca cctt gtcgcc ttgcgtataa tatttgccca 4320
tagtgaaaac gggggcgaag aagttgtcca tattggccac gtttaaatca aaactggtga 4380
aactcaccca gggattggct gagacgaaaa acatattctc aataaaccct ttagggaaat 4440
aggccaggtt ttcaccgtaa cacgccacat cttgcgaata tatgtgtaga aactgccgga 4500
aatcgtcgtg gtattcactc cagagcgatg aaaacgttc agttttgctca tggaaaacgg 4560
tgtaacaagg gtgaacacta tcccatatca ccagctcacc gtctttcatt gccatacgaa 4620
attccggatg agcattcatc aggcgggcaa gaatgtgaat aaaggccgga taaaacttgt 4680
gcttatttttt ctttacggtc tttaaaaagg ccgtaatatc cagctgaacg gtctggttat 4740
aggtacattg agcaactgac tgaaatgcct caaaatgttc tttacgatgc cattgggata 4800
tatcaacggt ggtatatcca gtgatttttt tctccatttt agcttcctta gctcctgaaa 4860
atctcgataa ctcaaaaaat acgcccggta gtgatcttat ttcattatgg tgaaagttgg 4920
aacctcttac gtgccgatca acgtctcatt ttcgccagat atcgacgtct aagaaaccat 4980
tatta t 4986

<210> 88
<211> 380
<212> DNA
<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01

<400> 88

ccatggcaca ggtgcagctg gtgcagtctg gggctgaggt gaagaagcct ggggcctcag 60

tgaaggtttc ctgcaaggca tctggataca cctttaccag ctactatatg cactgggtgc 120

gacaggcccc tggacaaggg cttgagtgga tgggaataat caaccctagt ggtggtagca 180

caagctacgc acagaagttc cagggcagag tcaccatgac cagggacacg tccacgagca 240

cagtctacat ggagctgagc agcctgagat ctgaggacac ggccgtgtat tactgtgcga 300

gagaggagta tagcagctcg tccgctgaat acttccagca ctggggccag ggcaccctgg 360

tcaccgtctc ctcagctagc 380

<210> 89

<211> 377

<212> DNA

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01

<400> 89

ccatggcaga ggtgcagctg gtgcagtctg gagcagaggt gaaaaagccc ggggagtctc 60

tgaagatctc ctgtaagggt tctggataca gctttaccag ctactggatc ggctgggtgc 120

gccagatgcc cgggaaaggc ctggagtgga tggggatcat ctatcctggt gactctgata 180

ccagatacag cccgtccttc caaggccagg tcaccatctc agccgacaag tccatcagca 240

ccgcctacct gcagtggagc agcctgaagg cctcggacac cgccatgtat tactgtgcga 300

gacgtggata cagctatggt tacgactact ttgactactg gggccaagga accctggtca 360

ccgtctcctc agctagc 377

<210> 90

<211> 398

<212> DNA

<213> Artificial Sequence

<220>

<223> VH6-1_IGHD3-3*01_IGHJ4*01

<400> 90

ccatggcaca ggtacagctg cagcagtcag gtccaggact ggtgaagccc tcgcagaccc 60

tctcactcac ctgtgccatc tccggggaca gtgtctctag caacagtgct gcttggaact 120

ggatcaggca gtccccatcg agaggcctcg agtggctggg aaggacatac tacaggtcca 180

agtggtataa tgattatgca gtatctgtga aaagtcgaat aaccatcaac ccagacacat 240

ccaagaacca gttctccctg cagctgaact ctgtgactcc cgaggacacg gctgtgtatt 300

actgtgcaag agagtattac gattttttga gtggttatta taccgactac tttgactact 360

ggggccaagg aaccctggtc accgtctcct cagctagc 398

<210> 91

<211> 389

<212> DNA

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD3-10*01_IGHJ4*01

<400> 91

ccatggcaca ggtgcagctg gtgcagtctg gggctgaggt gaagaagcct ggggcctcag 60

tgaaggtttc ctgcaaggca tctggatacа cctcaccag ctactatatg cactgggtgc 120

gacaggcccc tggacaaggg cttgagtgga tgggaataat caaccctagt ggtggtagca 180

caagctacgc acagaagttc cagggcagag tcaccatgac cagggacacg tccacgagca 240

cagtctacat ggagctgagc agcctgagat ctgaggacac ggccgtgtat tactgtgcga 300

gagagtatta ctatggttcg gggagttatt atаacgacta ctttgactac tggggccaag 360

gaaccctggt caccgtctcc tcagctagc 389

<210> 92

<211> 380

<212> DNA

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-13*01_IGHJ4*01

<400> 92

ccatggcaca ggtgcagctg gtgcagtctg gggctgaggt gaagaagcct ggggcctcag 60

tgaaggtttc ctgcaaggca tctggataca cctttaccag ctactatatg cactgggtgc 120

gacaggcccc tggacaaggg cttgagtgga tgggaataat caaccctagt ggtggtagca 180

caagctacgc acagaagttc cagggcagag tcaccatgac cagggacacg tccacgagca 240

cagtctacat ggagctgagc agcctgagat ctgaggacac ggccgtgtat tactgtgcga 300

gagaggggta tagcagcagc tggtacgact acttttgact actggggccaa ggaaccctgg 360

tcaccgtctc ctcagctagc 380

<210> 93

<211> 392

<212> DNA

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD2-15*01_IGHJ2*01

<400> 93

ccatggcaca ggtgcagctg gtgcagtctg gggctgaggt gaagaagcct ggggcctcag 60

tgaaggtttc ctgcaaggca tctggataca cctttaccag ctactatatg cactgggtgc 120

gacaggcccc tggacaaggg cttgagtgga tgggaataat caaccctagt ggtggtagca 180

caagctacgc acagaagttc cagggcagag tcaccatgac cagggacacg tccacgagca 240

cagtctacat ggagctgagc agcctgagat ctgaggacac ggccgtgtat tactgtgcga 300

gagaaggata ttgtagtggt ggtagctgct actcctactg gtacttcgat ctctggggcc 360

gtggcaccct ggtcactgtc tcctcagcta gc 392

<210> 94

<211> 365

<212> DNA

<213> Artificial Sequence

<220>

<223> VH4-34_IGHD7-27*01_IGHJ4*01

<400> 94

ccatggcaca ggtgcagcta cagcagtggg gcgcaggact gttgaagcct tcggagaccc 60

tgtccctcac ctgcgctgtc tatggtgggt cctcagtggt tactactggg agctggattc 120

gccagccccc agggaagggg ctggagtgga ttggggaaat caatcatagt ggaagcacca 180

actacaaccc gtccctcaag agtcgagtca ccatatcagt agacacgtcc aagaaccagt 240

tctccctgaa gctgagctct gtgaccgccg cggacacggc tgtgtattac tgtgcgagag 300

ctaactgggg agactacttt gactactggg gccaaggaac cctggtcacc gtctcctcag 360

ctagc 365

<210> 95

<211> 377

<212> DNA

<213> Artificial Sequence

<220>

<223> VH1-3_IGHD4-23*01_IGHJ4*01

<400> 95

ccatggcaca ggttcagctg gtgcagtctg gggctgaggt gaagaagcct ggggcctcag 60

tgaaggtttc ctgcaaggct tctggataca cctttactag ctatgctatg catttgggtg 120

gccaggcccc cggacaaagg cttgagtgga tgggatggag caacgctggc aatggtaaca 180

caaaatattc acaggagttc cagggcagag tcaccattac cagggacaca tccgcgagca 240

cagcctacat ggagctgagc agcctgagat ctgaggacat ggctgtgtat tactgtgcga 300

gagatgacta cggtggtaac tccgactact ttgactactg gggccaagga accctggtca 360

ccgtctcctc agctagc 377

<210> 96

<211> 404

<212> DNA

<213> Artificial Sequence

<220>

<223> VH1-8_IGHD2-2*01_IGHJ6*01

<400> 96

ccatggcaca ggtgcagctg gtgcagtctg gggctgaggt gaagaagcct ggggcctcag 60

tgaaggtctc ctgcaaggct tctggataca cctttaccag ttatgatatc aactgggtgc 120

gacaggccac tggacaaggg cttgagtgga tgggatggat gaaccctaac agtggtaaca 180

caggctatgc acagaagttc cagggcagag tcaccatgac caggaacacc tccataagca 240

cagcctacat ggagctgagc agcctgagat ctgaggacac ggccgtgtat tactgtgcga 300

gaggaggata ttgtagtagt accagctgct atgccgatta ctactactac tacggtatgg 360

acgtctgggg gcaagggacc acggtcaccg tctcctcagc tagc 404

<210> 97

<211> 395

<212> DNA

<213> Artificial Sequence

<220>

<223> VH4-31_IGHD2-15*01_IGHJ2*01

<400> 97

ccatggcaca ggtgcagctg caggagtcgg gcccaggact ggtgaagcct tcacagaccc 60

tgtccctcac ctgtactgtc tctggtggct ccatcagcag tggtggttac tactggagct 120

ggattcgcca gcacccaggg aagggcctgg agtggattgg gtacatctat tacagtggga 180

gcacctacta caacccgtcc ctcaagagtc gagttaccat atcagtagac acgtctaaga 240

accagttctc cctgaagctg agctctgtga ctgccgcgga cacggccgtg tattactgtg 300

cgagagaagg atattgtagt ggtggtagct gctactccta ctggtacttc gatctctggg 360

gccgtggcac cctggtcact gtctcctcag ctagc 395

<210> 98

<211> 338

<212> DNA

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01

<400> 98

ccatggcgga aattgtgttg acacagtctc cagccaccct gtctttgtct ccaggggaaa 60

gagccaccct ctcctgcagg gccagtcaga gtgttagcag ctacttagcc tggtaccaac 120

agaaacctgg ccaggctccc aggctcctca tctatgatgc atccaacagg gccactggca 180

tcccagccag gttcagtggc agtgggtctg ggacagactt cactctcacc atcagcagcc 240

tagagcctga agattttgca gtttattact gtcagcagcg tagcaactgg cctccgtgga 300

cgttcggcca agggaccaag gtggaaatca aacgtact 338

<210> 99

<211> 343

<212> DNA

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01

<400> 99

ccatggcgca gactgtggtg acccaggagc catcgttctc agtgtcccct ggagggacag 60

tcacactcac ttgtggcttg agctctggct cagtctctac tagttactac cccagctggt 120

accagcagac cccaggccag gctccacgca cgctcatcta cagcacaaac actcgctctt 180

ctggggtccc tgatcgcttc tctggctcca tcctttgggaa caaagctgcc ctcaccatca 240

cgggggccca ggcagatgat gaatctgatt attactgtgt gctgtatatg ggtagtggca 300

tttcttatgt cttcggaact gggaccaagg tcaccgtcct agg 343

<210> 100

<211> 358

<212> DNA

<213> Artificial Sequence

<220>

<223> V4-3_IGLJ4*01

<400> 100

ccatggcgca gcctgtgctg actcagccaa ctt ccctctc agcatctcct ggagcatcag 60

ccagactcac ctgcaccttg cgcagtggca tcaatcttgg tagctacagg atattctggt 120

accagcagaa gccagagagc cctccccggt atctcctgag ctactactca gactcaagta 180

agcatcaggg ctctggagtc cccagccgct tctctggctc caaagatgct tcgagcaatg 240

cagggatttt agtcatctct gggctccagt ctgaggatga ggctgactat tactgtatga 300

tttggcacag cagtgcttct tttgtatttg gtggaggaac ccagctgatc atcctagg 358

<210> 101

<211> 341

<212> DNA

<213> Artificial Sequence

<220>

<223> A27_IGKJ1*01

<400> 101

ccatggcgga attgtgttg acgcagtctc caggcaccct gtctttgtct ccaggggaaa 60

gagccaccct ctcctgcagg gccagtcaga gtgttagcag cagctacttа gcctggtacc 120

agcagaaacc tggccaggct cccaggctcc tcatctatgg tgcatccagc agggccactg 180

gcatcccaga caggttcagt ggcagtgggt ctgggacaga cttcactctc accatcagca 240

gactggagcc tgaagatttt gcagtgtatt actgtcagca gtatggtagc tcacctccgt 300

ggacgttcgg ccaagggacc aaggtggaaa tcaaacgtac g 341

<210> 102

<211> 338

<212> DNA

<213> Artificial Sequence

<220>

<223> L2_IGKJ1*01

<400> 102

ccatggcgga aatagtgatg acgcagtctc cagccaccct gtctgtgtct ccaggggaaa 60

gagccaccct ctcctgcagg gccagtcaga gtgttagcag caacttagcc tggtaccagc 120

agaaacctgg ccaggctccc aggctcctca tctatggtgc atccaccagg gccactggta 180

tcccagccag gttcagtggc agtgggtctg ggacagagtt cactctcacc atcagcagcc 240

tgcagtctga agattttgca gtttattact gtcagcagta taataactgg cctccgtgga 300

cgttcggcca agggaccaag gtggaaatca aacgtact 338

<210> 103

<211> 338

<212> DNA

<213> Artificial Sequence

<220>

<223> L5_IGKJ1*01

<400> 103

ccatggcgga catccagatg acccagtctc catcttccgt gtctgcatct gtaggagaca 60

gagtcaccat cacttgtcgg gcgagtcagg gtattagcag ctggttagcc tggtatcagc 120

agaaaccagg gaaagcccct aagctcctga tctatgctgc atccagtttg caaagtgggg 180

tcccatcaag gttcagcggc agtggatctg ggacagattt cactctcacc atcagcagcc 240

tgcagcctga agatttttgca acttactatt gtcaacaggc taacagtttc cctccgtgga 300

cgttcggcca agggaccaag gtggaaatca aacgtact 338

<210> 104

<211> 338

<212> DNA

<213> Artificial Sequence

<220>

<223> L12_IGKJ1*01

<400> 104

ccatggcgga catccagatg acccagtctc cttccaccct gtctgcatct gtaggagaca 60

gagtcaccat cacttgccgg gccagtcaga gtattagtag ctggttggcc tggtatcagc 120

agaaaccagg gaaagcccct aagctcctga tctatgatgc ctccagttg gaaagtgggg 180
tcccatcaag gttcagcggc agtggatctg ggacagaatt tactctcacc atcagcagcc 240
tgcagcctga tgattttgca acttattact gccaacagta taatagttat tctccgtgga 300
cgttcggcca agggaccaag gtggaaatca aacgtact 338

<210> 105
<211> 356
<212> DNA
<213> Artificial Sequence

<220>
<223> O1_IGKJ1*01

<400> 105
ccatggcgga tattgtgatg acccagactc cactctccct gcccgtcacc cctggagagc 60
cggcctccat ctcctgcagg tctagtcaga gcctcttgga tagtgatgat ggaaacacct 120
atttggactg gtacctgcag aagccagggc agtctccaca gctcctgatc tatacgcttt 180
cctatcgggc ctctggagtc ccagacaggt tcagtggcag tgggtcaggc actgatttca 240
cactgaaaat cagcagggtg gaggctgagg atgttggagt ttattactgc atgcaacgta 300
tagagttcc ttcgtggacg ttcggccaag gaccaaggt ggaaatcaaa cgtact 356

<210> 106
<211> 343
<212> DNA
<213> Artificial Sequence

<220>
<223> V1-4_IGLJ4*01

<400> 106
ccatggcgca gtctgccctg actcagcctg cctccgtgtc tgggtctcct ggacagtcga 60
tcaccatctc ctgcactgga accagcagtg acgttggtgg ttatAactat gtctcctggt 120
accaacagca cccaggcaaa gcccccaaac tcatgattta tgaggtcagt aatcggccct 180
caggggttc taatcgcttc tctggctcca agtctggcaa cacggcctcc ctgaccatct 240

ctgggctcca ggctgaggac gaggctgatt attactgcag ctcatatgca agcagcagca 300

ctctctttgt atttggtgga ggaacccagc tgatcatcct agg 343

<210> 107

<211> 358

<212> DNA

<213> Artificial Sequence

<220>

<223> V4-6_IGLJ4*01

<400> 107

ccatggcgcg gcccgtgctg actcagccgc cctctctgtc tgcatccccg ggagcaacag 60

ccagactccc ctgcaccctg agcagtgacc tcagtgttgg tggtaaaaac atgttctggt 120

accagcagaa gccagggagc tctcccaggt tattcctgta tcactactca gactcagaca 180

agcagctggg acctggggtc cccagtcgag tctctggctc caaggagacc tcaagtaaca 240

cagcgttttt gctcatctct gggctccagc ctgaggacga ggccgattat tactgccagg 300

tgtacgaaag tagtgctaat tttgtatttg gtggaggaac ccagctgatc atcctagg 358

<210> 108

<211> 6

<212> DNA

<213> Artificial Sequence

<220>

<223> NcoI Restriction Site

<400> 108

ccatgg 6

<210> 109

<211> 6

<212> DNA

<213> Artificial Sequence

<220>

<223> NheI Restriction Site

<400> 109

gctagc 6

<210> 110

<211> 6

<212> DNA

<213> Artificial Sequence

<220>

<223> BsiWI Restriction Site

<400> 110

cgtacg 6

<210> 111

<211> 6

<212> DNA

<213> Artificial Sequence

<220>

<223> AvrII Restriction Site

<400> 111

cctagg 6

<210> 112

<211> 8

<212> DNA

<213> Artificial Sequence

<220>

<223> NotI Restriction Site

<400> 112

gcggccgc 8

<210> 113

<211> 2678

<212> DNA

<213> Homo sapiens

<220>

<223> hDLL4 cDNA

<400> 113

aggccaaagg ggagcagcgt cccgagagga gcgcctcttt tcagggaccc cgccggctgg 60

cggacgcgcg ggaaagcggc gtcgcgaaca gagccagatt gagggcccgc gggtggagag 120

agcgacgccc gaggggatgg cggcagcgtc ccggagcgcc tctggctggg cgctactgct 180

gctggtggca ctttggcagc agcgcgcggc cggctccggc gtcttccagc tgcagctgca 240

ggagttcatc aacgagcgcg gcgtactggc cagtgggcgg cctgcgagc ccggctgccg 300

gacttttctc cgcgtctgcc ttaagcactt ccaggcggtc gtctcgcccg gaccctgcac 360

cttcgggacc gtctccacgc cggtattggg caccaactcc ttcgctgtcc gggacgacag 420

tagcggcggg gggcgcaacc ctcctccaact gcccttcaat ttcacctggc cgggtacctt 480

ctcgctcatc atcgaagctt ggcacgcgcc aggagacgac ctgcggccag aggccttgcc 540

accagatgca ctcatcagca agatcgccat ccagggctcc ctagctgtgg gtcagaactg 600

gttattggat gagcaaacca gcaccctcac aaggctgcgc tactcttacc gggtcatctg 660

cagtgacaac tactatggag acaactgctc ccgcctgtgc aagaagcgca atgaccactt 720

cggccactat gtgtgccagc cagatggcaa cttgtcctgc ctgcccggtt ggactgggga 780

atattgccaa cagcctatct gtctttcggg ctgtcatgaa cagaatggct actgcagcaa 840

gccagcagag tgcctctgcc gcccaggctg gcagggccgg ctgtgtaacg aatgcatccc 900

ccacaatggc tgtcgccacg gcacctgcag cactccctgg caatgtactt gtgatgaggg 960

ctggggaggc ctgtttttgt gaccaagatc caactactgc acccaccact ccccatgcaa 1020

gaatggggca acgtgctcca acagtgggca gcgaagctac acctgcacct gtcgcccagg 1080

ctacactggt gtggactgtg agctggagct cagcgagtgt gacagcaacc cctgtcgcaa 1140

t ggaggcagc t gt aaggacc aggaggat gg ct accact gc ct gt gt cct c cgggct act a 1200

t ggcct gcat t gt gaacaca gcacct t gag ct gcgccgac t ccccct gct t caat ggggg 1260

ct cct gccgg gagcgcaacc agggggccaa ct at gct t gt gaat gt cccc ccaact t cac 1320

cggct ccaac t gcgagaaga aagt ggacag gt gcaccagc aacccct gt g ccaacggggg 1380

acagt gcct g aaccgaggt c caagccgcat gt gccgct gc cgt cct ggat t cacgggcac 1440

ct act gt gaa ct ccacgt ca gcgact gt gc ccgt aaccct t gcgcccacg gt ggcact t g 1500

ccat gacct g gagaat gggc t cat gt gcac ct gccct gcc ggct t ct ct g gccgacgct g 1560

t gaggt gcgg acat ccat cg at gcct gt gc ct cgagt ccc t gct t caaca gggccacct g 1620

ct acaccgac ct ct ccacag acacct t t gt gt gcaact gc cct t at ggct t t gt gggcag 1680

ccgct gcgag t t ccccgt gg gct t gccgcc cagct t cccc t gggt ggccg t ct cgct ggg 1740

t gt ggggct g gcagt gct gc t ggt act gct gggcat ggt g gcagt ggct g t gcggcagct 1800

gcggct t cga cggccggacg acggcagcag ggaagccat g aacaact t gt cggact t cca 1860

gaaggacaac ct gat t cct g ccgcccagct t aaaaacaca aaccagaaga aggagct gga 1920

agt ggact gt ggcct ggaca agt ccaact g t ggcaaacag caaaaccaca cat t ggact a 1980

t aat ct ggcc ccagggcccc t ggggcgggg gaccat gcca ggaaagt t t c cccacagt ga 2040

caagagct t a ggagagaagg cgccact gcg gt t acacagt gaaaagccag agt gt cggat 2100

at cagcgat a t gct ccccca gggact ccat gt accagt ct gt gt gt t t ga t at cagagga 2160

gaggaat gaa t gt gt cat t g ccacggaggt at aaggcagg agcct acct g gacat ccct g 2220

ct cagccccg cggct ggacc t t cct t ct gc at t gt t t aca t t gcat cct g gat gggacgt 2280

t t t t cat at g caacgt gct g ct ct caggag gaggagggaa t ggcaggaac cggacagact 2340

gt gaact t gc caagagat gc aat accct t c cacacct t t g ggt gt ct gt c t ggcat caga 2400

t t ggcagct g caccaaccag aggaacagaa gagaagagag at gccact gg gcact gccct 2460

gccagt agt g gcct t caggg ggct cct t cc ggggct ccgg cct gt t t t cc agagagagt g 2520

gcagt agccc cat ggggccc ggagct gct g t ggcct ccac t ggcat ccgt gt t t ccaaaa 2580

gt gcct t t gg cccaggct cc acggcgacag t t gggcccaa at cagaaagg agagaggggg 2640

ccaat gaggg cagggcct cc t gt gggct gg aaaaccac 2678

<210> 114

<211> 685

<212> PRT

<213> Homo sapi ens

<220>

<223> hDLL4

<400> 114

Met Ala Ala Ala Ser Arg Ser Ala Ser Gly Trp Ala Leu Leu Leu Leu
1 5 10 15

Val Ala Leu Trp Gln Gln Arg Ala Ala Gly Ser Gly Val Phe Gln Leu
20 25 30

Gln Leu Gln Glu Phe Ile Asn Glu Arg Gly Val Leu Ala Ser Gly Arg
35 40 45

Pro Cys Glu Pro Gly Cys Arg Thr Phe Phe Arg Val Cys Leu Lys His
50 55 60

Phe Gln Ala Val Val Ser Pro Gly Pro Cys Thr Phe Gly Thr Val Ser
65 70 75 80

Thr Pro Val Leu Gly Thr Asn Ser Phe Ala Val Arg Asp Asp Ser Ser
85 90 95

Gly Gly Gly Arg Asn Pro Leu Gln Leu Pro Phe Asn Phe Thr Trp Pro
100 105 110

Gly Thr Phe Ser Leu Ile Ile Glu Ala Trp His Ala Pro Gly Asp Asp
115 120 125

Leu Arg Pro Glu Ala Leu Pro Pro Asp Ala Leu Ile Ser Lys Ile Ala
130 135 140

Ile Gln Gly Ser Leu Ala Val Gly Gln Asn Trp Leu Leu Asp Glu Gln
145 150 155 160

Thr Ser Thr Leu Thr Arg Leu Arg Tyr Ser Tyr Arg Val Ile Cys Ser
165 170 175

Asp Asn Tyr Tyr Gly Asp Asn Cys Ser Arg Leu Cys Lys Lys Arg Asn
180 185 190

Asp His Phe Gly His Tyr Val Cys Gln Pro Asp Gly Asn Leu Ser Cys
195 200 205

Leu Pro Gly Trp Thr Gly Glu Tyr Cys Gln Gln Pro Ile Cys Leu Ser
210 215 220

Gly Cys His Glu Gln Asn Gly Tyr Cys Ser Lys Pro Ala Glu Cys Leu
225 230 235 240

Cys Arg Pro Gly Trp Gln Gly Arg Leu Cys Asn Glu Cys Ile Pro His
245 250 255

Asn Gly Cys Arg His Gly Thr Cys Ser Thr Pro Trp Gln Cys Thr Cys
260 265 270

Asp Glu Gly Trp Gly Gly Leu Phe Cys Asp Gln Asp Leu Asn Tyr Cys
275 280 285

Thr His His Ser Pro Cys Lys Asn Gly Ala Thr Cys Ser Asn Ser Gly
290 295 300

Gln Arg Ser Tyr Thr Cys Thr Cys Arg Pro Gly Tyr Thr Gly Val Asp
305 310 315 320

Cys Glu Leu Glu Leu Ser Glu Cys Asp Ser Asn Pro Cys Arg Asn Gly
325 330 335

Gly Ser Cys Lys Asp Gln Glu Asp Gly Tyr His Cys Leu Cys Pro Pro
340 345 350

Gly Tyr Tyr Gly Leu His Cys Glu His Ser Thr Leu Ser Cys Ala Asp
355 360 365

Ser Pro Cys Phe Asn Gly Gly Ser Cys Arg Glu Arg Asn Gln Gly Ala
370 375 380

Asn Tyr Ala Cys Glu Cys Pro Pro Asn Phe Thr Gly Ser Asn Cys Glu
385 390 395 400

Lys Lys Val Asp Arg Cys Thr Ser Asn Pro Cys Ala Asn Gly Gly Gln
405 410 415

Cys Leu Asn Arg Gly Pro Ser Arg Met Cys Arg Cys Arg Pro Gly Phe
420 425 430

Thr Gly Thr Tyr Cys Glu Leu His Val Ser Asp Cys Ala Arg Asn Pro
435 440 445

Cys Ala His Gly Gly Thr Cys His Asp Leu Glu Asn Gly Leu Met Cys
450 455 460

Thr Cys Pro Ala Gly Phe Ser Gly Arg Arg Cys Glu Val Arg Thr Ser
465 470 475 480

Ile Asp Ala Cys Ala Ser Ser Pro Cys Phe Asn Arg Ala Thr Cys Tyr
485 490 495

Thr Asp Leu Ser Thr Asp Thr Phe Val Cys Asn Cys Pro Tyr Gly Phe
500 505 510

Val Gly Ser Arg Cys Glu Phe Pro Val Gly Leu Pro Pro Ser Phe Pro
515 520 525

```
Trp Val Ala Val Ser Leu Gly Val Gly Leu Ala Val Leu Leu Val Leu
    530                 535                 540
Leu Gly Met Val Ala Val Ala Val Arg Gln Leu Arg Leu Arg Arg Pro
545                 550                 555                 560
Asp Asp Gly Ser Arg Glu Ala Met Asn Asn Leu Ser Asp Phe Gln Lys
                565                 570                 575
Asp Asn Leu Ile Pro Ala Ala Gln Leu Lys Asn Thr Asn Gln Lys Lys
            580                 585                 590
Glu Leu Glu Val Asp Cys Gly Leu Asp Lys Ser Asn Cys Gly Lys Gln
        595                 600                 605
Gln Asn His Thr Leu Asp Tyr Asn Leu Ala Pro Gly Pro Leu Gly Arg
    610                 615                 620
Gly Thr Met Pro Gly Lys Phe Pro His Ser Asp Lys Ser Leu Gly Glu
625                 630                 635                 640
Lys Ala Pro Leu Arg Leu His Ser Glu Lys Pro Glu Cys Arg Ile Ser
                645                 650                 655
Ala Ile Cys Ser Pro Arg Asp Ser Met Tyr Gln Ser Val Cys Leu Ile
            660                 665                 670
Ser Glu Glu Arg Asn Glu Cys Val Ile Ala Thr Glu Val
        675                 680                 685
```

<210> 115

<211> 686

<212> PRT

<213> Mus musculus

<220>

<223> mDLL4

<400> 115

```
Met Thr Pro Ala Ser Arg Ser Ala Cys Arg Trp Ala Leu Leu Leu Leu
 1               5                  10                  15
Ala Val Leu Trp Pro Gln Gln Arg Ala Ala Gly Ser Gly Ile Phe Gln
```

```
                20                  25                  30
Leu Arg Leu Gln Glu Phe Val Asn Gln Arg Gly Met Leu Ala Asn Gly
        35                  40                  45
Gln Ser Cys Glu Pro Gly Cys Arg Thr Phe Phe Arg Ile Cys Leu Lys
    50                  55                  60
His Phe Gln Ala Thr Phe Ser Glu Gly Pro Cys Thr Phe Gly Asn Val
65                  70                  75                  80
Ser Thr Pro Val Leu Gly Thr Asn Ser Phe Val Val Arg Asp Lys Asn
                85                  90                  95
Ser Gly Ser Gly Arg Asn Pro Leu Gln Leu Pro Phe Asn Phe Thr Trp
            100                 105                 110
Pro Gly Thr Phe Ser Leu Asn Ile Gln Ala Trp His Thr Pro Gly Asp
        115                 120                 125
Asp Leu Arg Pro Glu Thr Ser Pro Gly Asn Ser Leu Ile Ser Gln Ile
    130                 135                 140
Ile Ile Gln Gly Ser Leu Ala Val Gly Lys Ile Trp Arg Thr Asp Glu
145                 150                 155                 160
Gln Asn Asp Thr Leu Thr Arg Leu Ser Tyr Ser Tyr Arg Val Ile Cys
                165                 170                 175
Ser Asp Asn Tyr Tyr Gly Glu Ser Cys Ser Arg Leu Cys Lys Lys Arg
            180                 185                 190
Asp Asp His Phe Gly His Tyr Glu Cys Gln Pro Asp Gly Ser Leu Ser
        195                 200                 205
Cys Leu Pro Gly Trp Thr Gly Lys Tyr Cys Asp Gln Pro Ile Cys Leu
    210                 215                 220
Ser Gly Cys His Glu Gln Asn Gly Tyr Cys Ser Lys Pro Asp Glu Cys
225                 230                 235                 240
Ile Cys Arg Pro Gly Trp Gln Gly Arg Leu Cys Asn Glu Cys Ile Pro
                245                 250                 255
His Asn Gly Cys Arg His Gly Thr Cys Ser Ile Pro Trp Gln Cys Ala
            260                 265                 270
Cys Asp Glu Gly Trp Gly Gly Leu Phe Cys Asp Gln Asp Leu Asn Tyr
        275                 280                 285
Cys Thr His His Ser Pro Cys Lys Asn Gly Ser Thr Cys Ser Asn Ser
```

290 295 300

Gly Pro Lys Gly Tyr Thr Cys Thr Cys Leu Pro Gly Tyr Thr Gly Glu
305 310 315 320
His Cys Glu Leu Gly Leu Ser Lys Cys Ala Ser Asn Pro Cys Arg Asn
325 330 335
Gly Gly Ser Cys Lys Asp Gln Glu Asn Ser Tyr His Cys Leu Cys Pro
340 345 350
Pro Gly Tyr Tyr Gly Gln His Cys Glu His Ser Thr Leu Thr Cys Ala
355 360 365
Asp Ser Pro Cys Phe Asn Gly Gly Ser Cys Arg Glu Arg Asn Gln Gly
370 375 380
Ser Ser Tyr Ala Cys Glu Cys Pro Pro Asn Phe Thr Gly Ser Asn Cys
385 390 395 400
Glu Lys Lys Val Asp Arg Cys Thr Ser Asn Pro Cys Ala Asn Gly Gly
405 410 415
Gln Cys Leu Asn Arg Gly Pro Ser Arg Thr Cys Arg Cys Arg Pro Gly
420 425 430
Phe Thr Gly Thr His Cys Glu Leu His Ile Ser Asp Cys Ala Arg Ser
435 440 445
Pro Cys Ala His Gly Gly Thr Cys His Asp Leu Glu Asn Gly Pro Val
450 455 460
Cys Thr Cys Pro Ala Gly Phe Ser Gly Arg Arg Cys Glu Val Arg Ile
465 470 475 480
Thr His Asp Ala Cys Ala Ser Gly Pro Cys Phe Asn Gly Ala Thr Cys
485 490 495
Tyr Thr Gly Leu Ser Pro Asn Asn Phe Val Cys Asn Cys Pro Tyr Gly
500 505 510
Phe Val Gly Ser Arg Cys Glu Phe Pro Val Gly Leu Pro Pro Ser Phe
515 520 525
Pro Trp Val Ala Val Ser Leu Gly Val Gly Leu Val Val Leu Leu Val
530 535 540
Leu Leu Val Met Val Val Val Ala Val Arg Gln Leu Arg Leu Arg Arg
545 550 555 560
Pro Asp Asp Glu Ser Arg Glu Ala Met Asn Asn Leu Ser Asp Phe Gln

565 570 575

Lys Asp Asn Leu Ile Pro Ala Ala Gln Leu Lys Asn Thr Asn Gln Lys

580 585 590

Lys Glu Leu Glu Val Asp Cys Gly Leu Asp Lys Ser Asn Cys Gly Lys

595 600 605

Leu Gln Asn His Thr Leu Asp Tyr Asn Leu Ala Pro Gly Leu Leu Gly

610 615 620

Arg Gly Ser Met Pro Gly Lys Tyr Pro His Ser Asp Lys Ser Leu Gly

625 630 635 640

Glu Lys Val Pro Leu Arg Leu His Ser Glu Lys Pro Glu Cys Arg Ile

645 650 655

Ser Ala Ile Cys Ser Pro Arg Asp Ser Met Tyr Gln Ser Val Cys Leu

660 665 670

Ile Ser Glu Glu Arg Asn Glu Cys Val Ile Ala Thr Glu Val

675 680 685

<210> 116

<211> 3519

<212> DNA

<213> Artificial Sequence

<220>

<223> pCR-BluntII TOPO plasmid

<400> 116

agcgcccaat acgcaaaccg cctctccccg cgcgttggcc gattcattaa tgcagctggc 60

acgacaggtt tcccgactgg aaagcgggca gtgagcgcaa cgcaattaat gtgagttagc 120

tcactcatta ggcaccccag gctttacact ttatgcttcc ggctcgtatg ttgtgtggaa 180

ttgtgagcgg ataacaattt cacacaggaa acagctatga ccatgattac gccaagctat 240

ttaggtgaca ctatagaata ctcaagctat gcatcaagct tggtaccgag ctcggatcca 300

ctagtaacgg ccgccagtgt gctggaattc gcccttaagg gcgaattctg cagatatcca 360

tcacactggc ggccgctcga gcatgcatct agagggccca attcgcccta tagtgagtcg 420

tattacaatt cactggccgt cgttttacaa cgtcgtgact gggaaaaccc tggcgttacc 480

caact t aat c gcct t gcagc acat ccccct t t cgccagct ggcgt aat ag cgaagaggcc 540

cgcaccgat c gccct t ccca acagt t gcgc agcct at acg t acggcagt t t aaggt t t ac 600

acct at aaaa gagagagccg t t at cgt ct g t t t gt ggat g t acagagt ga t at t at t gac 660

acgccggggc gacggat ggt gat ccccct g gccagt gcac gt ct gct gt c agat aaagt c 720

t cccgt gaac t t t acccggt ggt gcat at c ggggat gaaa gct ggcgcat gat gaccacc 780

gat at ggcca gt gt gccggt ct ccgt t at c ggggaagaag t ggct gat ct cagccaccgc 840

gaaaat gaca t caaaaacgc cat t aacct g at gt t ct ggg gaat at aaat gt caggcat g 900

agat t at caa aaaggat ct t cacct agat c ct t t t cacgt agaaagccag t ccgcagaaa 960

cggt gct gac cccggat gaa t gt cagct ac t gggct at ct ggacaaggga aaacgcaagc 1020

gcaaagagaa agcaggt agc t t gcagt ggg ct t acat ggc gat agct aga ct gggcggt t 1080

t t at ggacag caagcgaacc ggaat t gcca gct ggggcgc cct ct ggt aa ggt t gggaag 1140

ccct gcaaag t aaact ggat ggct t t ct cg ccgccaagga t ct gat ggcg caggggat ca 1200

agct ct gat c aagagacagg at gaggat cg t t t cgcat ga t t gaacaaga t ggat t gcac 1260

gcaggt t ct c cggccgct t g ggt ggagagg ct at t cggct at gact gggc acaacagaca 1320

at cggct gct ct gat gccgc cgt gt t ccgg ct gt cagcgc aggggcgccc ggt t ct t t t t 1380

gt caagaccg acct gt ccgg t gccct gaat gaact gcaag acgaggcagc gcggct at cg 1440

t ggct ggcca cgacgggcgt t cct t gcgca gct gt gct cg acgt t gt cac t gaagcggga 1500

agggact ggc t gct at t ggg cgaagt gccg gggcaggat c t cct gt cat c t cacct t gct 1560

cct gccgaga aagt at ccat cat ggct gat gcaat gcggc ggct gcat ac gct t gat ccg 1620

gct acct gcc cat t cgacca ccaagcgaaa cat cgcat cg agcgagcacg t act cggat g 1680

gaagccggt c t t gt cgat ca ggat gat ct g gacgaagagc at caggggct cgcgccagcc 1740

gaact gt t cg ccaggct caa ggcgagcat g cccgacggcg aggat ct cgt cgt gacccat 1800

ggcgat gcct gct t gccgaa t at cat ggt g gaaaat ggcc gct t t t ct gg at t cat cgac 1860

t gt ggccggc t gggt gt ggc ggaccgct at caggacat ag cgt t ggct ac ccgt gat at t 1920

gct gaagagc t t ggcggcga at gggct gac cgct t cct cg t gct t t acgg t at cgccgct 1980

cccgat t cgc agcgcat cgc ct t ct at cgc ct t ct t gacg agt t ct t ct g aat t at t aac 2040

gct t acaat t t cct gat gcg gt at t t t ct c ct t acgcat c t gt gcggt at t t cacaccgc 2100

at acaggt gg cact t t t cgg ggaaat gt gc gcggaacccc t at t t gt t t a t t t t t ct aaa 2160

t acat t caaa t at gt at ccg ct cat gagac aat aaccct g at aaat gct t caat aat agc 2220

acgt gaggag ggccaccat g gccaagt t ga ccagt gccgt t ccggt gct c accgcgcgcg 2280

acgt cgccgg agcggt cgag t t ct ggaccg accggct cgg gt t ct cccgg gact t cgt gg 2340

aggacgact t cgccggt gt g gt ccgggacg acgt gaccct gt t cat cagc gcggt ccagg 2400

accaggt ggt gccggacaac accct ggcct gggt gt gggt gcgcggcct g gacgagct gt 2460

acgccgagt g gt cggaggt c gt gt ccacga act t ccggga cgcct ccggg ccggccat ga 2520

ccgagatcgg cgagcagccg tgggggcggg agttcgccct gcgcgacccg gccggcaact 2580
gcgtgcactt cgtggccgag gagcaggact gacacgtgct aaaacttcat ttttaattta 2640
aaaggatcta ggtgaagatc ctttttgata atctcatgac caaaatccct taacgtgagt 2700
tttcgttcca ctgagcgtca gaccccgtag aaaagatcaa aggatcttct tgagatcctt 2760
tttttctgcg cgtaatctgc tgcttgcaaa caaaaaaacc accgctacca gcggtggttt 2820
gtttgccgga tcaagagcta ccaactcttt ttccgaaggt aactggcttc agcagagcgc 2880
agataccaaa tactgtcctt ctagtgtagc cgtagttagg ccaccacttc aagaactctg 2940
tagcaccgcc tacatacctc gctctgctaa tcctgttacc agtggctgct gccagtggcg 3000
ataagtcgtg tcttaccggg ttggactcaa gacgatagtt accggataag gcgcagcggt 3060
cgggctgaac ggggggttcg tgcacacagc ccagcttgga gcgaacgacc tacaccgaac 3120
tgagatacct acagcgtgag ctatgagaaa gcgccacgct tcccgaaggg agaaaggcgg 3180
acaggtatcc ggtaagcggc agggtcggaa caggagagcg cacgagggag cttccagggg 3240
gaaacgcctg gtatctttat agtcctgtcg ggtttcgcca cctctgactt gagcgtcgat 3300
ttttgtgatg ctcgtcaggg gggcggagcc tatggaaaaa cgccagcaac gcggcctttt 3360
tacggttcct gggcttttgc tggccttttg ctcacatgtt ctttcctgcg ttatcccctg 3420
attctgtgga taaccgtatt accgccttg agtgagctga taccgctcgc cgcagccgaa 3480
cgaccgagcg cagcgagtca gtgagcgagg aagcggaag 3519

<210> 117
<211> 5070
<212> DNA
<213> Artificial Sequence

<220>
<223> pcDNA5/FRT

<400> 117
gacggatcgg gagatctccc gatcccctat ggtgcactct cagtacaatc tgctctgatg 60
ccgcatagtt aagccagtat ctgctccctg cttgtgtgtt ggaggtcgct gagtagtgcg 120
cgagcaaaat ttaagctaca acaaggcaag gcttgaccga caattgcatg aagaatctgc 180
ttagggttag gcgttttgcg ctgcttcgcg atgtacgggc agatatacg cgttgacatt 240
gattattgac tagttattaa tagtaatcaa ttacggggtc attagttcat agcccatata 300
tggagttccg cgttacataa cttacggtaa atggcccgcc tggctgaccg cccaacgacc 360
cccgcccatt gacgtcaata atgacgtatg ttcccatagt aacgccaata gggactttcc 420

at t gacgt ca at gggt ggag t at t t acggt aaact gccca ct t ggcagt a cat caagt gt 480

at cat at gcc aagt acgccc cct at t gacg t caat gacgg t aaat ggccc gcct ggcat t 540

at gcccagt a cat gacct t a t gggact t t c ct act t ggca gt acat ct ac gt at t agt ca 600

t cgct at t ac cat ggt gat g cggt t t t ggc agt acat caa t gggcgt gga t agcggt t t g 660

act cacgggg at t t ccaagt ct ccacccca t t gacgt caa t gggagt t t g t t t t ggcacc 720

aaaat caacg ggact t t cca aaat gt cgt a acaact ccgc cccat t gacg caaat gggcg 780

gt aggcgt gt acggt gggag gt ct at at aa gcagagct ct ct ggct aact agagaaccca 840

ct gct t act g gct t at cgaa at t aat acga ct cact at ag ggagacccaa gct ggct agc 900

gt t t aaact t aagct t ggt a ccgagct cgg at ccact agt ccagt gt ggt ggaat t ct gc 960

agat at ccag cacagt ggcg gccgct cgag t ct agagggc ccgt t t aaac ccgct gat ca 1020

gcct cgact g t gcct t ct ag t t gccagcca t ct gt t gt t t gcccct cccc cgt gcct t cc 1080

t t gaccct gg aaggt gccac t cccact gt c ct t t cct aat aaaat gagga aat t gcat cg 1140

cat t gt ct ga gt aggt gt ca t t ct at t ct g gggggt gggg t ggggcagga cagcaagggg 1200

gaggat t ggg aagacaat ag caggcat gct ggggat gcgg t gggct ct at ggct t ct gag 1260

gcggaaagaa ccagct gggg ct ct aggggg t at ccccacg cgccct gt ag cggcgcat t a 1320

agcgcggcgg gt gt ggt ggt t acgcgcagc gt gaccgct a cact t gccag cgccct agcg 1380

cccgct cct t t cgct t t ct t ccct t cct t t ct cgccacgt t cgccggct t t ccccgt caa 1440

gct ct aaat c gggggct ccc t t t agggt t c cgat t t agt g ct t t acggca cct cgacccc 1500

aaaaaact t g at t agggt ga t ggt t cacgt acct agaagt t cct at t ccg aagt t cct at 1560

t ct ct agaaa gt at aggaac t t cct t ggcc aaaaagcct g aact caccgc gacgt ct gt c 1620

gagaagt t t c t gat cgaaaa gt t cgacagc gt ct ccgacc t gat gcagct ct cggagggc 1680

gaagaat ct c gt gct t t cag ct t cgat gt a ggagggcgt g gat at gt cct gcgggt aaat 1740

agct gcgccg at ggt t t ct a caaagat cgt t at gt t t at c ggcact t t gc at cggccgcg 1800

ct cccgat t c cggaagt gct t gacat t ggg gaat t cagcg agagcct gac ct at t gcat c 1860

t cccgccgt g cacagggt gt cacgt t gcaa gacct gcct g aaaccgaact gcccgct gt t 1920

ct gcagccgg t cgcggaggc cat ggat gcg at cgct gcgg ccgat ct t ag ccagacgagc 1980

gggt t cggcc cat t cggacc gcaaggaat c ggt caat aca ct acat ggcg t gat t t cat a 2040

t gcgcgat t g ct gat cccca t gt gt at cac t ggcaaact g t gat ggacga caccgt cagt 2100

gcgt ccgt cg cgcaggct ct cgat gagct g at gct t t ggg ccgaggact g ccccgaagt c 2160

cggcacct cg t gcacgcgga t t t cggct cc aacaat gt cc t gacggacaa t ggccgcat a 2220

acagcggt ca t t gact ggag cgaggcgat g t t cggggat t cccaat acga ggt cgccaac 2280

at ct t ct t ct ggaggccgt g gt t ggct t gt at ggagcagc agacgcgct a ct t cgagcgg 2340

aggcat ccgg agct t gcagg at cgccgcgg ct ccgggcgt at at gct ccg cat t ggt ct t 2400

gaccaact ct at cagagct t ggt t gacggc aat t t cgat g at gcagct t g ggcgcagggt 2460

cgat gcgacg caat cgt ccg at ccggagcc gggact gt cg ggcgt acaca aat cgcccgc 2520

agaagcgcgg ccgt ct ggac cgat ggct gt gt agaagt ac t cgccgat ag t ggaaaccga 2580

cgccccagca ct cgt ccgag ggcaaaggaa t agcacgt ac t acgagat t t cgat t ccacc 2640

gccgcct t ct at gaaaggt t gggct t cgga at cgt t t t cc gggacgccgg ct ggat gat c 2700

ct ccagcgcg gggat ct cat gct ggagt t c t t cgcccacc ccaact t gt t t at t gcagct 2760

t at aat ggt t acaaat aaag caat agcat c acaaat t t ca caaat aaagc at t t t t t t ca 2820

ct gcat t ct a gt t gt ggt t t gt ccaaact c at caat gt at ct t at cat gt ct gt at accg 2880

t cgacct ct a gct agagct t ggcgt aat ca t ggt cat agc t gt t t cct gt gt gaaat t gt 2940

t at ccgct ca caat t ccaca caacat acga gccggaagca t aaagt gt aa agcct ggggt 3000

gcct aat gag t gagct aact cacat t aat t gcgt t gcgct cact gcccgc t t t ccagt cg 3060

ggaaacct gt cgt gccagct gcat t aat ga at cggccaac gcgcggggag aggcggt t t g 3120

cgt at t gggc gct ct t ccgc t t cct cgct c act gact cgc t gcgct cggt cgt t cggct g 3180

cggcgagcgg t at cagct ca ct caaaggcg gt aat acggt t at ccacaga at caggggat 3240

aacgcaggaa agaacat gt g agcaaaaggc cagcaaaagg ccaggaaccg t aaaaaggcc 3300

gcgt t gct gg cgt t t t t cca t aggct ccgc cccct gacg agcat cacaa aaat cgacgc 3360

t caagt caga ggt ggcgaaa cccgacagga ct at aaagat accaggcgt t t ccccct gga 3420

agct ccct cg t gcgct ct cc t gt t ccgacc ct gccgct t a ccggat acct gt ccgcct t t 3480

ct ccct t cgg gaagcgt ggc gct t t ct cat agct cacgct gt aggt at ct cagt t cggt g 3540

t aggt cgt t c gct ccaagct gggct gt gt g cacgaacccc ccgt t cagcc cgaccgct gc 3600

gcct t at ccg gt aact at cg t ct t gagt cc aacccggt aa gacacgact t at cgccact g 3660

gcagcagcca ct ggt aacag gat t agcaga gcgaggt at g t aggcggt gc t acagagt t c 3720

t t gaagt ggt ggcct aact a cggct acact agaaggacag t at t t ggt at ct gcgct ct g 3780

ct gaagccag t t acct t cgg aaaaagagt t ggt agct ct t gat ccggcaa acaaaccacc 3840

gct ggt agcg gt ggt t t t t t t gt t t gcaag cagcagat t a cgcgcagaaa aaaaggat ct 3900

caagaagat c ct t t gat ct t t t ct acgggg t ct gacgct c agt ggaacga aaact cacgt 3960

t aagggat t t t ggt cat gag at t at caaaa aggat ct t ca cct agat cct t t t aaat t aa 4020

aaat gaagt t t t aaat caat ct aaagt at a t at gagt aaa ct t ggt ct ga cagt t accaa 4080

t gct t aat ca gt gaggcacc t at ct cagcg at ct gt ct at t t cgt t cat c cat agt t gcc 4140

t gact ccccg t cgt gt agat aact acgat a cgggagggct t accat ct gg ccccagt gct 4200

gcaat gat ac cgcgagaccc acgct caccg gct ccagat t t at cagcaat aaaccagcca 4260

gccggaaggg ccgagcgcag aagt ggt cct gcaact t t at ccgcct ccat ccagt ct at t 4320

aat t gt t gcc gggaagct ag agt aagt agt t cgccagt t a at agt t t gcg caacgt t gt t 4380

gccat t gct a caggcat cgt ggt gt cacgc t cgt cgt t t g gt at ggct t c at t cagct cc 4440

ggt t cccaac gat caaggcg agt t acat ga t cccccat gt t gt gcaaaaa agcggt t agc 4500

tcctcggtc ctccgatcgt tgtcagaagt aagttggccg cagtgttatc actcatggtt 4560
atggcagcac tgcataattc tcttactgtc atgccatccg taagatgctt ttctgtgact 4620
ggtgagtact caaccaagtc attctgagaa tagtgtatgc ggcgaccgag ttgctcttgc 4680
ccggcgtcaa tacgggataa taccgcgcca catagcagaa ctttaaaagt gctcatcatt 4740
ggaaaacgtt cttcggggcg aaaactctca aggatcttac cgctgttgag atccagttcg 4800
atgtaaccca ctcgtgcacc caactgatct tcagcatctt ttactttcac cagcgtttct 4860
gggtgagcaa aaacaggaag gcaaaatgcc gcaaaaaagg gaataagggc gacacggaaa 4920
tgttgaatac tcatactctt cctttttcaa tattattgaa gcatttatca gggttattgt 4980
ctcatgagcg gatacatatt tgaatgtatt tagaaaaata aacaaatagg ggttccgcgc 5040
acatttcccc gaaaagtgcc acctgacgtc 5070

<210> 118
<211> 5785
<212> DNA
<213> Artificial Sequence

<220>
<223> pCG44

<400> 118
ccgcggtctt tcggacttta gaaagtgatg gtggtggggg aaggattcga accttcgaag 60
tcgatgacgg cagatttaga gtctgctccc tgcttgtgtg ttggaggtcg ctgagtagtg 120
cgcgagcaaa attaagctac caacaaggca aggcttgacc gacaattgca tgaagaatct 180
gcttagggtt aggcgttttg cgctgcttcg cgatgtacgg gccagatata cgcgttgaca 240
ttgattattg actagttatt aatagtaatc aattacgggg tcattagttc atagcccata 300
tatggagttc cgcgttacat aacttacggt aaatggcccg cctggctgac cgcccaacga 360
cccccgccca ttgacgtcaa taatgacgta tgttcccata gtaacgccaa tagggacttt 420
ccattgacgt caatgggtgg agtatttacg gtaaactgcc cacttggcag tacatcaagt 480
gtatcatatg ccaagtacgc cccctattga cgtcaatgac ggtaaatggc ccgcctggca 540
ttatgcccag tacatgacct tatgggactt tcctacttgg cagtacatct acgtattagt 600
catcgcttat taccatggtg atgcggtttt gcagtacatc aatgggcgtg gatagcggtt 660
tgactcacgg ggatttccaa gtctccaccc cattgacgtc aatgggagtt tgttttggca 720
ccaaaatcaa cgggactttc caaaatgtcg taacaactcc gccccattga cgcaaatggg 780

cggt aggcgt gt acggt ggg aggt ct at at aagcagagct ct ct ggct aa ct agagaacc 840

cact gct t ac t ggct t at cg aaat t aat ac gact cact at agggagaccc aagct t ct ag 900

aat t cgct gt ct gcgagggc cagct gt t gg ggt gagt act ccct ct caaa agcgggcat g 960

act t ct gcgc t aagat t gt c agt t t ccaaa aacgaggagg at t t gat at t cacct ggccc 1020

gcggt gat gc ct t t gagggt ggccgcgt cc at ct ggt cag aaaagacaat ct t t t t gt t g 1080

t caagct t ga ggt gt ggcag gct t gagat c t ggccat aca ct t gagt gac aat gacat cc 1140

act t t gcct t t ct ct ccaca ggt gt ccact cccaggt cca act gcagccc aagct t ccac 1200

cat gccacaa t t t gat at at t at gt aaaac accacct aag gt gct t gt t c gt cagt t t gt 1260

ggaaaggt t t gaaagacct t caggt gagaa aat agcat t a t gt gct gct g aact aacct a 1320

t t t at gt t gg at gat t acac at aacggaac agcaat caag agagccacat t cat gagct a 1380

t aat act at c at aagcaat t cgct gagt t t ggat at t gt c aacaagt cac t gcagt t t aa 1440

at acaagacg caaaaagcaa caat t ct gga agcct cat t a aagaaat t ga t t cct gct t g 1500

ggaat t t aca at t at t cct t act at ggaca aaaacat caa t ct gat at ca ct gat at t gt 1560

aagt agt t t g caat t acagt t cgaat cat c ggaagaagca gat aagggaa at agccacag 1620

t aaaaaaat g ct t aaagcac t t ct aagt ga gggt gaaagc at ct gggaga t cact gagaa 1680

aat act aaat t cgt t t gagt at act t cgag at t t acaaaa acaaaaact t t at accaat t 1740

cct ct t cct a gct act t t ca t caat t gt gg aagat t cagc gat at t aaga acgt t gat cc 1800

gaaat cat t t aaat t agt cc aaaat aagt a t ct gggagt a at aat ccagt gt t t agt gac 1860

agagacaaag acaagcgt t a gt aggcacat at act t ct t t agcgcaaggg gt aggat cga 1920

t ccact t gt a t at t t ggat g aat t t t t gag gaat t ct gaa ccagt cct aa aacgagt aaa 1980

t aggaccggc aat t ct t caa gcaacaagca ggaat accaa t t at t aaaag at aact t agt 2040

cagat cgt ac aacaaagct t t gaagaaaaa t gcgcct t at t caat ct t t g ct at aaaaaa 2100

t ggcccaaaa t ct cacat t g gaagacat t t gat gacct ca t t t ct t t caa t gaagggcct 2160

aacggagt t g act aat gt t g t gggaaat t g gagcgat aag cgt gct t ct g ccgt ggccag 2220

gacaacgt at act cat caga t aacagcaat acct gat cac t act t cgcac t agt t t ct cg 2280

gt act at gca t at gat ccaa t at caaagga aat gat agca t t gaaggat g agact aat cc 2340

aat t gaggag t ggcagcat a t agaacagct aaagggt agt gct gaaggaa gcat acgat a 2400

ccccgcat gg aat gggat aa t at cacagga ggt act agac t acct t t cat cct acat aaa 2460

t agacgcat a t aagt acgca t t t aagcat a aacacgcact at gccgt t ct t ct cat gt at 2520

at at at at ac aggcaacacg cagat at agg t gcgacgt ga acagt gagct gt at gt gcgg 2580

gt accgagct cct cgaggat cagacat gat aagat acat t gat gagt t t g gacaaaccac 2640

aact agaat g cagt gaaaaa aat gct t t at t t gt gaaat t t gt gat gct a t t gct t t at t 2700

t gt aaccat t at aagct gca at aaacaagt t at cct cgag gagct cat ga gcgct t gt t t 2760

cggcgt gggt at ggt ggcag gcccgt ggcc gggggact gt t gggcgccat ct cct t gcat 2820

gcaccat t cc t t gcggcggc ggt gct caac ggcct caacc t act act ggg ct gct t cct a 2880

at gcaggagt cgcat aaggg agagcgt cga cct cgagggg gggcccggt a cccagct t t t 2940

gt t ccct t t a gt gagggt t a at t gcgcgct t ggcgt aat c at ggt cat ag ct gt t t cct g 3000

t gt gaaat t g t t at ccgct c acaat t ccac acaacat acg agccgggagc at aaagt gt a 3060

aagcct gggg t gcct aat ga gt gagct aac t cacat t aat t gcgt t gcgc t cact gcccg 3120

ct t t ccagt c gggaaacct g t cgt gccagc t gcat t aat g aat cggccaa cgcgcgggga 3180

gaggcggt t t gcgt at t ggg cgct ct t ccg ct t cct cgct cact gact cg ct gcgct cgg 3240

t cgt t cggct gcggcgagcg gt at cagct c act caaaggc ggt aat acgg t t at ccacag 3300

aat cagggga t aacgcagga aagaacat gt gagcaaaagg ccagcaaaag gccaggaacc 3360

gt aaaaaggc cgcgt t gct g gcgt t t t t cc at aggct ccg ccccct gac gagcat caca 3420

aaaat cgacg ct caagt cag aggt ggcgaa acccgacagg act at aaaga t accaggcgt 3480

t t ccccct gg aagct ccct c gt gcgct ct c ct gt t ccgac cct gccgct t accggat acc 3540

t gt ccgcct t t ct ct t cggg aagcgt ggcg ct t t ct cat a gct cacgct g t aggt at ct c 3600

agt t cggt gt aggt cgt t cg ct ccaagct g ggct gt gt gc acgaaccccc cgt t cagccc 3660

gaccct gcgc ct t at ccggt aact at cgt c t t gagt ccaa cccggt aaga cacgact t at 3720

cgccact ggc agcagccact ggt aacagga t t agcagagc gaggt at gt a ggcggt gct a 3780

cagagt t ct t gaagt ggt gg cct aact acg gct acact ag aagaacagt a t t t ggt at ct 3840

gcgct ct gct gaagccagt t act t cggaaa aagagt t ggt agct ct t gat ccggcaaaca 3900

aaccgct ggt agcggt ggt t t t t t gt t t g caagcagcag at t acgcgca gaaaaaaagg 3960

at ct caagaa gat cct t t ga t ct t t t ct ac ggggt ct gac gct cagt gga acgaaaact c 4020

acgt t aaggg at t t t ggt ca t gagat t at c aaaaaggat c t t cacct aga t cct t t t aaa 4080

t t aaaaat ga agt t t t aaat caat ct aaag t at at at gag t aaact t ggt ct gacagt t a 4140

ccaat gct t a at cagt gagg cacct at ct c agcgat ct gt ct at t t cgt t cat ccat agt 4200

t gcct gact c cccgt cgt gt agat aact ac gat acgggag ggct t accat ct ggccccag 4260

t gct gcaat g at accgcgag acccacgct c accggct cca gat t t at cag caat aaacca 4320

gccagccgga agggccgagc gcagaagt gg t cct gcaact t t at ccgcct ccat ccagt c 4380

t at t aat t gt t gccgggaag ct agagt aag t agt t cgcca gt t aat agt t t gcgcaacgt 4440

t gt t gccat t gct acaggca t cgt ggt gt c acgct cgt cg t t t ggt at gg ct t cat t cag 4500

ct ccggt t cc caacgat caa ggcgagt t ac at gat ccccc at gt t gt gca aaaaagcggt 4560

t agct cct t c ggt cct ccga t cgt t gt cag aagt aagt t g gccgcagt gt t at cact cat 4620

ggt t at ggca gcact gcat a at t ct ct t ac t gt cat gcca t ccgt aagat gct t t t ct gt 4680

gact ggt gag t act caacca agt cat t ct g agaat agt gt at gcggcgac cgagt t gct c 4740

t t gcccggcg t caat acggg at aat accgc gccacat agc agaact t t aa aagt gct cat 4800

cat t ggaaaa cgt t ct t cgg ggcgaaaact ct caaggat c t t accgct gt t gagat ccag 4860

ttcgatgtaa cccactcgtg cacccaactg atcttcagca tcttttactt tcaccagcgt 4920

ttctgggtga gcaaaaacag gaaggcaaaa tgccgcaaaa aagggaataa gggcgacacg 4980

gaaatgttga atactcatac tcttcctttt tcaatattat tgaagcattt atcagggtta 5040

ttgtctcatg agcggataca tatttgaatg tatttagaaa aataaacaaa taggggttcc 5100

gcgcacattt ccccgaaaag tgccactaaa ttgtaagcgt taatatttg ttaaaattcg 5160

cgttaaattt ttgttaaatc agctcatttt ttaaccaata ggccgaaatc ggcaaaatcc 5220

cttataaatc aaaagaatag accgagatag ggttgagtgt tgttccagtt tggaacaaga 5280

gtccactatt aaagaacgtg gactccaacg tcaaagggcg aaaaaccgtc tatcagggcg 5340

atggcccact acgtgaacca tcaccctaat caagttttt ggggtcgagg tgccgtaaag 5400

cactaaatcg gaaccctaaa gggagccccc gatttagagc ttgacgggga aagccggcga 5460

acgtggcgag aaaggaaggg aagaaagcga aaggagcggg cgctagggcg ctggcaagtg 5520

tagcggtcac gctgcgcgta accaccacac ccgccgcgct taatgcgccg ctacagggcg 5580

cgtcccattc gccattcagg ctgcgcaact gttgggaagg gcgatcggtg cgggcctctt 5640

cgctattacg ccagctggcg aaaggggatg tgctgcaag gcgattaagt tgggtaacgc 5700

cagggttttc ccagtcacga cgttgtaaaa cgacggccag tgagcgcgcg taatacgact 5760

cactataggg cgaattggag ctcca 5785

<210> 119

<211> 31

<212> DNA

<213> Artificial Sequence

<220>

<223> DLL4 ECD forward

<400> 119

tgacctaggc tagcatggcg gcagcgtccc g 31

<210> 120

<211> 47

<212> DNA

<213> Artificial Sequence

<220>

<223> DLL4 ECD reverse1

<400> 120

cagatcctct tctgagatga gttttgttc cggcaagccc acgggga 47

<210> 121

<211> 59

<212> DNA

<213> Artificial Sequence

<220>

<223> DLL4 ECD reverse2

<400> 121

ttactgacgc ggccgctcat caatggtgat ggtgatgatg cagatcctct tctgagatg 59

<210> 122

<211> 71

<212> DNA

<213> Artificial Sequence

<220>

<223> DLL4 pre-DSL reverse1

<400> 122

ttactgacgc ggccgctcat cacagatcct cttctgagat gagttttgt tcccggtaag 60

agtagcgcag c 71

<210> 123

<211> 73

<212> DNA

<213> Artificial Sequence

<220>

<223> DLL4 DSL reverse1

<400> 123

ttactgacgc ggccgctcat cacagatcct cttctgagat gagttttgt tcgcaatatt 60

ccccagtcca acc 73

<210> 124

<211> 71

<212> DNA

<213> Artificial Sequence

<220>

<223> DLL4 Egf1 reverse1

<400> 124

ttactgacgc ggccgctcat cacagatcct cttctgagat gagttttgt tcgttacaca 60

gccggccctg c 71

<210> 125

<211> 73

<212> DNA

<213> Artificial Sequence

<220>

<223> DLL4 Egf4 reverse1

<400> 125

ttactgacgc ggccgctcat cacagatcct cttctgagat gagttttgt tcttcacaat 60

gcaggccata gta 73

<210> 126

<211> 71

<212> DNA

<213> Artificial Sequence

<220>

<223> DLL4 Egf7 reverse1

<400> 126

ttactgacgc ggccgctcat cacagatcct cttctgagat gagttttgt tcctcacagc 60

gtcggccaga g 71

<210> 127

<211> 259

<212> DNA

<213> Artificial Sequence

<220>

<223> CBF-1

<400> 127

ggtacctgag ctcgctagcg atctggtgta aacacgccgt gggaaaaaat ttatggatct 60

ggtgtaaaca cgccgtggga aaaaatttat ggagctcgct agcgatctgg tgtaaacacg 120

ccgtgggaaa aaatttatgg atctggtgta aacacgccgt gggaaaaaat ttatgctcga 180

ggatctggtg taaacacgcc gtgggaaaaa atttatggat ctggtgtaaa cacgccgtgg 240

gaaaaaattt atgaagctt 259

<210> 128

<211> 4283

<212> DNA

<213> Artificial Sequence

<220>

<223> pGL4.23

<400> 128

ggcctaactg gccggtacct gagctcgcta gcctcgagga tatcaagatc tggcctcggc 60

ggccaagct t agacact aga gggt at at aa t ggaagct cg act t ccagct t ggcaat ccg 120

gt act gt t gg t aaagccacc at ggaagat g ccaaaaacat t aagaagggc ccagcgccat 180

t ct acccact cgaagacggg accgccggcg agcagct gca caaagccat g aagcgct acg 240

ccct ggt gcc cggcaccat c gcct t t accg acgcacat at cgaggt ggac at t acct acg 300

ccgagt act t cgagat gagc gt t cggct gg cagaagct at gaagcgct at gggct gaat a 360

caaaccat cg gat cgt ggt g t gcagcgaga at agct t gca gt t ct t cat g cccgt gt t gg 420

gt gccct gt t cat cggt gt g gct gt ggccc cagct aacga cat ct acaac gagcgcgagc 480

t gct gaacag cat gggcat c agccagccca ccgt cgt at t cgt gagcaag aaagggct gc 540

aaaagat cct caacgt gcaa aagaagct ac cgat cat aca aaagat cat c at cat ggat a 600

gcaagaccga ct accagggc t t ccaaagca t gt acacct t cgt gact t cc cat t t gccac 660

ccggct t caa cgagt acgac t t cgt gcccg agagct t cga ccgggacaaa accat cgccc 720

t gat cat gaa cagt agt ggc agt accggat t gcccaaggg cgt agccct a ccgcaccgca 780

ccgct t gt gt ccgat t cagt cat gcccgcg accccat ct t cggcaaccag at cat ccccg 840

acaccgct at cct cagcgt g gt gccat t t c accacggct t cggcat gt t c accacgct gg 900

gct act t gat ct gcggct t t cgggt cgt gc t cat gt accg ct t cgaggag gagct at t ct 960

t gcgcagct t gcaagact at aagat t caat ct gccct gct ggt gcccaca ct at t t agct 1020

t ct t cgct aa gagcact ct c at cgacaagt acgacct aag caact t gcac gagat cgcca 1080

gcggcggggc gccgct cagc aaggaggt ag gt gaggccgt ggccaaacgc t t ccacct ac 1140

caggcat ccg ccagggct ac ggcct gacag aaacaaccag cgccat t ct g at caccccg 1200

aaggggacga caagcct ggc gcagt aggca aggt ggt gcc ct t ct t cgag gct aaggt gg 1260

t ggact t gga caccggt aag acact gggt g t gaaccagcg cggcgagct g t gcgt ccgt g 1320

gccccat gat cat gagcggc t acgt t aaca accccgaggc t acaaacgct ct cat cgaca 1380

aggacggct g gct gcacagc ggcgacat cg cct act ggga cgaggacgag cact t ct t ca 1440

t cgt ggaccg gct gaagagc ct gat caaat acaagggct a ccaggt agcc ccagccgaac 1500

t ggagagcat cct gct gcaa caccccaaca t ct t cgacgc cggggt cgcc ggcct gcccg 1560

acgacgat gc cggcgagct g cccgccgcag t cgt cgt gct ggaacacggt aaaaccat ga 1620

ccgagaagga gat cgt ggac t at gt ggcca gccaggt t ac aaccgccaag aagct gcgcg 1680

gt ggt gt t gt gt t cgt ggac gaggt gcct a aaggact gac cggcaagt t g gacgcccgca 1740

agat ccgcga gat t ct cat t aaggccaaga agggcggcaa gat cgccgt g t aat aat t ct 1800

agagt cgggg cggccggccg ct t cgagcag acat gat aag at acat t gat gagt t t ggac 1860

aaaccacaac t agaat gcag t gaaaaaaat gct t t at t t g t gaaat t t gt gat gct at t g 1920

ct t t at t t gt aaccat t at a agct gcaat a aacaagt t aa caacaacaat t gcat t cat t 1980

t t at gt t t ca ggt t cagggg gaggt gt ggg aggt t t t t t a aagcaagt aa aacct ct aca 2040

aat gt ggt aa aat cgat aag gat ccgt cga ccgat gccct t gagagcct t caacccagt c 2100

agct cct t cc ggt gggcgcg gggcat gact at cgt cgccg cact t at gac t gt ct t ct t t 2160

at cat gcaac t cgt aggaca ggt gccggca gcgct ct t cc gct t cct cgc t cact gact c 2220

gct gcgct cg gt cgt t cggc t gcggcgagc ggt at cagct cact caaagg cggt aat acg 2280

gt t at ccaca gaat cagggg at aacgcagg aaagaacat g t gagcaaaag gccagcaaaa 2340

ggccaggaac cgt aaaaagg ccgcgt t gct ggcgt t t t t c cat aggct cc gccccct ga 2400

cgagcat cac aaaaat cgac gct caagt ca gaggt ggcga aacccgacag gact at aaag 2460

at accaggcg t t t ccccct g gaagct ccct cgt gcgct ct cct gt t ccga ccct gccgct 2520

t accggat ac ct gt ccgcct t t ct ccct t c gggaagcgt g gcgct t t ct c at agct cacg 2580

ct gt aggt at ct cagt t cgg t gt aggt cgt t cgct ccaag ct gggct gt g t gcacgaacc 2640

ccccgt t cag cccgaccgct gcgcct t at c cggt aact at cgt ct t gagt ccaacccggt 2700

aagacacgac t t at cgccac t ggcagcagc cact ggt aac aggat t agca gagcgaggt a 2760

t gt aggcggt gct acagagt t ct t gaagt g gt ggcct aac t acggct aca ct agaagaac 2820

agt at t t ggt at ct gcgct c t gct gaagcc agt t acct t c ggaaaaagag t t ggt agct c 2880

t t gat ccggc aaacaaacca ccgct ggt ag cggt ggt t t t t t t gt t t gca agcagcagat 2940

t acgcgcaga aaaaaaggat ct caagaaga t cct t t gat c t t t t ct acgg ggt ct gacgc 3000

t cagt ggaac gaaaact cac gt t aagggat t t t ggt cat g agat t at caa aaaggat ct t 3060

cacct agat c ct t t t aaat t aaaaat gaag t t t t aaat ca at ct aaagt a t at at gagt a 3120

aact t ggt ct gacagcggcc gcaaat gct a aaccact gca gt ggt t acca gt gct t gat c 3180

agt gaggcac cgat ct cagc gat ct gcct a t t t cgt t cgt ccat agt ggc ct gact cccc 3240

gt cgt gt aga t cact acgat t cgt gagggc t t accat cag gccccagcgc agcaat gat g 3300

ccgcgagagc cgcgt t cacc ggcccccgat t t gt cagcaa t gaaccagcc agcagggagg 3360

gccgagcgaa gaagt ggt cc t gct act t t g t ccgcct cca t ccagt ct at gagct gct gt 3420

cgt gat gct a gagt aagaag t t cgccagt g agt agt t t cc gaagagt t gt ggccat t gct 3480

act ggcat cg t ggt at cacg ct cgt cgt t c ggt at ggct t cgt t caact c t ggt t cccag 3540

cggt caagcc gggt cacat g at cacccat a t t at gaagaa at gcagt cag ct cct t aggg 3600

cct ccgat cg t t gt cagaag t aagt t ggcc gcggt gt t gt cgct cat ggt aat ggcagca 3660

ct acacaat t ct ct t accgt cat gccat cc gt aagat gct t t t ccgt gac cggcgagt ac 3720

t caaccaagt cgt t t t gt ga gt agt gt at a cggcgaccaa gct gct ct t g cccggcgt ct 3780

at acgggaca acaccgcgcc acat agcagt act t t gaaag t gct cat cat cgggaat cgt 3840

t ct t cggggc ggaaagact c aaggat ct t g ccgct at t ga gat ccagt t c gat at agccc 3900

act ct t gcac ccagt t gat c t t cagcat ct t t t act t t ca ccagcgt t t c ggggt gt gca 3960

aaaacaggca agcaaaat gc cgcaaagaag ggaat gagt g cgacacgaaa at gt t ggat g 4020

ct cat act cg t cct t t t t ca at at t at t ga agcat t t at c agggt t act a gt acgt ct ct 4080

caaggat aag t aagt aat at t aaggt acgg gaggt at t gg acaggccgca at aaaat at c 4140

tttattttca ttacatctgt gtgttggttt tttgtgtgaa tcgatagtac taacatacgc 4200

tctccatcaa aacaaaacga aacaaaacaa actagcaaaa taggctgtcc ccagtgcaag 4260

tgcaggtgcc agaacatttc tct 4283

<210> 129

<211> 259

<212> DNA

<213> Artificial Sequence

<220>

<223> P6xCBF

<400> 129

ggtacctgag ctcgctagcg atctggtgta aacacgccgt gggaaaaaat ttatggatct 60

ggtgtaaaca cgccgtggga aaaaatttat ggagctcgct agcgatctgg tgtaaacacg 120

ccgtgggaaa aaatttatgg atctggtgta aacacgccgt gggaaaaaat ttatgctcga 180

ggatctggtg taaacacgcc gtgggaaaaa atttatggat ctggtgtaaa cacgccgtgg 240

gaaaaaattt atgaagctt 259

<210> 130

<211> 4281

<212> DNA

<213> Artificial Sequence

<220>

<223> pGL4.75

<400> 130

ggcctaactg gcctcaatat tggccattag ccatattatt cattggttat atagcataaa 60

tcaatattgg ctattggcca ttgcatacgt tgtatctata tcatattatg tacatttata 120

ttggctcatg tccaatatga ccgccatgtt ggcattgatt attgactagt tattaatagt 180

aatcaattac ggggtcatta gttcatagcc catatatgga gttccgcgtt acataactta 240

cggtaaatgg cccgcctggc tgaccgccca acgacccccg cccattgacg tcaataatga 300

cgtatgttcc catagtaacg ccaataggga ctttccattg acgtcaatgg gtggagtatt 360

t acggt aaac t gcccact t g gcagt acat c aagt gt at ca t at gccaagt ccgcccct a 420

t t gacgt caa t gacggt aaa t ggcccgcct ggcat t at gc ccagt acat g acct t acggg 480

act t t cct ac t t ggcagt ac at ct acgt at t agt cat cgc t at t accat g gt gat gcggt 540

t t t ggcagt a caccaat ggg cgt ggat agc ggt t t gact c acggggat t t ccaagt ct cc 600

accccat t ga cgt caat ggg agt t t gt t t t ggcaccaaaa t caacgggac t t t ccaaaat 660

gt cgt aat aa ccccgccccg t t gacgcaaa t gggcggt ag gcgt gt acgg t gggaggt ct 720

at at aagcag agct cgt t t a gt gaaccgt c agat cact ag aagct t t at t gcggt agt t t 780

at cacagt t a aat t gct aac gcagt cagt g ggcct cggcg gccaagct t g gcaat ccggt 840

act gt t ggt a aagccaccat ggct t ccaag gt gt acgacc ccgagcaacg caaacgcat g 900

at cact gggc ct cagt ggt g ggct cgct gc aagcaaat ga acgt gct gga ct cct t cat c 960

aact act at g at t ccgagaa gcacgccgag aacgccgt ga t t t t t ct gca t ggt aacgct 1020

gcct ccagct acct gt ggag gcacgt cgt g cct cacat cg agcccgt ggc t agat gcat c 1080

at ccct gat c t gat cggaat gggt aagt cc ggcaagagcg ggaat ggct c at at cgcct c 1140

ct ggat cact acaagt acct caccgct t gg t t cgagct gc t gaacct t cc aaagaaaat c 1200

at ct t t gt gg gccacgact g gggggct t gt ct ggcct t t c act act cct a cgagcaccaa 1260

gacaagat ca aggccat cgt ccat gct gag agt gt cgt gg acgt gat cga gt cct gggac 1320

gagt ggcct g acat cgagga ggat at cgcc ct gat caaga gcgaagaggg cgagaaaat g 1380

gt gct t gaga at aact t ct t cgt cgagacc at gct cccaa gcaagat cat gcggaaact g 1440

gagcct gagg agt t cgct gc ct acct ggag ccat t caagg agaagggcga ggt t agacgg 1500

cct accct ct cct ggcct cg cgagat ccct ct cgt t aagg gaggcaagcc cgacgt cgt c 1560

cagat t gt cc gcaact acaa cgcct acct t cgggccagcg acgat ct gcc t aagat gt t c 1620

at cgagt ccg accct gggt t ct t t t ccaac gct at t gt cg agggagct aa gaagt t ccct 1680

aacaccgagt t cgt gaaggt gaagggcct c cact t cagcc aggaggacgc t ccagat gaa 1740

at gggt aagt acat caagag ct t cgt ggag cgcgt gct ga agaacgagca gt aat t ct ag 1800

agt cggggcg gccggccgct t cgagcagac at gat aagat acat t gat ga gt t t ggacaa 1860

accacaact a gaat gcagt g aaaaaaat gc t t t at t t gt g aaat t t gt ga t gct at t gct 1920

t t at t t gt aa ccat t at aag ct gcaat aaa caagt t aaca acaacaat t g cat t cat t t t 1980

at gt t t cagg t t caggggga ggt gt gggag gt t t t t t aaa gcaagt aaaa cct ct acaaa 2040

t gt ggt aaaa t cgat aagga t ccgt cgacc gat gccct t g agagcct t ca acccagt cag 2100

ct cct t ccgg t gggcgcggg gcat gact at cgt cgccgca ct t at gact g t ct t ct t t at 2160

cat gcaact c gt aggacagg t gccggcagc gct ct t ccgc t t cct cgct c act gact cgc 2220

t gcgct cggt cgt t cggct g cggcgagcgg t at cagct ca ct caaaggcg gt aat acggt 2280

t at ccacaga at caggggat aacgcaggaa agaacat gt g agcaaaaggc cagcaaaagg 2340

ccaggaaccg t aaaaaggcc gcgt t gct gg cgt t t t t cca t aggct ccgc cccct gacg 2400

agcat cacaa aaat cgacgc t caagt caga ggt ggcgaaa cccgacagga ct at aaagat 2460

accaggcgt t t ccccct gga agct ccct cg t gcgct ct cc t gt t ccgacc ct gccgct t a 2520

ccggat acct gt ccgcct t t ct ccct t cgg gaagcgt ggc gct t t ct cat agct cacgct 2580

gt aggt at ct cagt t cggt g t aggt cgt t c gct ccaagct gggct gt gt g cacgaacccc 2640

ccgt t cagcc cgaccgct gc gcct t at ccg gt aact at cg t ct t gagt cc aacccggt aa 2700

gacacgact t at cgccact g gcagcagcca ct ggt aacag gat t agcaga gcgaggt at g 2760

t aggcggt gc t acagagt t c t t gaagt ggt ggcct aact a cggct acact agaagaacag 2820

t at t t ggt at ct gcgct ct g ct gaagccag t t acct t cgg aaaaagagt t ggt agct ct t 2880

gat ccggcaa acaaaccacc gct ggt agcg gt ggt t t t t t t gt t t gcaag cagcagat t a 2940

cgcgcagaaa aaaaggat ct caagaagat c ct t t gat ct t t t ct acgggg t ct gacgct c 3000

agt ggaacga aaact cacgt t aagggat t t t ggt cat gag at t at caaaa aggat ct t ca 3060

cct agat cct t t t aaat t aa aaat gaagt t t t aaat caat ct aaagt at a t at gagt aaa 3120

ct t ggt ct ga cagcggccgc aaat gct aaa ccact gcagt ggt t accagt gct t gat cag 3180

t gaggcaccg at ct cagcga t ct gcct at t t cgt t cgt cc at agt ggcct gact ccccgt 3240

cgt gt agat c act acgat t c gt gagggct t accat caggc cccagcgcag caat gat gcc 3300

gcgagagccg cgt t caccgg cccccgat t t gt cagcaat g aaccagccag cagggagggc 3360

cgagcgaaga agt ggt cct g ct act t t gt c cgcct ccat c cagt ct at ga gct gct gt cg 3420

t gat gct aga gt aagaagt t cgccagt gag t agt t t ccga agagt t gt gg ccat t gct ac 3480

t ggcat cgt g gt at cacgct cgt cgt t cgg t at ggct t cg t t caact ct g gt t cccagcg 3540

gt caagccgg gt cacat gat cacccat at t at gaagaaat gcagt cagct cct t agggcc 3600

t ccgat cgt t gt cagaagt a agt t ggccgc ggt gt t gt cg ct cat ggt aa t ggcagcact 3660

acacaat t ct ct t accgt ca t gccat ccgt aagat gct t t t ccgt gaccg gcgagt act c 3720

aaccaagt cg t t t t gt gagt agt gt at acg gcgaccaagc t gct ct t gcc cggcgt ct at 3780

acgggacaac accgcgccac at agcagt ac t t t gaaagt g ct cat cat cg ggaat cgt t c 3840

t t cggggcgg aaagact caa ggat ct t gcc gct at t gaga t ccagt t cga t at agcccac 3900

t ct t gcaccc agt t gat ct t cagcat ct t t t act t t cacc agcgt t t cgg ggt gt gcaaa 3960

aacaggcaag caaaat gccg caaagaaggg aat gagt gcg acacgaaaat gt t ggat gct 4020

cat act cgt c ct t t t t caat at t at t gaag cat t t at cag ggt t act agt acgt ct ct ca 4080

aggat aagt a agt aat at t a aggt acggga ggt at t ggac aggccgcaat aaaat at ct t 4140

t at t t t cat t acat ct gt gt gt t ggt t t t t t gt gt gaat c gat agt act a acat acgct c 4200

t ccat caaaa caaaacgaaa caaaacaaac t agcaaaat a ggct gt cccc agt gcaagt g 4260

caggt gccag aacat t t ct c t 4281

<210> 131

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01

<400> 131

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ser Ser Ser Ser Ala Glu Tyr Phe Gln His Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 132

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01

<400> 132

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

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

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Arg Gly Tyr Ser Tyr Gly Tyr Asp Tyr Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 133

<211> 130

<212> PRT

<213> Artificial Sequence

<220>

<223> VH6-1_IGHD3-3*01_IGHJ4*01

<400> 133

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

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
20 25 30

Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu

35 40 45

Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
50 55 60

Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
65 70 75 80

Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
85 90 95

Tyr Tyr Cys Ala Arg Glu Tyr Tyr Asp Phe Trp Ser Gly Tyr Tyr Thr
100 105 110

Asp Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

Ala Ser
130

<210> 134
<211> 127
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD3-10*01_IGHJ4*01

<400> 134
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Tyr Tyr Tyr Gly Ser Gly Ser Tyr Tyr Asn Asp Tyr Phe
100 105 110
Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120 125

<210> 135
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-13*01_IGHJ4*01

<400> 135
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Gly Tyr Ser Ser Ser Trp Tyr Asp Tyr Phe Asp Tyr Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 136

<211> 128

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD2-15*01_IGHJ2*01

<400> 136

```
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50                  55                  60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Gly Tyr Cys Ser Gly Gly Ser Cys Tyr Ser Tyr Trp Tyr
            100                 105                 110
Phe Asp Leu Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser Ala Ser
        115                 120                 125
```

<210> 137

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> VH4-34_IGHD7-27*01_IGHJ4*01

<400> 137

Gln Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu
1 5 10 15
Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Gly Tyr
20 25 30
Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45
Gly Glu Ile Asn His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60
Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65 70 75 80
Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95
Arg Ala Asn Trp Gly Asp Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ser Ala Ser
115

<210> 138
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-3_IGHD4-23*01_IGHJ4*01

<400> 138

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met
35 40 45
Gly Trp Ser Asn Ala Gly Asn Gly Asn Thr Lys Tyr Ser Gln Glu Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Arg Asp Thr Ser Ala Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Met Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Asp Tyr Gly Gly Asn Ser Asp Tyr Phe Asp Tyr Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 139
<211> 132
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-8_IGHD2-2*01_IGHJ6*01

<400> 139
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Asp Ile Asn Trp Val Arg Gln Ala Thr Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Trp Met Asn Pro Asn Ser Gly Asn Thr Gly Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asn Thr Ser Ile Ser 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 Gly Gly Tyr Cys Ser Ser Thr Ser Cys Tyr Ala Asp Tyr Tyr

100 105 110

Tyr Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val

115 120 125

Ser Ser Ala Ser

130

<210> 140

<211> 129

<212> PRT

<213> Artificial Sequence

<220>

<223> VH4-31_IGHD2-15*01_IGHJ2*01

<400> 140

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln

1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly

20 25 30

Gly 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 Tyr 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 Glu Gly Tyr Cys Ser Gly Gly Ser Cys Tyr Ser Tyr Trp

100 105 110

Tyr Phe Asp Leu Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser Ala

115 120 125

Ser

<210> 141

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01

<400> 141

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 142

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01

<400> 142

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ser
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 143

<211> 116

<212> PRT

<213> Artificial Sequence

<220>

<223> V4-3_IGLJ4*01

<400> 143

Gln Pro Val Leu Thr Gln Pro Thr Ser Leu Ser Ala Ser Pro Gly Ala
1 5 10 15

Ser Ala Arg Leu Thr Cys Thr Leu Arg Ser Gly Ile Asn Leu Gly Ser
20 25 30

Tyr Arg Ile Phe Trp Tyr Gln Gln Lys Pro Glu Ser Pro Pro Arg Tyr
35 40 45

Leu Leu Ser Tyr Tyr Ser Asp Ser Ser Lys His Gln Gly Ser Gly Val
50 55 60
Pro Ser Arg Phe Ser Gly Ser Lys Asp Ala Ser Ser Asn Ala Gly Ile
65 70 75 80
Leu Val Ile Ser Gly Leu Gln Ser Glu Asp Glu Ala Asp Tyr Tyr Cys
85 90 95
Met Ile Trp His Ser Ser Ala Ser Phe Val Phe Gly Gly Gly Thr Gln
100 105 110
Leu Ile Ile Leu
115

<210> 144
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> A27_IGKJ1*01

<400> 144
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30
Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45
Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro
85 90 95
Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr

100 105 110

<210> 145

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L2_IGKJ1*01

<400> 145

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Asn Trp Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 146

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L5_IGKJ1*01

<400> 146

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 147

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L12_IGKJ1*01

<400> 147

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Ser Pro
85 90 95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 148
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> O1_IGKJ1*01

<400> 148
Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu Asp Ser
20 25 30
Asp Asp Gly Asn Thr Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln
35 40 45
Ser Pro Gln Leu Leu Ile Tyr Thr Leu Ser Tyr Arg Ala Ser Gly Val
50 55 60
Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys
65 70 75 80
Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln
85 90 95
Arg Ile Glu Phe Pro Ser Trp Thr Phe Gly Gln Gly Thr Lys Val Glu
100 105 110
Ile Lys Arg Thr

115

<210> 149

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V1-4_IGLJ4*01

<400> 149

Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

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

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Glu Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser
85 90 95

Ser Thr Leu Phe Val Phe Gly Gly Gly Thr Gln Leu Ile Ile Leu
100 105 110

<210> 150

<211> 116

<212> PRT

<213> Artificial Sequence

<220>

<223> V4-6_IGLJ4*01

<400> 150

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

<210> 151
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S104F

<400> 151

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ser Ser Phe Ser Ala Glu Tyr Phe Gln His Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 152
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S104A

<400> 152
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ser Ser Ala Ser Ala Glu Tyr Phe Gln His Trp

100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser

115 120

<210> 153

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S103P

<400> 153

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr

20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met

35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe

50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ser Pro Ser Ser Ala Glu Tyr Phe Gln His Trp

100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser

115 120

<210> 154

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A

<400> 154

```
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50                  55                  60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Ser Ser Ser Ala Glu Tyr Phe Gln His Trp
            100                 105                 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
        115                 120
```

<210> 155

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F

<400> 155

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln His Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 156

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F

<400> 156

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met

35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 157
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111Y

<400> 157
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Tyr Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 158
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104Y/H111Y

<400> 158
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Tyr Ser Ala Glu Tyr Phe Gln Tyr Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 159

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 E100A

<400> 159

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Ala Tyr Ser Ser Ser Ser Ala Glu Tyr Phe Gln His Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 160

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 Y101A

<400> 160

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Ala Ser Ser Ser Ser Ala Glu Tyr Phe Gln His Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 161

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S103A

<400> 161

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ser Ala Ser Ser Ala Glu Tyr Phe Gln His Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 162
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S105A

<400> 162
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ser Ser Ser Ala Ala Glu Tyr Phe Gln His Trp

100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser

115 120

<210> 163

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 E107A

<400> 163

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr

20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met

35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe

50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ser Ser Ser Ser Ala Ala Tyr Phe Gln His Trp

100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser

115 120

<210> 164

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 Q110A

<400> 164

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ser Ser Ser Ser Ala Glu Tyr Phe Ala His Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 165

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 H111A

<400> 165

```
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50                  55                  60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ser Ser Ser Ser Ala Glu Tyr Phe Gln Ala Trp
            100                 105                 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
        115                 120
```

<210> 166

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102Q

<400> 166

```
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
```

50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Gln Ser Ser Ser Ala Glu Tyr Phe Gln His Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 167
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102V

<400> 167
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Val Ser Ser Ser Ala Glu Tyr Phe Gln His Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 168
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102I

<400> 168
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ile Ser Ser Ser Ala Glu Tyr Phe Gln His Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 169
<211> 124
<212> PRT

<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102G

<400> 169
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20   25   30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45
Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50   55   60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Gly Ser Ser Ser Ala Glu Tyr Phe Gln His Trp
            100   105   110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
        115   120

<210> 170
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S103L

<400> 170
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr

20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met

35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe

50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ser Leu Ser Ser Ala Glu Tyr Phe Gln His Trp

100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser

115 120

<210> 171

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S103W

<400> 171

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr

20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met

35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe

50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ser Trp Ser Ser Ala Glu Tyr Phe Gln His Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 172
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S103F

<400> 172
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ser Phe Ser Ser Ala Glu Tyr Phe Gln His Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser

115 120

<210> 173

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S103N

<400> 173

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ser Asn Ser Ser Ala Glu Tyr Phe Gln His Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 174

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S103H

<400> 174

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ser His Ser Ser Ala Glu Tyr Phe Gln His Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 175

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S103C

<400> 175

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ser Cys Ser Ser Ala Glu Tyr Phe Gln His Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 176
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S103G

<400> 176
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ser Gly Ser Ser Ala Glu Tyr Phe Gln His Trp

100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser

115 120

<210> 177

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S104C

<400> 177

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr

20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met

35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe

50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ser Ser Gly Ser Ala Glu Tyr Phe Gln His Trp

100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser

115 120

<210> 178

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S104G

<400> 178

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ser Ser Cys Ser Ala Glu Tyr Phe Gln His Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 179

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S104H

<400> 179

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ser Ser His Ser Ala Glu Tyr Phe Gln His Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 180

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S104L

<400> 180

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr

20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ser Ser Leu Ser Ala Glu Tyr Phe Gln His Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 181

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S104R

<400> 181

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ser Ser Arg Ser Ala Glu Tyr Phe Gln His Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 182
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F G55W

<400> 182
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asn Pro Ser Trp Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln His Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 183

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F G55D

<400> 183

```
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ile Asn Pro Ser Asp Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50                  55                  60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln His Trp
            100                 105                 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
        115                 120
```

<210> 184

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F A106E

<400> 184

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Glu Glu Tyr Phe Gln His Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 185

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F H111S

<400> 185

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Ser Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 186
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
T28A

<400> 186
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 Ala Ser Gly Tyr Ala Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 187
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F F29A

<400> 187
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 Ala Ser Gly Tyr Thr Ala Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 188

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
T30A

<400> 188

```
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 Ala Ser Gly Tyr Thr Phe Ala Ser Tyr
            20                  25                  30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50                  55                  60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
            100                 105                 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
        115                 120
```

<210> 189

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
S31A

<400> 189

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 Ala Ser Gly Tyr Thr Phe Thr Ala Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 190

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
Y33A

<400> 190

```
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50                  55                  60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
            100                 105                 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
        115                 120
```

<210> 191

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F I50A

<400> 191

```
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
```

Gly Ala Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 192
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
I51A

<400> 192
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ala Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 193
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
N52A

<400> 193
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Ala Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 194

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
P53A

<400> 194

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Ala Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 195

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
S54A

<400> 195

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asn Pro Ala Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 196
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
G55A

<400> 196

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asn Pro Ser Ala Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 197
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
G56A

<400> 197
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asn Pro Ser Gly Ala Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 198
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
S57A

<400> 198
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asn Pro Ser Gly Gly Ala Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 199
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
T58A

<400> 199
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asn Pro Ser Gly Gly Ser Ala Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 200
<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
S59A

<400> 200

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ala Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 201

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
I51T/N52V

<400> 201

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Thr Val Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 202

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
N52G

<400> 202

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Gly Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 203
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
N52T

<400> 203
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Thr Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 204
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
N52P

<400> 204
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Pro Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 205

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
N52L

<400> 205

```
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ile Leu Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50                  55                  60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
            100                 105                 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
        115                 120
```

<210> 206

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
N52W

<400> 206

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Trp Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 207

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
N52Y

<400> 207

```
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ile Tyr Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50                  55                  60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
            100                 105                 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
        115                 120
```

<210> 208

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F N52V

<400> 208

```
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
```

Gly Ile Ile Val Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 209
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
N52S

<400> 209
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Ser Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 210
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
N52Q

<400> 210
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Gln Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 211

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
N52K

<400> 211

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Lys Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 212

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
G56V

<400> 212

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asn Pro Ser Gly Val Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 213
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
G56E

<400> 213

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asn Pro Ser Gly Glu Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 214
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
G56S

<400> 214
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asn Pro Ser Gly Ser Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 215
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
G56K

<400> 215
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asn Pro Ser Gly Lys Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 216
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
G56T

<400> 216
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asn Pro Ser Gly Thr Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 217
<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F G56L

<400> 217

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Ser Gly Leu Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 218

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F G56R

<400> 218

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Ser Gly Arg Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 219

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
G56H

<400> 219

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asn Pro Ser Gly His Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 220
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
G56I

<400> 220
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asn Pro Ser Gly Ile Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 221
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F G56W

<400> 221
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asn Pro Ser Gly Trp Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 222

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
S54I

<400> 222

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Ile Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 223

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
S54E

<400> 223

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Glu Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 224

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
S54R

<400> 224

```
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ile Asn Pro Arg Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50                  55                  60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
            100                 105                 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
        115                 120
```

<210> 225

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
S54G

<400> 225

```
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
```

Gly Ile Ile Asn Pro Gly Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 226
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
S54T

<400> 226
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asn Pro Thr Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 227
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
S54L

<400> 227
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asn Pro Leu Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 228

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
S54V

<400> 228

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Val Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 229

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
S54N

<400> 229

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asn Pro Asn Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 230
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
S54P

<400> 230

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asn Pro Pro Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 231
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
I50T/S54P

<400> 231
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Thr Ile Asn Pro Pro Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 232
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
S54A/S59N

<400> 232
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asn Pro Ala Gly Gly Ser Thr Asn Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 233
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
N52L/S54T/G56H

<400> 233
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Leu Pro Thr Gly His Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 234
<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
I51A/N52L/S54T/G56H

<400> 234

```
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ala Leu Pro Thr Gly His Ser Thr Ser Tyr Ala Gln Lys Phe
    50                  55                  60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
            100                 105                 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
        115                 120
```

<210> 235

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
I51T/N52L/S54T/G56H

<400> 235

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Thr Leu Pro Thr Gly His Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 236

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
I51Y/N52L/S54T/G56H

<400> 236

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Tyr Leu Pro Thr Gly His Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 237
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
I51H/N52L/S54T/G56H

<400> 237
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile His Leu Pro Thr Gly His Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 238
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
I51E/N52L/S54T/G56H

<400> 238
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Glu Leu Pro Thr Gly His Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 239

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
I51G/N52L/S54T/G56H

<400> 239

```
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Gly Leu Pro Thr Gly His Ser Thr Ser Tyr Ala Gln Lys Phe
    50                  55                  60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
            100                 105                 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
        115                 120
```

<210> 240

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
I51V/N52L/S54T/G56H

<400> 240

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Val Leu Pro Thr Gly His Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 241

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
I51S/N52L/S54T/G56H

<400> 241

```
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ser Leu Pro Thr Gly His Ser Thr Ser Tyr Ala Gln Lys Phe
    50                  55                  60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
            100                 105                 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
        115                 120
```

<210> 242

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
I51W/N52L/S54T/G56H

<400> 242

```
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
```

Gly Ile Trp Leu Pro Thr Gly His Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 243
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
I51R/N52L/S54T/G56H

<400> 243
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Arg Leu Pro Thr Gly His Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 244

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
I51N/N52L/S54T/G56H

<400> 244

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Asn Leu Pro Thr Gly His Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 245

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
I51T/N52L/P53V/S54T/G56H

<400> 245

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Thr Leu Val Thr Gly His Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 246

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
I51T/N52L/P53G/S54T/G56H

<400> 246

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	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Ser	Tyr
			20					25					30		
Tyr	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met
		35					40					45			
Gly	Ile	Thr	Leu	Gly	Thr	Gly	His	Ser	Thr	Ser	Tyr	Ala	Gln	Lys	Phe
	50					55					60				
Gln	Gly	Arg	Val	Thr	Met	Thr	Arg	Asp	Thr	Ser	Thr	Ser	Thr	Val	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	Glu	Glu	Tyr	Ala	Pro	Phe	Ser	Ala	Glu	Tyr	Phe	Gln	Phe	Trp
			100					105					110		
Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser				
		115					120								

<210> 247
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
I51T/N52L/P53S/S54T/G56H

<400> 247

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Thr Leu Ser Thr Gly His Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 248
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
I51T/N52L/P53W/S54T/G56H

<400> 248
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Thr Leu Trp Thr Gly His Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 249
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
I51T/N52L/P53R/S54T/G56H

<400> 249
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Thr Leu Arg Thr Gly His Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 250
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
I51T/N52L/P53N/S54T/G56H

<400> 250
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Thr Leu Asn Thr Gly His Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 251
<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
I51T/N52L/P53A/S54T/G56H

<400> 251

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Thr Leu Ala Thr Gly His Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 252

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
I51T/N52L/P53T/S54T/G56H

<400> 252

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Thr Leu Thr Thr Gly His Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 253

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
I51T/N52L/P53Y/S54T/G56H

<400> 253

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Thr Leu Pro Thr Gly His Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 254
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
I51T/N52L/P53H/S54T/G56H

<400> 254
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Thr Leu His Thr Gly His Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 255
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
I51T/N52L/P53E/S54T/G56H

<400> 255
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Thr Leu Glu Thr Gly His Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 256

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
I51T/N52L/P53M/S54T/G56H

<400> 256

```
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Thr Leu Met Thr Gly His Ser Thr Ser Tyr Ala Gln Lys Phe
    50                  55                  60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val 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 Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
            100                 105                 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
        115                 120
```

<210> 257

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
S84G

<400> 257

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

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

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

Ala Arg Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 258

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
S84Q

<400> 258

```
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50                  55                  60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80
Met Glu Leu Gln Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
            100                 105                 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
        115                 120
```

<210> 259

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F S84N

<400> 259

```
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
```

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80
Met Glu Leu Asn Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 260
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
S84H

<400> 260
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80
Met Glu Leu His Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 261
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
S84R

<400> 261
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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80
Met Glu Leu Arg Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 262

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
S84K

<400> 262

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

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

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

Ala Arg Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 263

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F
S84T

<400> 263

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 Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80
Met Glu Leu Thr Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Glu Tyr Ala Pro Phe Ser Ala Glu Tyr Phe Gln Phe Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 264
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> L6_IGKJ1*01 S28P

<400> 264

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Pro Val Ser Ser Tyr

20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 265

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S30N

<400> 265

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Asn Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 266
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> L6_IGKJ1*01 S31K

<400> 266
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Lys Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 267
<211> 110
<212> PRT
<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 R91P

<400> 267

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Pro Ser Asn Trp Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 268

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 R91L

<400> 268

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile

```
        35                  40                  45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Leu Ser Asn Trp Pro Pro
                85                  90                  95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
            100                 105                 110
```

<210> 269

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 R91G

<400> 269

```
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1               5                  10                  15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
            20                  25                  30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Gly Ser Asn Trp Pro Pro
                85                  90                  95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
            100                 105                 110
```

<210> 270

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 R91Q

<400> 270

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Gln Ser Asn Trp Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 271

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S92N

<400> 271

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Asn Asn Trp Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 272

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S92C

<400> 272

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly

50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Cys Asn Trp Pro Pro
85 90 95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 273
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> L6_IGKJ1*01 N93Y

<400> 273
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Tyr Trp Pro Pro
85 90 95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 274

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 N93S

<400> 274

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Ser Trp Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 275

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 N93H

<400> 275

```
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1               5                  10                  15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
            20                  25                  30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser His Trp Pro Pro
                85                  90                  95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
            100                 105                 110
```

<210> 276

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 N93Q

<400> 276

```
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1               5                  10                  15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
            20                  25                  30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
```

65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Gln Trp Pro Pro

85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr

100 105 110

<210> 277

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 W94R

<400> 277

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly

1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr

20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile

35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly

50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro

65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Arg Pro Pro

85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr

100 105 110

<210> 278

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 W94S

<400> 278

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Ser Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 279

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 W94T

<400> 279

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
            20   25   30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35   40   45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65   70   75   80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Thr Pro Pro
                85   90   95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
            100   105   110

<210> 280
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> L6_IGKJ1*01 W94L

<400> 280
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1   5   10   15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
            20   25   30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35   40   45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65   70   75   80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Leu Pro Pro

85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 281
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> L6_IGKJ1*01 W94P

<400> 281
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Pro Pro Pro
85 90 95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 282
<211> 110
<212> PRT
<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 W94M

<400> 282

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Met Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 283

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S92P

<400> 283

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Pro Asn Trp Pro Pro
85 90 95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 284
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> L6_IGKJ1*01 S92A

<400> 284
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ala Asn Trp Pro Pro
85 90 95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr

100 105 110

<210> 285

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S92Q

<400> 285

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Gln Asn Trp Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 286

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S92V

<400> 286

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Val Asn Trp Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 287

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S92T

<400> 287

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Thr Asn Trp Pro Pro
85 90 95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 288
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> L6_IGKJ1*01 S92R

<400> 288
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Arg Asn Trp Pro Pro
85 90 95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 289

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S92G

<400> 289

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Gly Asn Trp Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 290

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S92V

<400> 290

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Val Asn Trp Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 291

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S92M

<400> 291

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Met Asn Trp Pro Pro
85 90 95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 292
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> L6_IGKJ1*01 S30W

<400> 292
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Trp Ser Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 293

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S30R

<400> 293

```
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1               5                  10                  15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Arg Ser Tyr
            20                  25                  30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
                85                  90                  95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
            100                 105                 110
```

<210> 294

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S30T

<400> 294

```
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
```

```
 1               5                  10                  15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Thr Ser Tyr
            20                  25                  30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
                85                  90                  95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
            100                 105                 110
```

<210> 295

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S30L

<400> 295

```
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1               5                  10                  15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Leu Ser Tyr
            20                  25                  30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80
```

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 296
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> L6_IGKJ1*01 R24G/Q27L

<400> 296
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Gly Ala Ser Leu Ser Val Ser Ser Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 297
<211> 110
<212> PRT

<213> Artificial Sequence

<220>
<223> L6_IGKJ1*01 Y32V

<400> 297
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1   5   10   15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Val
            20   25   30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35   40   45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65   70   75   80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
                85   90   95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
            100   105   110

<210> 298
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> L6_IGKJ1*01 Y32S

<400> 298
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1   5   10   15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser

20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 299

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S28G

<400> 299

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Gly Val Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 300
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> L6_IGKJ1*01 S28K

<400> 300
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Lys Val Ser Ser Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 301
<211> 110
<212> PRT
<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S28V

<400> 301

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Val Val Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 302

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S28F

<400> 302

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Phe Val Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile

35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 303

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S28T

<400> 303

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Thr Val Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 304

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S28L

<400> 304

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Leu Val Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 305

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S28Q

<400> 305

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Gln Val Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 306

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S28A

<400> 306

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ala Val Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly

50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 307
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> L6_IGKJ1*01 S28N

<400> 307
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asn Val Ser Ser Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 308

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S28H

<400> 308

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln His Val Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 309

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S28I

<400> 309

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ile Val Ser Ser Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 310
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> L6_IGKJ1*01 S28R

<400> 310
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Arg Val Ser Ser Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro

65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro

85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr

100 105 110

<210> 311

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S28W

<400> 311

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly

1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Trp Val Ser Ser Tyr

20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile

35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly

50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro

65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro

85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr

100 105 110

<210> 312

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S28M

<400> 312

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Met Val Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 313

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S28E

<400> 313

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Glu Val Ser Ser Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 314
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> L6_IGKJ1*01 S30C

<400> 314
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Cys Ser Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro

85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 315
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> L6_IGKJ1*01 S30D

<400> 315
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Asp Ser Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 316
<211> 110
<212> PRT
<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S30L

<400> 316

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Leu Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 317

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S30T

<400> 317

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Thr Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 318
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> L6_IGKJ1*01 S30R

<400> 318
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Arg Ser Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr

100 105 110

<210> 319

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S30P

<400> 319

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Pro Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 320

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S30W

<400> 320

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Trp Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 321

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S30Y

<400> 321

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Tyr Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 322
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> L6_IGKJ1*01 S30Q

<400> 322
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Gln Ser Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 323

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S30A

<400> 323

```
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1               5                  10                  15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ala Ser Tyr
            20                  25                  30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
                85                  90                  95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
            100                 105                 110
```

<210> 324

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S30G

<400> 324

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Gly Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 325

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S30V

<400> 325

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Val Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 326
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> L6_IGKJ1*01 S31T

<400> 326
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Thr Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 327

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S31N

<400> 327

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Asn Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 328

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S31L

<400> 328

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly

```
 1               5                  10                  15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Leu Tyr
            20                  25                  30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
                85                  90                  95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
            100                 105                 110
```

<210> 329

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S31M

<400> 329

```
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1               5                  10                  15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Met Tyr
            20                  25                  30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80
```

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 330
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> L6_IGKJ1*01 S31F

<400> 330
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Phe Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 331
<211> 110
<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S31I

<400> 331

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ile Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 332

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S31V

<400> 332

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Val Tyr

20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 333

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S31H

<400> 333

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser His Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 334
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> L6_IGKJ1*01 S31A

<400> 334
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ala Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 335
<211> 110
<212> PRT
<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S31P

<400> 335

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Pro Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 336

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S31D

<400> 336

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Asp Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile

```
        35                  40                  45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
                85                  90                  95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
            100                 105                 110
```

<210> 337

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S31R

<400> 337

```
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1               5                  10                  15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Arg Tyr
            20                  25                  30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
                85                  90                  95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
            100                 105                 110
```

<210> 338

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S31Y

<400> 338

```
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1               5                  10                  15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Tyr Tyr
            20                  25                  30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
                85                  90                  95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
            100                 105                 110
```

<210> 339

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S31Q

<400> 339

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Gln Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 340

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S31E

<400> 340

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Glu Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly

50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 341
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> L6_IGKJ1*01 S31G

<400> 341
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Gly Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 342

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S28P/S30N/S31K

<400> 342

```
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1               5                  10                  15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Pro Val Asn Lys Tyr
            20                  25                  30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
                85                  90                  95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
            100                 105                 110
```

<210> 343

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S28N/S30D/S31H

<400> 343

```
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1               5                  10                  15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asn Val Asp His Tyr
            20                  25                  30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
                85                  90                  95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
            100                 105                 110
```

<210> 344

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 D50A

<400> 344

```
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1               5                  10                  15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
            20                  25                  30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45
Tyr Ala Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
```

65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro

85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr

100 105 110

<210> 345

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 A51T

<400> 345

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly

1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr

20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile

35 40 45

Tyr Asp Thr Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly

50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro

65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro

85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr

100 105 110

<210> 346

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S52A

<400> 346

```
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1               5                  10                  15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
            20                  25                  30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45
Tyr Asp Ala Ala Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
                85                  90                  95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
            100                 105                 110
```

<210> 347

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 N53A

<400> 347

```
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1               5                  10                  15
```

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Ala Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 348
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> L6_IGKJ1*01 R54A

<400> 348
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Asn Ala Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro

85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr

100 105 110

<210> 349

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 A55T

<400> 349

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly

1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr

20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile

35 40 45

Tyr Asp Ala Ser Asn Arg Thr Thr Gly Ile Pro Ala Arg Phe Ser Gly

50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro

65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro

85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr

100 105 110

<210> 350

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 T56A

<400> 350

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Ala Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 351

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S28N/S30D/S31H S52L

<400> 351

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asn Val Asp His Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Asp Ala Leu Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 352
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> L6_IGKJ1*01 S28N/S30D/S31H S52T

<400> 352
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asn Val Asp His Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Asp Ala Thr Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr

100 105 110

<210> 353

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S28N/S30D/S31H S52R

<400> 353

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asn Val Asp His Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Arg Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 354

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S28N/S30D/S31H S52W

<400> 354

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asn Val Asp His Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Trp Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 355

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S28N/S30D/S31H S52N

<400> 355

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asn Val Asp His Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Asn Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 356
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> L6_IGKJ1*01 S28N/S30D/S31H S52P

<400> 356
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asn Val Asp His Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Asp Ala Pro Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 357

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S28N/S30D/S31H S52M

<400> 357

```
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1               5                  10                  15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asn Val Asp His Tyr
            20                  25                  30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45
Tyr Asp Ala Met Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
                85                  90                  95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
            100                 105                 110
```

<210> 358

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S28N/S30D/S31H N53E

<400> 358

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asn Val Asp His Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Glu Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 359

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S28N/S30D/S31H N53G

<400> 359

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asn Val Asp His Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Gly Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 360
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> L6_IGKJ1*01 S28N/S30D/S31H N53M

<400> 360
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asn Val Asp His Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Met Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 361

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S28N/S30D/S31H N53C

<400> 361

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asn Val Asp His Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Cys Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 362

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S28N/S30D/S31H N53H

<400> 362

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly

```
 1               5                  10                  15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asn Val Asp His Tyr
            20                  25                  30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45
Tyr Asp Ala Ser His Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
                85                  90                  95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
            100                 105                 110
```

<210> 363

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S28N/S30D/S31H N53P

<400> 363

```
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1               5                  10                  15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asn Val Asp His Tyr
            20                  25                  30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45
Tyr Asp Ala Ser Pro Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80
```

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 364
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> L6_IGKJ1*01 S28N/S30D/S31H N53A

<400> 364
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asn Val Asp His Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Ala Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 365
<211> 110
<212> PRT

<213> Artificial Sequence

<220>
<223> L6_IGKJ1*01 S28N/S30D/S31H A55R

<400> 365
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1   5   10   15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asn Val Asp His Tyr
            20   25   30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35   40   45
Tyr Asp Ala Ser Asn Arg Arg Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65   70   75   80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
                85   90   95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
            100   105   110

<210> 366
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> L6_IGKJ1*01 S28N/S30D/S31H A55C

<400> 366
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1   5   10   15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asn Val Asp His Tyr

20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Cys Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 367

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S28N/S30D/S31H A55S

<400> 367

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asn Val Asp His Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ser Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 368
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> L6_IGKJ1*01 S28N/S30D/S31H A55G

<400> 368
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asn Val Asp His Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 369
<211> 110
<212> PRT
<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S28N/S30D/S31H S52L/A55G

<400> 369

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asn Val Asp His Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Leu Asn Arg Gly Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 370

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S28N/S30D/S31H S52L/A55S

<400> 370

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asn Val Asp His Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile

```
        35                  40                  45
Tyr Asp Ala Leu Asn Arg Ser Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
                85                  90                  95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
            100                 105                 110
```

<210> 371

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S76L

<400> 371

```
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1               5                  10                  15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
            20                  25                  30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Leu Ser Leu Glu Pro
65                  70                  75                  80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
                85                  90                  95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
            100                 105                 110
```

<210> 372

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S76T

<400> 372

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Thr Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 373

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S76G

<400> 373

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Gly Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 374

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S76A

<400> 374

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly

50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ala Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 375
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> L6_IGKJ1*01 S76Y

<400> 375
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Tyr Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 376

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 F62L

<400> 376

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Leu Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 377

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S76E

<400> 377

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Glu Ser Leu Glu Pro
65 70 75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 378
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> L6_IGKJ1*01 S76Q

<400> 378
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Gln Ser Leu Glu Pro

65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro

85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr

100 105 110

<210> 379

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S76P

<400> 379

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly

1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr

20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile

35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly

50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Pro Ser Leu Glu Pro

65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro

85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr

100 105 110

<210> 380

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> L6_IGKJ1*01 S76N

<400> 380

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 381

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K

<400> 381

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Arg Lys Tyr Ser Tyr Gly Tyr Asp Tyr Phe Asp Tyr Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 382
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100R

<400> 382
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr

65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Arg Arg Tyr Ser Tyr Gly Tyr Asp Tyr Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 383

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G104T

<400> 383

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

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

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Arg Gly Tyr Ser Tyr Thr Tyr Asp Tyr Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 384

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T

<400> 384

```
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1               5                  10                  15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
            20                  25                  30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
    50                  55                  60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95
Ala Arg Arg Lys Tyr Ser Tyr Thr Tyr Asp Tyr Phe Asp Tyr Trp Gly
            100                 105                 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
        115                 120
```

<210> 385

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 R99A

<400> 385

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Ala Gly Tyr Ser Tyr Gly Tyr Asp Tyr Phe Asp Tyr Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 386

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100A

<400> 386

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr

20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met

35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe

50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr

65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys

85 90 95

Ala Arg Arg Ala Tyr Ser Tyr Gly Tyr Asp Tyr Phe Asp Tyr Trp Gly

100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser

115 120

<210> 387

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 Y101A

<400> 387

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu

1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr

20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met

35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe

50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr

65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Arg Gly Ala Ser Tyr Gly Tyr Asp Tyr Phe Asp Tyr Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 388
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 S102A

<400> 388
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Arg Gly Tyr Ala Tyr Gly Tyr Asp Tyr Phe Asp Tyr Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 389

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 Y103A

<400> 389

```
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1               5                  10                  15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
            20                  25                  30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
    50                  55                  60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95
Ala Arg Arg Gly Tyr Ser Ala Gly Tyr Asp Tyr Phe Asp Tyr Trp Gly
            100                 105                 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
        115                 120
```

<210> 390

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G104A

<400> 390

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Arg Gly Tyr Ser Tyr Ala Tyr Asp Tyr Phe Asp Tyr Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 391

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 Y105A

<400> 391

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Arg Gly Tyr Ser Tyr Gly Ala Asp Tyr Phe Asp Tyr Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 392
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 D106A

<400> 392
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys

85 90 95

Ala Arg Arg Gly Tyr Ser Tyr Gly Tyr Ala Tyr Phe Asp Tyr Trp Gly

100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser

115 120

<210> 393

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100L

<400> 393

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu

1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr

20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met

35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe

50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr

65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys

85 90 95

Ala Arg Arg Leu Tyr Ser Tyr Gly Tyr Asp Tyr Phe Asp Tyr Trp Gly

100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser

115 120

<210> 394

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100D

<400> 394

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

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

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Arg Asp Tyr Ser Tyr Gly Tyr Asp Tyr Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 395

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100T

<400> 395

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

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

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Arg Thr Tyr Ser Tyr Gly Tyr Asp Tyr Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 396

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G104D

<400> 396

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met

35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Arg Gly Tyr Ser Tyr Asp Tyr Asp Tyr Phe Asp Tyr Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 397
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G104L

<400> 397
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Arg Gly Tyr Ser Tyr Leu Tyr Asp Tyr Phe Asp Tyr Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 398
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G104P

<400> 398
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Arg Gly Tyr Ser Tyr Pro Tyr Asp Tyr Phe Asp Tyr Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 399

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G104R

<400> 399

```
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1               5                  10                  15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
            20                  25                  30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
    50                  55                  60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95
Ala Arg Arg Gly Tyr Ser Tyr Arg Tyr Asp Tyr Phe Asp Tyr Trp Gly
            100                 105                 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
        115                 120
```

<210> 400

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G104M

<400> 400

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

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

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Arg Gly Tyr Ser Tyr Met Tyr Asp Tyr Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 401

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G104K

<400> 401

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Arg Gly Tyr Ser Tyr Lys Tyr Asp Tyr Phe Asp Tyr Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 402
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G104S

<400> 402
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Arg Gly Tyr Ser Tyr Ser Tyr Asp Tyr Phe Asp Tyr Trp Gly

100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser

115 120

<210> 403

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G104R/Y101H

<400> 403

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu

1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr

20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met

35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe

50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr

65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys

85 90 95

Ala Arg Arg Gly His Ser Tyr Arg Tyr Asp Tyr Phe Asp Tyr Trp Gly

100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser

115 120

<210> 404

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T G24A

<400> 404

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

Ser Leu Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

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

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Arg Lys Tyr Ser Tyr Thr Tyr Asp Tyr Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 405

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T I34A

<400> 405

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

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

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

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

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Arg Lys Tyr Ser Tyr Thr Tyr Asp Tyr Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 406

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T G35A

<400> 406

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

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

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe

```
    50                  55                  60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95
Ala Arg Arg Lys Tyr Ser Tyr Thr Tyr Asp Tyr Phe Asp Tyr Trp Gly
            100                 105                 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
        115                 120
```

<210> 407

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T S28A

<400> 407

```
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1               5                  10                  15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ala Phe Thr Ser Tyr
            20                  25                  30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
    50                  55                  60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95
Ala Arg Arg Lys Tyr Ser Tyr Thr Tyr Asp Tyr Phe Asp Tyr Trp Gly
            100                 105                 110
```

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 408
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T F29A

<400> 408
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Ala Thr Ser Tyr
20 25 30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Arg Lys Tyr Ser Tyr Thr Tyr Asp Tyr Phe Asp Tyr Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 409
<211> 123
<212> PRT

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T T30A

<400> 409

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Ala Ser Tyr
20 25 30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Arg Lys Tyr Ser Tyr Thr Tyr Asp Tyr Phe Asp Tyr Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 410

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T W33A

<400> 410

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu

1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr

20 25 30

Ala Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met

35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe

50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr

65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys

85 90 95

Ala Arg Arg Lys Tyr Ser Tyr Thr Tyr Asp Tyr Phe Asp Tyr Trp Gly

100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser

115 120

<210> 411

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T G24L

<400> 411

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu

1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Leu Ser Gly Tyr Ser Phe Thr Ser Tyr

20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met

35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe

50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Arg Lys Tyr Ser Tyr Thr Tyr Asp Tyr Phe Asp Tyr Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 412
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T G24S

<400> 412
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Ser Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Arg Lys Tyr Ser Tyr Thr Tyr Asp Tyr Phe Asp Tyr Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser

115 120

<210> 413

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T G24R

<400> 413

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

Ser Leu Lys Ile Ser Cys Lys Arg Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

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

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Arg Lys Tyr Ser Tyr Thr Tyr Asp Tyr Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 414

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T S28R

<400> 414

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Arg Phe Thr Ser Tyr
20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

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

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Arg Lys Tyr Ser Tyr Thr Tyr Asp Tyr Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 415

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T S28K

<400> 415

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Lys Phe Thr Ser Tyr
20 25 30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Arg Lys Tyr Ser Tyr Thr Tyr Asp Tyr Phe Asp Tyr Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 416
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T S28N

<400> 416
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Asn Phe Thr Ser Tyr
20 25 30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr

65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Arg Lys Tyr Ser Tyr Thr Tyr Asp Tyr Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 417

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T G35T

<400> 417

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

Trp Ile Thr Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

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

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Arg Lys Tyr Ser Tyr Thr Tyr Asp Tyr Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 418

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T G35A

<400> 418

```
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1               5                  10                  15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
            20                  25                  30
Trp Ile Ala Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
    50                  55                  60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95
Ala Arg Arg Lys Tyr Ser Tyr Thr Tyr Asp Tyr Phe Asp Tyr Trp Gly
            100                 105                 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
        115                 120
```

<210> 419

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T G35V

<400> 419

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

Trp Ile Val Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

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

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Arg Lys Tyr Ser Tyr Thr Tyr Asp Tyr Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 420

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T
G24L/S28R/G35V

<400> 420

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

Ser Leu Lys Ile Ser Cys Lys Leu Ser Gly Tyr Arg Phe Thr Ser Tyr
20 25 30
Trp Ile Val Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Arg Lys Tyr Ser Tyr Thr Tyr Asp Tyr Phe Asp Tyr Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 421
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T D57A

<400> 421
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Tyr Pro Gly Asp Ser Ala Thr Arg Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr

65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Arg Lys Tyr Ser Tyr Thr Tyr Asp Tyr Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 422

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T I50A

<400> 422

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ala Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

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

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Arg Lys Tyr Ser Tyr Thr Tyr Asp Tyr Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 423

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T I51A

<400> 423

```
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1               5                  10                  15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
            20                  25                  30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ala Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
    50                  55                  60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95
Ala Arg Arg Lys Tyr Ser Tyr Thr Tyr Asp Tyr Phe Asp Tyr Trp Gly
            100                 105                 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
        115                 120
```

<210> 424

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T Y52A

<400> 424

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Ala Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

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

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Arg Lys Tyr Ser Tyr Thr Tyr Asp Tyr Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 425

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T P53A

<400> 425

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr

20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met

35 40 45

Gly Ile Ile Tyr Ala Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe

50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr

65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys

85 90 95

Ala Arg Arg Lys Tyr Ser Tyr Thr Tyr Asp Tyr Phe Asp Tyr Trp Gly

100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser

115 120

<210> 426

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T D55A

<400> 426

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu

1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr

20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met

35 40 45

Gly Ile Ile Tyr Pro Gly Ala Ser Asp Thr Arg Tyr Ser Pro Ser Phe

50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr

65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Arg Lys Tyr Ser Tyr Thr Tyr Asp Tyr Phe Asp Tyr Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 427
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T T58D

<400> 427
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Asp Arg Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Arg Lys Tyr Ser Tyr Thr Tyr Asp Tyr Phe Asp Tyr Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 428

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T T58A

<400> 428

```
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1               5                  10                  15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
            20                  25                  30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Ala Arg Tyr Ser Pro Ser Phe
    50                  55                  60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95
Ala Arg Arg Lys Tyr Ser Tyr Thr Tyr Asp Tyr Phe Asp Tyr Trp Gly
            100                 105                 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
        115                 120
```

<210> 429

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T S56G

<400> 429

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Tyr Pro Gly Asp Gly Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Arg Lys Tyr Ser Tyr Thr Tyr Asp Tyr Phe Asp Tyr Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 430
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T S84V

<400> 430

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Val Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Arg Lys Tyr Ser Tyr Thr Tyr Asp Tyr Phe Asp Tyr Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 431
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T S84L

<400> 431
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Leu Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys

85 90 95

Ala Arg Arg Lys Tyr Ser Tyr Thr Tyr Asp Tyr Phe Asp Tyr Trp Gly

100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser

115 120

<210> 432

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T D109A

<400> 432

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu

1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr

20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met

35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe

50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr

65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys

85 90 95

Ala Arg Arg Lys Tyr Ser Tyr Thr Tyr Asp Tyr Phe Ala Tyr Trp Gly

100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser

115 120

<210> 433

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T
G24T/S28R/G35V

<400> 433

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

Ser Leu Lys Ile Ser Cys Lys Thr Ser Gly Tyr Arg Phe Thr Ser Tyr
20 25 30

Trp Ile Val Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

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

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Arg Lys Tyr Ser Tyr Thr Tyr Asp Tyr Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 434

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T
G24A/S28R/G35V

<400> 434

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Ala Ser Gly Tyr Arg Phe Thr Ser Tyr
20 25 30
Trp Ile Val Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Arg Lys Tyr Ser Tyr Thr Tyr Asp Tyr Phe Asp Tyr Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 435
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T
G24T/S28R/G35V Y105H

<400> 435

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

Ser Leu Lys Ile Ser Cys Lys Thr Ser Gly Tyr Arg Phe Thr Ser Tyr
20 25 30
Trp Ile Val Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Arg Lys Tyr Ser Tyr Thr His Asp Tyr Phe Asp Tyr Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 436
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T
G24T/S28R/G35V Y105N

<400> 436
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Thr Ser Gly Tyr Arg Phe Thr Ser Tyr
20 25 30
Trp Ile Val Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Arg Lys Tyr Ser Tyr Thr Asn Asp Tyr Phe Asp Tyr Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 437
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T
G24T/S28R/G35V Y107F

<400> 437
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Thr Ser Gly Tyr Arg Phe Thr Ser Tyr
20 25 30
Trp Ile Val Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Arg Lys Tyr Ser Tyr Thr Tyr Asp Phe Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 438
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T
G24T/S28R/G35V D109Q

<400> 438
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Thr Ser Gly Tyr Arg Phe Thr Ser Tyr
20 25 30
Trp Ile Val Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Arg Lys Tyr Ser Tyr Thr Tyr Asp Tyr Phe Gln Tyr Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 439
<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91A

<400> 439

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Ala Leu Tyr Met Gly Ser
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 440

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 L92A

<400> 440

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45
Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Ala Tyr Met Gly Ser
85 90 95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 441
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> V3-4_IGLJ1*01 Y93A

<400> 441
Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15
Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45
Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Ala Met Gly Ser

85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu

100 105 110

<210> 442

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 M94A

<400> 442

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly

1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser

20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr

35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe

50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala

65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Ala Gly Ser

85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu

100 105 110

<210> 443

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 G95A

<400> 443

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

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

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 444

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 G97A

<400> 444

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45
Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ser
85 90 95
Ala Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 445
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> V3-4_IGLJ1*01 S96A

<400> 445
Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15
Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45
Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ala
85 90 95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu

100 105 110

<210> 446

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 I98A

<400> 446

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ser
85 90 95

Gly Ala Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 447

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 S99A

<400> 447

Gln	Thr	Val	Val	Thr	Gln	Glu	Pro	Ser	Phe	Ser	Val	Ser	Pro	Gly	Gly
1				5					10					15	
Thr	Val	Thr	Leu	Thr	Cys	Gly	Leu	Ser	Ser	Gly	Ser	Val	Ser	Thr	Ser
			20					25					30		
Tyr	Tyr	Pro	Ser	Trp	Tyr	Gln	Gln	Thr	Pro	Gly	Gln	Ala	Pro	Arg	Thr
		35					40					45			
Leu	Ile	Tyr	Ser	Thr	Asn	Thr	Arg	Ser	Ser	Gly	Val	Pro	Asp	Arg	Phe
	50					55					60				
Ser	Gly	Ser	Ile	Leu	Gly	Asn	Lys	Ala	Ala	Leu	Thr	Ile	Thr	Gly	Ala
65					70					75					80
Gln	Ala	Asp	Asp	Glu	Ser	Asp	Tyr	Tyr	Cys	Val	Leu	Tyr	Met	Gly	Ser
				85					90					95	
Gly	Ile	Ala	Tyr	Val	Phe	Gly	Thr	Gly	Thr	Lys	Val	Thr	Val	Leu	
			100					105					110		

<210> 448

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91P

<400> 448

Gln	Thr	Val	Val	Thr	Gln	Glu	Pro	Ser	Phe	Ser	Val	Ser	Pro	Gly	Gly
1				5					10					15	
Thr	Val	Thr	Leu	Thr	Cys	Gly	Leu	Ser	Ser	Gly	Ser	Val	Ser	Thr	Ser
			20					25					30		
Tyr	Tyr	Pro	Ser	Trp	Tyr	Gln	Gln	Thr	Pro	Gly	Gln	Ala	Pro	Arg	Thr
		35					40					45			

Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Pro Leu Tyr Met Gly Ser
85 90 95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 449
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> V3-4_IGLJ1*01 V91T

<400> 449
Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15
Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45
Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Thr Leu Tyr Met Gly Ser
85 90 95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 450

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91S

<400> 450

```
Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
 1               5                  10                  15
Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
            20                  25                  30
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
        35                  40                  45
Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
    50                  55                  60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65                  70                  75                  80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Ser Leu Tyr Met Gly Ser
                85                  90                  95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
            100                 105                 110
```

<210> 451

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91L

<400> 451

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Ser
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 452

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91R

<400> 452

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Arg Leu Tyr Met Gly Ser
85 90 95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 453
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> V3-4_IGLJ1*01 V91C

<400> 453
Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15
Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45
Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Cys Leu Tyr Met Gly Ser
85 90 95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 454

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91E

<400> 454

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Glu Leu Tyr Met Gly Ser
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 455

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91W

<400> 455

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly

1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Trp Leu Tyr Met Gly Ser
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 456

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91N

<400> 456

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Asn Leu Tyr Met Gly Ser
85 90 95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 457
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> V3-4_IGLJ1*01 V91I

<400> 457
Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15
Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45
Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Ile Leu Tyr Met Gly Ser
85 90 95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 458
<211> 111
<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91G

<400> 458

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Gly Leu Tyr Met Gly Ser
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 459

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91H

<400> 459

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser

20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr

35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe

50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala

65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys His Leu Tyr Met Gly Ser

85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu

100 105 110

<210> 460

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 M94E

<400> 460

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly

1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser

20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr

35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe

50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala

65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Glu Gly Ser

85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 461
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> V3-4_IGLJ1*01 M94S

<400> 461
Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15
Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45
Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Ser Gly Ser
85 90 95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 462
<211> 111
<212> PRT
<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 M94G

<400> 462

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Gly Gly Ser
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 463

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 M94L

<400> 463

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr

35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Leu Gly Ser
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 464

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 M94P

<400> 464

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Pro Gly Ser
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 465

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 M94V

<400> 465

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Val Gly Ser
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 466

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 M94D

<400> 466

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Asp Gly Ser
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 467

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 M94R

<400> 467

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe

50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Arg Gly Ser
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 468

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 M94N

<400> 468

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Asn Gly Ser
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 469

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 M94T

<400> 469

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Thr Gly Ser
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 470

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 M94F

<400> 470

```
Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
 1               5                  10                  15
Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
            20                  25                  30
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
        35                  40                  45
Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
    50                  55                  60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65                  70                  75                  80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Phe Gly Ser
                85                  90                  95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
            100                 105                 110
```

<210> 471

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 S96W

<400> 471

```
Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
 1               5                  10                  15
Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
            20                  25                  30
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
        35                  40                  45
Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
    50                  55                  60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
```

65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Trp

85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu

100 105 110

<210> 472

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 S96G

<400> 472

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly

1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser

20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr

35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe

50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala

65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Gly

85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu

100 105 110

<210> 473

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 S96P

<400> 473

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Pro
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 474

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 S96R

<400> 474

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45
Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Arg
85 90 95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 475
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> V3-4_IGLJ1*01 S96L

<400> 475
Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15
Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45
Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Leu

85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu

100 105 110

<210> 476

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 S96M

<400> 476

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly

1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser

20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr

35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe

50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala

65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Met

85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu

100 105 110

<210> 477

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 S96E

<400> 477

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Glu
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 478

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 S96V

<400> 478

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45
Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Val
85 90 95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 479
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> V3-4_IGLJ1*01 M94R/S96M

<400> 479
Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15
Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45
Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Arg Gly Met
85 90 95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu

100 105 110

<210> 480

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 L24A

<400> 480

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Ala Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ser
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 481

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 S26A

<400> 481

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ala Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ser
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 482

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 G27A

<400> 482

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Ala Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ser
85 90 95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 483
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> V3-4_IGLJ1*01 S28A

<400> 483
Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15
Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ala Val Ser Thr Ser
20 25 30
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45
Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ser
85 90 95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 484

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V29A

<400> 484

```
Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
 1               5                  10                  15
Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Ala Ser Thr Ser
            20                  25                  30
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
        35                  40                  45
Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
    50                  55                  60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65                  70                  75                  80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ser
                85                  90                  95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
            100                 105                 110
```

<210> 485

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 S30A

<400> 485

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ala Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ser
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 486

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 T31A

<400> 486

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Ala Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ser
85 90 95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 487
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> V3-4_IGLJ1*01 S32A

<400> 487
Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15
Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ala
20 25 30
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45
Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ser
85 90 95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 488

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 Y33A

<400> 488

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Ala Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ser
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 489

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 Y34A

<400> 489

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly

1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Ala Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ser
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 490

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 P35A

<400> 490

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Ala Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ser
85 90 95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 491
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> V3-4_IGLJ1*01 S36A

<400> 491
Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15
Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30
Tyr Tyr Pro Ala Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45
Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ser
85 90 95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 492
<211> 111
<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 G23A

<400> 492

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Ala Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ser
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 493

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 S25A

<400> 493

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ala Ser Gly Ser Val Ser Thr Ser

20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr

35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe

50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala

65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ser

85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu

100 105 110

<210> 494

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 G23R

<400> 494

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly

1 5 10 15

Thr Val Thr Leu Thr Cys Arg Leu Ser Ser Gly Ser Val Ser Thr Ser

20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr

35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe

50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala

65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ser

85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 495
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> V3-4_IGLJ1*01 G23L

<400> 495
Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15
Thr Val Thr Leu Thr Cys Leu Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45
Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ser
85 90 95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 496
<211> 111
<212> PRT
<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 S52A

<400> 496

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ala Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ser
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 497

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 T53A

<400> 497

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr

```
        35                  40                  45
Leu Ile Tyr Ser Ala Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
    50                  55                  60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65                  70                  75                  80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ser
                85                  90                  95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
            100                 105                 110



<210> 498
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> V3-4_IGLJ1*01 N54A

<400> 498
Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
 1               5                  10                  15
Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
            20                  25                  30
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
        35                  40                  45
Leu Ile Tyr Ser Thr Ala Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
    50                  55                  60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65                  70                  75                  80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ser
                85                  90                  95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
            100                 105                 110
```

<210> 499

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 T55A

<400> 499

```
Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
 1               5                  10                  15
Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
            20                  25                  30
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
        35                  40                  45
Leu Ile Tyr Ser Thr Asn Ala Arg Ser Ser Gly Val Pro Asp Arg Phe
    50                  55                  60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65                  70                  75                  80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ser
                85                  90                  95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
            100                 105                 110
```

<210> 500

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 R56A

<400> 500

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Thr Asn Thr Ala Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ser
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 501

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 S57A

<400> 501

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Ala Ser Gly Val Pro Asp Arg Phe

50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ser
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 502

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 S58A

<400> 502

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ala Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ser
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 503

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 S52G

<400> 503

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Gly Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ser
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 504

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 S52C

<400> 504

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15
Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45
Leu Ile Tyr Cys Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ser
85 90 95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 505
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> V3-4_IGLJ1*01 S52R

<400> 505
Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15
Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45
Leu Ile Tyr Arg Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala

65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ser

85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu

100 105 110

<210> 506

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 R56I

<400> 506

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly

1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser

20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr

35 40 45

Leu Ile Tyr Ser Thr Asn Thr Ile Ser Ser Gly Val Pro Asp Arg Phe

50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala

65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ser

85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu

100 105 110

<210> 507

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 R56Y

<400> 507

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Thr Asn Thr Tyr Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ser
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 508

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 R56D

<400> 508

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45
Leu Ile Tyr Ser Thr Asn Thr Asp Ser Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ser
85 90 95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 509
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> V3-4_IGLJ1*01 R56G

<400> 509
Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15
Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45
Leu Ile Tyr Ser Thr Asn Thr Gly Ser Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ser

85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu

100 105 110

<210> 510

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 R56S

<400> 510

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly

1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser

20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr

35 40 45

Leu Ile Tyr Ser Thr Asn Thr Ser Ser Ser Gly Val Pro Asp Arg Phe

50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala

65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ser

85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu

100 105 110

<210> 511

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 T78S

<400> 511

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Ser Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ser
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 512

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 T78E

<400> 512

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45
Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Glu Gly Ala
65 70 75 80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ser
85 90 95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 513
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> V3-4_IGLJ1*01 T78Y

<400> 513
Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15
Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45
Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Tyr Gly Ala
65 70 75 80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ser
85 90 95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu

100 105 110

<210> 514

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 T78M

<400> 514

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Met Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ser
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 515

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 T78L

<400> 515

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15
Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45
Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Leu Gly Ala
65 70 75 80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ser
85 90 95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 516
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> V3-4_IGLJ1*01 T78K

<400> 516

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15
Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Lys Gly Ala
65 70 75 80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ser
85 90 95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 517
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> V3-4_IGLJ1*01 T78V

<400> 517
Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15
Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45
Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Val Gly Ala
65 70 75 80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ser
85 90 95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 518

<211> 217

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 G23A/N175K

<400> 518

```
Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
 1               5                  10                  15
Thr Val Thr Leu Thr Cys Ala Leu Ser Ser Gly Ser Val Ser Thr Ser
            20                  25                  30
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
        35                  40                  45
Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
    50                  55                  60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65                  70                  75                  80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ser
                85                  90                  95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu Gly
            100                 105                 110
Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
        115                 120                 125
Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
    130                 135                 140
Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
145                 150                 155                 160
Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Lys Lys
                165                 170                 175
Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
            180                 185                 190
```

His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
195 200 205

Lys Thr Val Ala Pro Thr Glu Cys Ser
210 215

<210> 519

<211> 217

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 S25A/A116T

<400> 519

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ala Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ser
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu Gly
100 105 110

Gln Pro Lys Thr Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
115 120 125

Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
130 135 140

Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val

145 150 155 160

Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
165 170 175

Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
180 185 190

His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
195 200 205

Lys Thr Val Ala Pro Thr Glu Cys Ser
210 215

<210> 520

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91L/S96P S52F

<400> 520

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Phe Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 521

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91L/S96P S52L

<400> 521

```
Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
 1               5                  10                  15
Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
            20                  25                  30
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
        35                  40                  45
Leu Ile Tyr Leu Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
    50                  55                  60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65                  70                  75                  80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro
                85                  90                  95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
            100                 105                 110
```

<210> 522

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91L/S96P S52I

<400> 522

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ile Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 523

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91L/S96P S52M

<400> 523

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Met Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe

50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 524

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91L/S96P S52V

<400> 524

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Val Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 525

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91L/S96P S52P

<400> 525

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Pro Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 526

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91L/S96P S52T

<400> 526

```
Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
 1               5                  10                  15
Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
            20                  25                  30
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
        35                  40                  45
Leu Ile Tyr Thr Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
    50                  55                  60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65                  70                  75                  80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro
                85                  90                  95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
            100                 105                 110
```

<210> 527

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91L/S96P S52Y

<400> 527

```
Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
 1               5                  10                  15
Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
            20                  25                  30
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
        35                  40                  45
Leu Ile Tyr Tyr Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
    50                  55                  60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
```

65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro

85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu

100 105 110

<210> 528

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91L/S96P S52H

<400> 528

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly

1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser

20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr

35 40 45

Leu Ile Tyr His Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe

50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala

65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro

85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu

100 105 110

<210> 529

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91L/S96P S52Q

<400> 529

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Gln Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 530

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91L/S96P S52N

<400> 530

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45
Leu Ile Tyr Asn Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro
85 90 95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 531
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> V3-4_IGLJ1*01 V91L/S96P S52K

<400> 531
Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15
Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45
Leu Ile Tyr Lys Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro

85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu

100 105 110

<210> 532

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91L/S96P S52D

<400> 532

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly

1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser

20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr

35 40 45

Leu Ile Tyr Asp Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe

50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala

65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro

85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu

100 105 110

<210> 533

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91L/S96P S52E

<400> 533

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Glu Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 534

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91L/S96P S52W

<400> 534

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45
Leu Ile Tyr Trp Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro
85 90 95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 535
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> V3-4_IGLJ1*01 V91L/S96P S52R

<400> 535
Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15
Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45
Leu Ile Tyr Arg Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro
85 90 95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu

100 105 110

<210> 536
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> V3-4_IGLJ1*01 V91L/S96P S52G

<400> 536
Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15
Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45
Leu Ile Tyr Gly Thr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro
85 90 95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 537
<211> 111
<212> PRT
<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91L/S96P

<400> 537

Gln	Thr	Val	Val	Thr	Gln	Glu	Pro	Ser	Phe	Ser	Val	Ser	Pro	Gly	Gly
1				5					10					15	
Thr	Val	Thr	Leu	Thr	Cys	Gly	Leu	Ser	Ser	Gly	Ser	Val	Ser	Thr	Ser
			20					25					30		
Tyr	Tyr	Pro	Ser	Trp	Tyr	Gln	Gln	Thr	Pro	Gly	Gln	Ala	Pro	Arg	Thr
		35					40					45			
Leu	Ile	Tyr	Ser	Thr	Asn	Thr	Arg	Ser	Ser	Gly	Val	Pro	Asp	Arg	Phe
	50					55					60				
Ser	Gly	Ser	Ile	Leu	Gly	Asn	Lys	Ala	Ala	Leu	Thr	Ile	Thr	Gly	Ala
65					70					75					80
Gln	Ala	Asp	Asp	Glu	Ser	Asp	Tyr	Tyr	Cys	Leu	Leu	Tyr	Met	Gly	Pro
				85					90					95	
Gly	Ile	Ser	Tyr	Val	Phe	Gly	Thr	Gly	Thr	Lys	Val	Thr	Val	Leu	
			100					105					110		

<210> 538

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91L/S96P T53F

<400> 538

Gln	Thr	Val	Val	Thr	Gln	Glu	Pro	Ser	Phe	Ser	Val	Ser	Pro	Gly	Gly
1				5					10					15	
Thr	Val	Thr	Leu	Thr	Cys	Gly	Leu	Ser	Ser	Gly	Ser	Val	Ser	Thr	Ser
			20					25					30		
Tyr	Tyr	Pro	Ser	Trp	Tyr	Gln	Gln	Thr	Pro	Gly	Gln	Ala	Pro	Arg	Thr
		35					40					45			

Leu Ile Tyr Ser Phe Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro
85 90 95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 539
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> V3-4_IGLJ1*01 V91L/S96P T53L

<400> 539
Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15
Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45
Leu Ile Tyr Ser Leu Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro
85 90 95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 540

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91L/S96P T53I

<400> 540

```
Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
 1               5                  10                  15
Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
            20                  25                  30
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
        35                  40                  45
Leu Ile Tyr Ser Ile Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
    50                  55                  60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65                  70                  75                  80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro
                85                  90                  95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
            100                 105                 110
```

<210> 541

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91L/S96P T53M

<400> 541

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Met Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 542

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91L/S96P T53V

<400> 542

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Val Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro
85 90 95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 543
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> V3-4_IGLJ1*01 V91L/S96P T53S

<400> 543
Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15
Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45
Leu Ile Tyr Ser Ser Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro
85 90 95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 544

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91L/S96P T53P

<400> 544

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Pro Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 545

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91L/S96P T53Y

<400> 545

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly

1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Tyr Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 546

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91L/S96P T53H

<400> 546

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser His Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro
85 90 95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 547
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> V3-4_IGLJ1*01 V91L/S96P T53Q

<400> 547
Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15
Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45
Leu Ile Tyr Ser Gln Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro
85 90 95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 548
<211> 111
<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91L/S96P T53N

<400> 548

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Asn Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 549

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91L/S96P T53K

<400> 549

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser

20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Lys Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 550

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91L/S96P T53D

<400> 550

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Asp Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 551
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> V3-4_IGLJ1*01 V91L/S96P T53E

<400> 551
Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15
Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45
Leu Ile Tyr Ser Glu Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro
85 90 95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 552
<211> 111
<212> PRT
<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91L/S96P T53W

<400> 552

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Trp Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 553

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91L/S96P T53R

<400> 553

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr

35 40 45

Leu Ile Tyr Ser Arg Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 554

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91L/S96P T53G

<400> 554

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Gly Asn Thr Arg Ser Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 555

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91L/S96P S57F

<400> 555

```
Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
 1               5                  10                  15
Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
            20                  25                  30
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
        35                  40                  45
Leu Ile Tyr Ser Thr Asn Thr Arg Phe Ser Gly Val Pro Asp Arg Phe
    50                  55                  60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65                  70                  75                  80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro
                85                  90                  95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
            100                 105                 110
```

<210> 556

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91L/S96P S57L

<400> 556

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Leu Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 557

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91L/S96P S57I

<400> 557

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Ile Ser Gly Val Pro Asp Arg Phe

50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 558

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91L/S96P S57M

<400> 558

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Met Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 559

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91L/S96P S57V

<400> 559

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Val Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 560

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91L/S96P S57P

<400> 560

```
Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
 1               5                  10                  15
Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
            20                  25                  30
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
        35                  40                  45
Leu Ile Tyr Ser Thr Asn Thr Arg Pro Ser Gly Val Pro Asp Arg Phe
    50                  55                  60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65                  70                  75                  80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro
                85                  90                  95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
            100                 105                 110
```

<210> 561

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91L/S96P S57T

<400> 561

```
Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
 1               5                  10                  15
Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
            20                  25                  30
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
        35                  40                  45
Leu Ile Tyr Ser Thr Asn Thr Arg Thr Ser Gly Val Pro Asp Arg Phe
    50                  55                  60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
```

65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 562

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91L/S96P S57Y

<400> 562

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Tyr Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 563

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91L/S96P S57H

<400> 563

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg His Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 564

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91L/S96P S57Q

<400> 564

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45
Leu Ile Tyr Ser Thr Asn Thr Arg Gln Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro
85 90 95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 565
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> V3-4_IGLJ1*01 V91L/S96P S57N

<400> 565
Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15
Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45
Leu Ile Tyr Ser Thr Asn Thr Arg Asn Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro

85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu

100 105 110

<210> 566

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91L/S96P S57K

<400> 566

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly

1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser

20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr

35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Lys Ser Gly Val Pro Asp Arg Phe

50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala

65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro

85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu

100 105 110

<210> 567

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91L/S96P S57D

<400> 567

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Asp Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 568

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91L/S96P S57E

<400> 568

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45
Leu Ile Tyr Ser Thr Asn Thr Arg Glu Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro
85 90 95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 569
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> V3-4_IGLJ1*01 V91L/S96P S57W

<400> 569
Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15
Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45
Leu Ile Tyr Ser Thr Asn Thr Arg Trp Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80
Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro
85 90 95
Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu

100 105 110

<210> 570

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91L/S96P S57R

<400> 570

Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Thr Ser
20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

Leu Ile Tyr Ser Thr Asn Thr Arg Arg Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Ile Leu Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Leu Leu Tyr Met Gly Pro
85 90 95

Gly Ile Ser Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 571

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> V3-4_IGLJ1*01 V91L/S96P S57G

<400> 571

Gln	Thr	Val	Val	Thr	Gln	Glu	Pro	Ser	Phe	Ser	Val	Ser	Pro	Gly	Gly
1				5					10					15	
Thr	Val	Thr	Leu	Thr	Cys	Gly	Leu	Ser	Ser	Gly	Ser	Val	Ser	Thr	Ser
			20					25					30		
Tyr	Tyr	Pro	Ser	Trp	Tyr	Gln	Gln	Thr	Pro	Gly	Gln	Ala	Pro	Arg	Thr
		35					40					45			
Leu	Ile	Tyr	Ser	Thr	Asn	Thr	Arg	Gly	Ser	Gly	Val	Pro	Asp	Arg	Phe
	50					55					60				
Ser	Gly	Ser	Ile	Leu	Gly	Asn	Lys	Ala	Ala	Leu	Thr	Ile	Thr	Gly	Ala
65					70					75					80
Gln	Ala	Asp	Asp	Glu	Ser	Asp	Tyr	Tyr	Cys	Leu	Leu	Tyr	Met	Gly	Pro
				85					90					95	
Gly	Ile	Ser	Tyr	Val	Phe	Gly	Thr	Gly	Thr	Lys	Val	Thr	Val	Leu	
			100					105					110		

<210> 572

<211> 125

<212> PRT

<213> Artificial Sequence

<220>

<223> VH1-69_IGHD1-1*01_IGHJ6*01

<400> 572

Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ser
1				5					10					15	
Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Gly	Thr	Phe	Ser	Ser	Tyr
			20					25					30		
Ala	Ile	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met
		35					40					45			
Gly	Gly	Ile	Ile	Pro	Ile	Phe	Gly	Thr	Ala	Asn	Tyr	Ala	Gln	Lys	Phe

50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser 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 Gly Tyr Asn Trp Asn Asp Asp Tyr Tyr Tyr Tyr Tyr Gly Met
100 105 110
Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 573
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> A17_IGKJ1*01

<400> 573
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
1 5 10 15
Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val Tyr Ser
20 25 30
Asp Gly Asn Thr Tyr Leu Asn Trp Phe Gln Gln Arg Pro Gly Gln Ser
35 40 45
Pro Arg Arg Leu Ile Tyr Lys Val Ser Asn Arg Asp Ser Gly Val Pro
50 55 60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly
85 90 95
Thr His Trp Pro Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
100 105 110

Lys

<210> 574

<211> 296

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV1-18*01

<400> 574

caggttcagc tggtgcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgcaagg cttctggtta cacctttacc agctatggta tcagctgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggatgg atcagcgctt acaatggtaa cacaaactat 180

gcacagaagc tccagggcag agtcaccatg accacagaca catccacgag cacagcctac 240

atggagctga ggagcctgag atctgacgac acggccgtgt attactgtgc gagaga 296

<210> 575

<211> 276

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV1-18*02

<400> 575

caggttcagc tggtgcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgcaagg cttctggtta cacctttacc agctatggta tcagctgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggatgg atcagcgctt acaatggtaa cacaaactat 180

gcacagaagc tccagggcag agtcaccatg accacagaca catccacgag cacagcctac 240

atggagctga ggagcctaag atctgacgac acggcc 276

<210> 576

<211> 296

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV1-2*01

<400> 576

caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgcaagg cttctggata cacctcacc ggctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggacgg atcaaccct acagtggtgg cacaaactat 180

gcacagaagt ttcagggcag ggtcaccagt accagggaca cgtccatcag cacagcctac 240

atggagctga gcaggctgag atctgacgac acggtcgtgt attactgtgc gagaga 296

<210> 577

<211> 296

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV1-2*02

<400> 577

caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgcaagg cttctggata cacctcacc ggctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggatgg atcaaccct acagtggtgg cacaaactat 180

gcacagaagt ttcagggcag ggtcaccatg accagggaca cgtccatcag cacagcctac 240

atggagctga gcaggctgag atctgacgac acggccgtgt attactgtgc gagaga 296

<210> 578

<211> 296

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV1-2*03

<220>

<221> misc_feature

<222> 113

<223> N = a or g or c or t

<400> 578

caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ttggggcctc agtgaaggtc 60

tcctgcaagg cttctggata cacctcacc ggctactata tgcactgggt gcnacaggcc 120

cctggacaag ggctgagtgg gatgggatgg atcaaccct a acagtggtgg cacaaactat 180

gcacagaagt ttcagggcag ggtcaccatg accagggaca cgtccatcag cacagcctac 240

atggagctga gcaggctgag atctgacgac acggccgtgt attactgtgc gagaga 296

<210> 579

<211> 294

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV1-2*04

<400> 579

caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgcaagg cttctggata cacctcacc ggctactata tgcactgggt gcgacaggcc 120

cctggacaag ggctgagtgg gatgggatgg atcaaccct a acagtggtgg cacaaactat 180

gcacagaagt ttcagggct g ggtcaccatg accagggaca cgtccatcag cacagcctac 240

atggagctga gcaggctgag atctgacgac acggccgtgt attactgtgc gaga 294

<210> 580

<211> 296

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV1-24*01

<400> 580

caggtccagc tggtacagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgcaagg tttccggata caccctcact gaattatcca tgcactgggt gcgacaggct 120

cctggaaaag ggcttgagtg gatgggaggt tttgatcctg aagatggtga aacaatctac 180

gcacagaagt tccagggcag agtcaccatg accgaggaca catctacaga cacagcctac 240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc aacaga 296

<210> 581

<211> 296

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV1-3*01

<400> 581

caggtccagc ttgtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60

tcctgcaagg cttctctgga tacacttact agctatgcta tcgattgggt gcgccaggcc 120

cccggacaaa ggcttgagtg gatgggatgg atcaacgctg gcaatggtaa cacaaaatat 180

tcacagaagt tccagggcag agtcaccatt accagggaca catccgcgag cacagcctac 240

atggagctga gcagcctgag atctgaagac acggctgtgt attactgtgc gagaga 296

<210> 582

<211> 296

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV1-3*02

<400> 582

caggttcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60
tcctgcaagg cttctggata cacctttact agctatgcta tgcattgggt gcgccaggcc 120
cccggacaaa ggcttgagtg gatgggatgg agcaacgctg gcaatggtaa cacaaaatat 180
tcacaggagt tccagggcag agtcaccatt accagggaca catccgcgag cacagcctac 240
atggagctga gcagcctgag atctgaggac atggctgtgt attactgtgc gagaga 296

<210> 583

<211> 294

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV1-45*01

<400> 583

cagatgcagc tggtgcagtc tggggctgag gtgaagaaga ctgggtcctc agtgaaggtt 60
tcctgcaagg cttccggata cacctttacc taccgctacc tgcactgggt gcgacaggcc 120
cccggacaag cgcttgagtg gatgggatgg atcacacctt tcaatggtaa caccaactac 180
gcacagaaat tccaggacag agtcaccatt actagggaca ggtctatgag cacagcctac 240
atggagctga gcagcctgag atctgaggac acagccatgt attactgtgc aaga 294

<210> 584

<211> 294

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV1-45*02

<400> 584

cagatgcagc tggtgcagtc tggggctgag gtgaagaaga ctgggtcctc agtgaaggtt 60
tcctgcaagg cttccggata cacctttacc taccgctacc tgcactgggt gcgacaggcc 120
cccggacaag cgcttgagtg gatgggatgg atcacacctt tcaatggtaa caccaactac 180

gcacagaaat tccaggacag agtcaccatt accagggaca ggtctatgag cacagcctac 240
atggagctga gcagcctgag atctgaggac acagccatgt attactgtgc aaga 294

<210> 585
<211> 260
<212> DNA
<213> Homo sapiens

<220>
<223> IGHV1-45*03

<400> 585
agaagactgg gtcctcagtg aaggttcctc gcaaggcttc cggatacacc ttcacctacc 60
gctacctgca ctgggtgcga caggccccca gacaagcgct tgagtggatg ggatggatca 120
cacctttcaa tggtaacacc aactacgcac agaaatttcca ggacagagtc accattacca 180
gggacaggtc tatgagcaca gcctacatgg agctgagcag cctgagatct gaggacacag 240
ccatgtatta ctgtgcaaga 260

<210> 586
<211> 296
<212> DNA
<213> Homo sapiens

<220>
<223> IGHV1-46*01

<400> 586
caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60
tcctgcaagg catctggata cacctttacc agctactata tgcactgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatgggaata atcaacccta gtggtggtag cacaagctac 180
gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240
atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagaga 296

<210> 587

<211> 296

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV1-46*02

<400> 587

caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60

tcctgcaagg catctggata cacctttaac agctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata atcaacccta gtggtggtag cacaagctac 180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagaga 296

<210> 588

<211> 296

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV1-46*03

<400> 588

caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtt 60

tcctgcaagg catctggata cacctttacc agctactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaata atcaacccta gtggtggtag cacaagctac 180

gcacagaagt tccagggcag agtcaccatg accagggaca cgtccacgag cacagtctac 240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc tagaga 296

<210> 589

<211> 296

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV1-58*01

<400> 589

caaatgcagc tggtgcagtc tgggcctgag gtgaagaagc ctgggacctc agtgaaggtc 60

tcctgcaagg cttctggatt cacctttact agctctgctg tgcagtgggt gcgacaggct 120

cgtggacaac gcctgagtgg gataggatgg atcgtcgttg gcagtggtaa cacaaactac 180

gcacagaagt tccaggaaag agtcaccatt accagggaca tgtccacaag cacagcctac 240

atggagctga gcagcctgag atccgaggac acggccgtgt attactgtgc ggcaga 296

<210> 590

<211> 296

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV1-58*02

<400> 590

caaatgcagc tggtgcagtc tgggcctgag gtgaagaagc ctgggacctc agtgaaggtc 60

tcctgcaagg cttctggatt cacctttact agctctgcta tgcagtgggt gcgacaggct 120

cgtggacaac gcctgagtgg gataggatgg atcgtcgttg gcagtggtaa cacaaactac 180

gcacagaagt tccaggaaag agtcaccatt accagggaca tgtccacaag cacagcctac 240

atggagctga gcagcctgag atccgaggac acggccgtgt attactgtgc ggcaga 296

<210> 591

<211> 296

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV1-69*01

<400> 591

caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctgggtcctc ggtgaaggtc 60
tcctgcaagg cttctggagg cacctcagc agctatgcta tcagctgggt gcgacaggcc 120
cctggacaag ggctgagtgg gatgggaggg atcatccct a tctttggtac agcaaactac 180
gcacagaagt tccagggcag agtcacgatt accgcggacg aatccacgag cacagcctac 240
atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagaga 296

<210> 592
<211> 294
<212> DNA
<213> Homo sapiens

<220>
<223> IGHV1-69*02

<400> 592
caggtccagc tggtgcaatc tggggctgag gtgaagaagc ctgggtcctc ggtgaaggtc 60
tcctgcaagg cttctggagg cacctcagc agctatgcta tcagctgggt gcgacaggcc 120
cctggacaag ggctgagtgg gatgggaagg atcatccct a tcctttggtat agcaaactac 180
gcacagaagt tccagggcag agtcacgatt accgcggaca aatccacgag cacagcctac 240
atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gaga 294

<210> 593
<211> 275
<212> DNA
<213> Homo sapiens

<220>
<223> IGHV1-69*03

<400> 593
caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctgggtcctc ggtgaaggtc 60
tcctgcaagg cttctggagg cacctcagc agctatgcta tcagctgggt gcgacaggcc 120
cctggacaag ggctgagtgg gatgggaggg atcatccct a tctttggtac agcaaactac 180
gcacagaagt tccagggcag agtcacgatt accgcggacg aatccacgag cacagcctac 240

atggagctga gcagcctgag atctgatgac acggc 275

<210> 594
<211> 296
<212> DNA
<213> Homo sapiens

<220>
<223> IGHV1-69*04

<400> 594
caggtccagc tggtgcagtc tggggctgag gtgaagaagc ctgggtcctc ggtgaaggtc 60
tcctgcaagg cttctggagg cacctcagc agctatgcta tcagctgggt gcgacaggcc 120
cctggacaag ggctgagtgg gatgggaagg atcatccctg tcctggtata agcaaactac 180
gcacagaagt tccagggcag agtcacgatt accgcggaca aatccacgag cacagcctac 240
atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagaga 296

<210> 595
<211> 294
<212> DNA
<213> Homo sapiens

<220>
<223> IGHV1-69*05

<400> 595
caggtccagc tggtgcagtc tggggctgag gtgaagaagc ctgggtcctc ggtgaaggtc 60
tcctgcaagg cttctggagg cacctcagc agctatgcta tcagctgggt gcgacaggcc 120
cctggacaag ggctgagtgg gatgggaggg atcatccctg tctttggtac agcaaactac 180
gcacagaagt tccagggcag agtcacgatt accacggacg aatccacgag cacagcctac 240
atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gaga 294

<210> 596
<211> 296

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV1-69*06

<400> 596

caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctgggtcctc ggtgaaggtc 60

tcctgcaagg cttctggagg caccttcagc agctatgcta tcagctgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaggg atcatcccta tctttggtac agcaaactac 180

gcacagaagt tccagggcag agtcacgatt accgcggaca aatccacgag cacagcctac 240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagaga 296

<210> 597

<211> 233

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV1-69*07

<400> 597

agaagcctgg gtcctcggtg aaggtctcct gcaaggcttc tggaggcacc ttcagcagct 60

atgctatcag ctgggtgcga caggcccctg gacaagggct tgagtggatg ggaaggatca 120

tccctatctt tggtacagca aactacgcac agaagttcca gggcagagtc acgattaccg 180

cggacgaatc cacgagcaca gcctacatgg agctgagcag cctgagatct gag 233

<210> 598

<211> 296

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV1-69*08

<400> 598
caggtccagc tggtgcaatc tggggctgag gtgaagaagc ctgggtcctc ggtgaaggtc 60
tcctgcaagg cttctggagg cacctcagc agctatactca tcagctgggt gcgacaggcc 120
cctggacaag ggctgagtgg gatgggaagg atcatccctg tcctggtac agcaaactac 180
gcacagaagt tccagggcag agtcacgatt accgcggaca aatccacgag cacagcctac 240
atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagaga 296

<210> 599
<211> 296
<212> DNA
<213> Homo sapiens

<220>
<223> IGHV1-69*09

<400> 599
caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctgggtcctc ggtgaaggtc 60
tcctgcaagg cttctggagg cacctcagc agctatgcta tcagctgggt gcgacaggcc 120
cctggacaag ggctgagtgg gatgggaagg atcatccctg tcctggtat agcaaactac 180
gcacagaagt tccagggcag agtcacgatt accgcggaca aatccacgag cacagcctac 240
atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagaga 296

<210> 600
<211> 296
<212> DNA
<213> Homo sapiens

<220>
<223> IGHV1-69*10

<400> 600
caggtccagc tggtgcagtc tggggctgag gtgaagaagc ctgggtcctc agtgaaggtc 60
tcctgcaagg cttctggagg cacctcagc agctatgcta tcagctgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaggg atcatccctatcctttggtat agcaaactac 180
gcacagaagt tccagggcag agtcacgatt accgcggaca aatccacgag cacagcctac 240
atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagaga 296

<210> 601
<211> 296
<212> DNA
<213> Homo sapiens

<220>
<223> IGHV1-69*11

<400> 601
caggtccagc tggtgcagtc tggggctgag gtgaagaagc ctgggtcctc ggtgaaggtc 60
tcctgcaagg cttctggagg cacctttagc agctatgcta tcagctgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatgggaagg atcatccctatcctttggtac agcaaactac 180
gcacagaagt tccagggcag agtcacgatt accgcggacg aatccacgag cacagcctac 240
atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagaga 296

<210> 602
<211> 296
<212> DNA
<213> Homo sapiens

<220>
<223> IGHV1-69*12

<400> 602
caggtccagc tggtgcagtc tggggctgag gtgaagaagc ctgggtcctc ggtgaaggtc 60
tcctgcaagg cttctggagg cacctttagc agctatgcta tcagctgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatgggaggg atcatccctatctttggtac agcaaactac 180
gcacagaagt tccagggcag agtcacgatt accgcggacg aatccacgag cacagcctac 240
atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagaga 296

<210> 603

<211> 296

<212> DNA

<213> Homo sapi ens

<220>

<223> I GHV1- 69* 13

<400> 603

caggt ccagc t ggt gcagt c t ggggct gag gt gaagaagc ct gggt cct c agt gaaggt c 60

t cct gcaagg ct t ct ggagg cacct t cagc agct at gct a t cagct gggt gcgacaggcc 120

cct ggacaag ggct t gagt g gat gggaggg at cat ccct a t ct t t ggt ac agcaaact ac 180

gcacagaagt t ccagggcag agt cacgat t accgcggacg aat ccacgag cacagcct ac 240

at ggagct ga gcagcct gag at ct gaggac acggccgt gt at t act gt gc gagaga 296

<210> 604

<211> 296

<212> DNA

<213> Homo sapi ens

<220>

<223> I GHV1- 8* 01

<400> 604

caggt gcagc t ggt gcagt c t ggggct gag gt gaagaagc ct ggggcct c agt gaaggt c 60

t cct gcaagg ct t ct ggat a cacct t cacc agt t at gat a t caact gggt gcgacaggcc 120

act ggacaag ggct t gagt g gat gggat gg at gaaccct a acagt ggt aa cacaggct at 180

gcacagaagt t ccagggcag agt caccat g accaggaaca cct ccat aag cacagcct ac 240

at ggagct ga gcagcct gag at ct gaggac acggccgt gt at t act gt gc gagagg 296

<210> 605

<211> 260

<212> DNA

<213> Homo sapi ens

<220>

<223> IGHV1-c*01

<400> 605

ggaagtctgg ggcctcagtg aaagtctcct gtagttttc tgggttt acc atcaccagct 60

acggtatata ttgggtgcaa cagtcccctg gacaagggct tgagtggatg ggatggatca 120

accctggcaa tggtagccca gctatgcca agaagttca gggcagattc accatgacca 180

gggacatgtc cacaaccaca gcctacacag acctgagcag cctgacatct gaggacatgg 240

ctgtgtatta ctatgcaaga 260

<210> 606

<211> 294

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV1-f*01

<400> 606

gaggtccagc tggtacagtc tggggctgag gtgaagaagc ctggggctac agtgaaaatc 60

tcctgcaagg tttctggata cacctttacc gactatata tgcactgggt gcaacaggcc 120

cctggaaaag ggcttgagtg gatgggactt gttgatcctg aagatggtga aacaatatac 180

gcagagaagt tccagggcag agtcaccata accgcggaca cgtctacaga cacagcctac 240

atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc aaca 294

<210> 607

<211> 233

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV1-f*02

<400> 607

agaagcctgg ggctacagtg aaaatctcct gcaaggttct ggatacacc ttcaccgact 60
actacatgca ctgggtgcaa caggcccctg gaaaagggct tgagtggatg ggacttgttg 120
atcctgaaga tggtgaaaca atatatgcag agaagttcca gggcagagtc accatgaccg 180
cggacacgtc tacagacaca gcctacatgg agctgagcag cctgagatct gag 233

<210> 608

<211> 296

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-28*01

<400> 608

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggacac cctgtccctc 60
acctgcgctg tctctggtta ctccatcagc agtagtaact ggtggggctg gatccggcag 120
ccccagggga agggactgga gtggattggg tacatctatt atagtgggag cacctactac 180
aacccgtccc tcaagagtcg agtcaccatg tcagtagaca cgtccaagaa ccagttctcc 240
ctgaagctga gctctgtgac cgccgtggac acggccgtgt attactgtgc gagaaa 296

<210> 609

<211> 296

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-28*02

<400> 609

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcacagac cctgtccctc 60
acctgcgctg tctctggtta ctccatcagc agtagtaact ggtggggctg gatccggcag 120
ccccagggga agggactgga gtggattggg tacatctatt atagtgggag catctactac 180
aacccgtccc tcaagagtcg agtcaccatg tcagtagaca cgtccaagaa ccagttctcc 240

ctgaagctgagctctgtgaccgccgtggacacggccgtgtattactgtgcgagaaa 296

<210> 610
<211> 296
<212> DNA
<213> Homo sapiens

<220>
<223> IGHV4-28*03

<400> 610
caggtgcagctgcaggagtcgggcccaggactggtgaagcctcggacaccctgtccctc 60
acctgcgctgtctctggttactccatcagcagtagtaactggtggggctggatccggcag 120
ccccccagggaagggactggagtggattgggtacatctatagtgggagcacctactac 180
aacccgtccctcaagagtcgagtcaccatgtcagtagacacgtccaagaaccagttctcc 240
ctgaagctgagctctgtgaccgccgtggacacggccgtgtattactgtgcgagaga 296

<210> 611
<211> 294
<212> DNA
<213> Homo sapiens

<220>
<223> IGHV4-28*04

<400> 611
caggtgcagctgcaggagtcgggcccaggactggtgaagcctcggacaccctgtccctc 60
acctgcgctgtctctggttactccatcagcagtagtaactggtggggctgggatccggcag 120
ccccccagggaagggactggagtggattgggtacatctatagtgggagcacctactac 180
aacccgtccctcaagagtcgagtcaccatgtcagtagacacgtccaagaaccagttctcc 240
ctgaagctgagctctgtgaccgccgtggacaccggcgtgtattactgtgcgaga 294

<210> 612
<211> 287

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-28*05

<400> 612

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggacac cctgtccctc 60

acctgcgctg tctctggtta ctccatcagc agtagtaact ggtggggctg gatccggcag 120

ccccccaggga agggactgga gtggattggg tacatctatt atagtgggag catctactac 180

aacccgtccc tcaagagtcg agtcaccatg tcagtagaca cgtccaagaa ccagttctcc 240

ctgaagctga gctctgtgac cgccgtggac acggccgtgt attactg 287

<210> 613

<211> 299

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-30-2*01

<400> 613

cagctgcagc tgcaggagtc cggctcagga ctggtgaagc cttcacagac cctgtccctc 60

acctgcgctg tctctggtgg ctccatcagc agtggtggtt actcctggag ctggatccgg 120

cagccaccag ggaagggcct ggagtggatt gggtacatct atcatagtgg gagcacctac 180

tacaacccgt ccctcaagag tcgagtcacc atatcagtag acaggtccaa gaaccagttc 240

tccctgaagc tgagctctgt gaccgccgcg gacacggccg tgtattactg tgccagaga 299

<210> 614

<211> 294

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-30-2*02

<400> 614

cagctgcagc tgcaggagtc cggctcagga ctggtgaagc cttcacagac cctgtccctc 60

acctgcgctg tctctggtgg ctccatcagc agtggtggtt actcctggag ctggatccgg 120

cagccaccag ggaagggcct ggagtggatt gggtacatct atcatagtgg gagcacctac 180

tacaacccgt ccctcaagag tcgagtcacc atatcagtag acaggtccaa gaaccagttc 240

tccctgaagc tgagctctgt gaccgctgcg gacacggccg tgtattactg tgcg 294

<210> 615

<211> 299

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-30-2*03

<400> 615

cagctgcagc tgcaggagtc cggctcagga ctggtgaagc cttcacagac cctgtccctc 60

acctgcgctg tctctggtgg ctccatcagc agtggtggtt actcctggag ctggatccgg 120

cagccaccag ggaagggcct ggagtggatt gggagtatct attatagtgg gagcacctac 180

tacaacccgt ccctcaagag tcgagtcacc atatccgtag acacgtccaa gaaccagttc 240

tccctgaagc tgagctctgt gaccgctgca gacacggctg tgtattactg tgcgagaca 299

<210> 616

<211> 227

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-30-2*04

<400> 616

tctggtggct ccatcagcag tggtggttac tcctggagct ggatccggca gccaccaggg 60

aagggcctgg agtggattgg gtacatctat catagtggga gcacctactaa caacccgtcc 120
ctcaagagtc gagtcaccat atcagtagac acgtccaaga accagttctc cctgaagctg 180
agctctgtga ccgccgcaga cacggccgtg tattactgtg cgagaga 227

<210> 617
<211> 299
<212> DNA
<213> Homo sapiens

<220>
<223> IGHV4-30-4*01

<400> 617
caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcacagac cctgtccctc 60
acctgcactg tctctggtgg ctccatcagc agtggtgatt actactggag ttggatccgc 120
cagccccag ggaagggcct ggagtggatt gggtacatct attacagtgg gagcacctac 180
tacaacccgt ccctcaagag tcgagttacc atatcagtag acacgtccaa gaaccagttc 240
tccctgaagc tgagctctgt gactgccgca gacacggccg tgtattactg tgccagaga 299

<210> 618
<211> 299
<212> DNA
<213> Homo sapiens

<220>
<223> IGHV4-30-4*02

<400> 618
caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggacac cctgtccctc 60
acctgcactg tctctggtgg ctccatcagc agtggtgatt actactggag ttggatccgc 120
cagccccag ggaagggcct ggagtggatt gggtacatct attacagtgg gagcacctac 180
tacaacccgt ccctcaagag tcgagttacc atatcagtag acacgtccaa gaaccagttc 240
tccctgaagc tgagctctgt gactgcagca gacacggccg tgtattactg tgccagaga 299

<210> 619

<211> 290

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-30-4*03

<400> 619

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcacagac cctgtccctc 60

acctgcactg tctctggtgg ctccatcagc agtggtgatt actactggag ttggatccgc 120

cagccccag ggaagggcct ggagtggatt gggtacatct attacagtgg gagcacctac 180

tacaacccgt ccctcaagag tcgagttacc atatcagtag acacgtccaa gaaccagttc 240

tccctgaagc tgagctctgt gactgccgcg gacacggccg tgtattactg 290

<210> 620

<211> 290

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-30-4*04

<400> 620

caggtgcagc tgcaggactc gggcccagga ctggtgaagc cttcacagac cctgtccctc 60

acctgcactg tctctggtgg ctccatcagc agtggtgatt actactggag ttggatccgc 120

cagccccag ggaagggcct ggagtggatt gggtactttct attacagtgg gagcacctac 180

tacaacccgt ccctcaagag tcgagttacc atatcagtag acacgtccaa gaaccagttc 240

tccctgaagc tgagctctgt gactgccgca gacacggccg tgtattactg 290

<210> 621

<211> 228

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-30-4*05

<220>

<221> misc_feature

<222> 54

<223> N = a or g or c or t

<400> 621

ctctggtggc tccatcagca gtggtgatta ctactggagt tggatccgcc agcncccagg 60

gaagggcctg gagtggattg ggtacatcta ttacagtggg agcacctact acaacccgtc 120

cctcaagagt cgagtcacca tatcagtaga cacgtccaag aaccagttct ccctgaagct 180

gagctctgtg actgccgcag acacggccgt gtattactgt gccagaga 228

<210> 622

<211> 227

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-30-4*06

<400> 622

tctggtggct ccatcagcag tggtgattac tactggagtt ggatccgcca gcacccaggg 60

aagggcctgg agtggattgg gtacatctat tacagtggga gcacctacta caacccgtcc 120

ctcaagagtc gagttaccat atcagtagac acgtccaaga accagttctc cctgaagctg 180

agctctgtga ctgccgcaga cacggccgtg tattactgtg ccagaga 227

<210> 623

<211> 299

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-31*01

<400> 623

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcacagac cctgtccctc 60

acctgcactg tctctggtgg ctccatcagc agtggtggtt actactggag ctggatccgc 120

cagcacccag ggaagggcct ggagtggatt gggtacatct attacagtgg gagcacctac 180

tacaacccgt ccctcaagag tctagttacc atatcagtag acacgtctaa gaaccagttc 240

tccctgaagc tgagctctgt gactgccgcg gacacggccg tgtattactg tgcgagaga 299

<210> 624

<211> 299

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-31*02

<400> 624

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcacagac cctgtccctc 60

acctgtactg tctctggtgg ctccatcagc agtggtggtt actactggag ctggatccgc 120

cagcacccag ggaagggcct ggagtggatt gggtacatct attacagtgg gagcacctac 180

tacaacccgt ccctcaagag tcgagttacc atatcagtag acacgtctaa gaaccagttc 240

tccctgaagc tgagctctgt gactgccgcg gacacggccg tgtattactg tgcgagaga 299

<210> 625

<211> 299

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-31*03

<400> 625

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc ctcacagac cctgtccctc 60
acctgcactg tctctggtgg ctccatcagc agtggtggtt actactggag ctggatccgc 120
cagcacccag ggaagggcct ggagtggatt gggtacatct attacagtgg gagcacctac 180
tacaacccgt ccctcaagag tcgagttacc atatcagtag acacgtctaa gaaccagttc 240
tccctgaagc tgagctctgt gactgccgcg gacacggccg tgtattactg tgcgagaga 299

<210> 626
<211> 294
<212> DNA
<213> Homo sapiens

<220>
<223> IGHV4-31*04

<400> 626
caggtgcggc tgcaggagtc gggcccagga ctggtgaagc ctcacagac cctgtccctc 60
acctgcactg tctctggtgg ctccatcagc agtggtggtt actactggag ctggatccgc 120
cagcacccag ggaagggcct ggagtggatt gggtacatct attacagtgg gagcacctac 180
tacaacccgt ccctcaagag tcgagttacc atatcagtag acacgtctaa gaaccagttc 240
tccctgaagc tgagctctgt gactgccgcg gacacggccg tgtattactg tgcg 294

<210> 627
<211> 291
<212> DNA
<213> Homo sapiens

<220>
<223> IGHV4-31*05

<400> 627
caggtgcagc tgcaggagtc gggcccagga ctggtgaagc ctcacagac cctgtccctc 60
acctgcactg tctctggtgg ctccatcagc agtggtggtt actactggag ctggatccgc 120
cagcacccag ggaagggcct ggagtggatt gggtacatct attacagtgg gagcacctac 180
tacaacccgt ccctcaagag tcgagttacc atatcagtag acacgtctaa gaaccagttc 240

tccctgaagctgagctctgtgaccgcggacgcggccgtgtattactgtgcg 291

<210> 628
<211> 290
<212> DNA
<213> Homo sapiens

<220>
<223> IGHV4-31*06

<400> 628
caggtgcagctgcaggagtcgggcccaggactggtgaagcctcacagaccctgtccctc 60
acctgcactgtctctggtggctccatcagcagtggtagtactactggagctggatccgc 120
cagcacccagggaagggcctggagtggattgggtacatctattacagtgggagcacctac 180
tacaacccgtcccaagagtcgagttaccatatcagtagacacgtctaagaaccagttc 240
tccctgaagctgagctctgtgactgccgcggacacggccgtgtattactg 290

<210> 629
<211> 290
<212> DNA
<213> Homo sapiens

<220>
<223> IGHV4-31*07

<400> 629
caggtgcagctgcaggagtcgggcccaggactggtgaagcctcacagaccctgtccctc 60
acctgcactgtctctggtggctccatcagcagtggtggttactactggagctggatccgc 120
cagcacccagggaagggcctggagtggattgggtacatctattacagtgggagcacctac 180
tacaacccgtcccaagagtcgagttaccatatcagtagacacgtctaagaaccagttc 240
tccctgaagctgagctctgtgactgccgcggacacggccgtgtattactg 290

<210> 630
<211> 290

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-31*08

<400> 630

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcacagac cctgtccctc 60

acctgcactg tctctggtgg ctccatcagc agtggtggtt actactggag ctggatccgc 120

cagcacccag ggaagggcct ggagtggatt gggtacatct attacagtgg gagcacctac 180

tacaacccgt ccctcaagag tcgagttacc atatccgtag acacgtccaa gaaccagttc 240

tccctgaagc tgagctctgt gactgccgcg gacacggccg tgtattactg 290

<210> 631

<211> 290

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-31*09

<400> 631

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcacagac cctgtccctc 60

acctgcactg tctctggtgg ctccatcagc agtggtggtt actactggag ctggatccgc 120

cagcacccag ggaagggcct ggagtggatt gggtacatct attacagtgg gagcacctac 180

tacaacccgt ccctcaagag tcgagttacc atatcagtag acaagtccaa gaaccagttc 240

tccctgaagc tgagctctgt gaccgccgcg gacacggccg tgtattactg 290

<210> 632

<211> 299

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-31*10

<400> 632

caggtgcagc tgcaggagtc gggcccagga ctgttgaagc cttcacagac cctgtccctc 60

acctgcactg tctctggtgg ctccatcagc agtggtggtt actactggag ctggatccgc 120

cagcacccag ggaagggcct ggagtggatt gggtgcatct attacagtgg gagcacctac 180

tacaacccgt ccctcaagag tcgagttacc atatcagtag acccgtccaa gaaccagttc 240

tccctgaagc cgagctctgt gactgccgcg gacacggccg tggattactg tgcgagaga 299

<210> 633

<211> 293

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-34*01

<400> 633

caggtgcagc tacagcagtg gggcgcagga ctgttgaagc cttcggagac cctgtccctc 60

acctgcgctg tctatggtgg gtcctcagt ggttactact ggagctggat ccgccagccc 120

ccagggaagg ggctggagtg gattggggaa atcaatcata gtggaagcac caactacaac 180

ccgtccctca agagtcgagt caccatatca gtagacacgt ccaagaacca gttctccctg 240

aagctgagct ctgtgaccgc cgcggacacg gctgtgtatt actgtgcgag agg 293

<210> 634

<211> 293

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-34*02

<400> 634

caggtgcagc tacaacagtg gggcgcagga ctgttgaagc cttcggagac cctgtccctc 60

acctgcgctg tctatggtgg gtccttcagt ggttactact ggagctggat ccgccagccc 120
ccagggaagg ggctggagtg gattggggaa atcaatcata gtggaagcac caactacaac 180
ccgtccctca agagtcgagt caccatatca gtagacacgt ccaagaacca gttctccctg 240
aagctgagct ctgtgaccgc cgcggacacg gctgtgtatt actgtgcgag agg 293

<210> 635
<211> 284
<212> DNA
<213> Homo sapiens

<220>
<223> IGHV4-34*03

<400> 635
caggtgcagc tacagcagtg gggcgcagga ctgttgaagc cttcggagac cctgtccctc 60
acctgcgctg tctatggtgg gtcctcagt ggttactact ggagctggat ccgccagccc 120
ccagggaagg ggctggagtg gattggggaa atcaatcata gtggaagcac caactacaac 180
ccgtccctca agagtcgagt caccatatca gtagacacgt ccaagaacca gttctccctg 240
aagctgagct ctgtgaccgc cgcggacacg gccgtgtatt actg 284

<210> 636
<211> 293
<212> DNA
<213> Homo sapiens

<220>
<223> IGHV4-34*04

<400> 636
caggtgcagc tacagcagtg gggcgcagga ctgttgaagc cttcggagac cctgtccctc 60
acctgcgctg tctatggtgg gtcctcagt ggttactact ggagctggat ccgccagccc 120
ccagggaagg ggctggagtg gattggggaa atcaatcata gtggaagcac caacaacaac 180
ccgtccctca agagtcgagc caccatatca gtagacacgt ccaagaacca gttctccctg 240
aagctgagct ctgtgaccgc cgcggacacg gctgtgtatt actgtgcgag agg 293

<210> 637

<211> 293

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-34*05

<400> 637

caggtgcagc tacagcagtg gggcgcagga ctgttgaagc cttcggagac cctgtccctc 60

acctgcgctg tctatggtgg gtcctcagt ggttactact ggtgctggat ccgccagccc 120

ctagggaagg ggctggagtg gattggggaa atcaatcata gtggaagcac caacaacaac 180

ccgtccctca agagtcgagc caccatatca gtagacacgt ccaagaacca gttctccctg 240

aagctgagct ctgtgaccgc cgcggacacg gctgtgtatt actgtgcgag agg 293

<210> 638

<211> 284

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-34*06

<400> 638

caggtgcagc tacagcagtg gggcgcagga ctgttgaagc cttcggagac cctgtccctc 60

acctgcgctg tctatggtgg gtcctcagt ggttactact ggagctggat ccgccagccc 120

ccagggaagg ggctggagtg gattggggaa atcaatcata gtggaagcac caactacaac 180

ccgtccctca agagtcgagt caccatatca gtagacacgt ccaagaacca gttctccctg 240

aagctgggct ctgtgaccgc cgcggacacg gccgtgtatt actg 284

<210> 639

<211> 284

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-34*07

<400> 639

caggtgcagc tacagcagtg gggcgcagga ctgttgaagc cttcggagac cctgtccctc 60

acctgcgctg tctatggtgg gtcctcagt ggttactact ggagctggat ccgccagccc 120

ccagggaagg ggctggagtg gattggggaa atcaaccata gtggaagcac caactacaac 180

ccgtccctca agagtcgagt caccatatca gtagacacgt ccaagaacca gttctccctg 240

aagctgagct ctgtgaccgc cgcggacacg gccgtgtatt actg 284

<210> 640

<211> 288

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-34*08

<400> 640

caggtgcagc tacagcagtg gggcgcagga ctgttgaagc cttcggagac cctgtccctc 60

acctgcgctg tctatggtgg gacctcagt ggttactact ggagctggat ccgccagccc 120

ccagggaagg ggctggagtg gattggggaa atcaatcata gtggaagcac caactacaac 180

ccgtccctca agagtcgagt caccatatca gtagacacgt ccaagaacca gttctccctg 240

aagctgagct ctgtgaccgc cgcggacacg gctgtgtatt actgtgcg 288

<210> 641

<211> 293

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-34*09

<400> 641

caggt gcagc t gcaggagt c gggcccagga ct ggt gaagc ct t cacagac cct gt ccct c 60

acct gcgct g t ct at ggt gg gt cct t cagt ggt t act act ggagct ggat ccgccagccc 120

ccagggaagg gact ggagt g gat t ggggaa at caat cat a gt ggaagcac caact acaac 180

ccgt ccct ca agagt cgagt t accat at ca gt agacacgt ct aagaacca gt t ct ccct g 240

aagct gagct ct gt gact gc cgcggacacg gccgt gt at t act gt gcgag aga 293

<210> 642

<211> 293

<212> DNA

<213> Homo sapi ens

<220>

<223> I GHV4- 34* 10

<400> 642

caggt gcagc t gcaggagt c gggcccagga ct ggt gaagc ct t cggagac cct gt ccct c 60

acct gcgct g t ct at ggt gg gt cct t cagt ggt t act act ggagct ggat ccgccagccc 120

ccagggaagg gact ggagt g gat t ggggaa at caat cat a gt ggaagcac caact acaac 180

ccgt ccct ca agagt cgaat caccat gt ca gt agacacgt ccaagaacca gt t ct acct g 240

aagct gagct ct gt gaccgc cgcggacacg gccgt gt at t act gt gcgag at a 293

<210> 643

<211> 293

<212> DNA

<213> Homo sapi ens

<220>

<223> I GHV4- 34* 11

<400> 643

caggt gcagc t acagcagt g gggcgcagga ct gt t gaagc ct t cggagac cct gt ccct c 60

acct gcgct g t ct at ggt gg gt ccgt cagt ggt t act act ggagct ggat ccggcagccc 120

ccagggaagg ggctggagtg gattgggtat atctattata gtgggagcac caacaacaac 180

ccctccctca agagtcgagc caccatatca gtagacacgt ccaagaacca gttctccctg 240

aacctgagct ctgtgaccgc cgcggacacg gccgtgtatt gctgtgcgag aga 293

<210> 644

<211> 291

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-34*12

<400> 644

caggtgcagc tacagcagtg gggcgcagga ctgttgaagc cttcggagac cctgtccctc 60

acctgcgctg tctatggtgg gtcctcagt ggtactact ggagctggat ccgccagccc 120

ccagggaagg ggctggagtg gattggggaa atcatttcat agtggaagcac caactacaac 180

ccgtccctca agagtcgagt caccatatca gtagacacgt ccaagaacca gttctccctg 240

aagctgagct ctgtgaccgc cgcggacacg gctgtgtatt actgtgcgag a 291

<210> 645

<211> 221

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-34*13

<400> 645

tatggtgggt cctcagtggt tactactgg agctggatcc gccagccccc agggaagggg 60

ctggagtgga ttggggaaat caatcatagt ggaagcacca actacaaccc ctccctcaag 120

agtcgagtca ccatatcagt agacacgtcc aagaaccagt tctccctgaa gctgagctct 180

gtgaccgccg cggacacggc tgtgtattac tgtgcgagag g 221

<210> 646

<211> 299

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-39*01

<400> 646

cagctgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60

acctgcactg tctctggtgg ctccatcagc agtagtagtt actactgggg ctggatccgc 120

cagccccag ggaaggggct ggagtggatt gggagtatct attatagtgg gagcacctac 180

tacaacccgt ccctcaagag tcgagtcacc atatccgtag acacgtccaa gaaccagttc 240

tccctgaagc tgagctctgt gaccgccgca gacacggctg tgtattactg tgcgagaca 299

<210> 647

<211> 299

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-39*02

<400> 647

cagctgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60

acctgcactg tctctggtgg ctccatcagc agtagtagtt actactgggg ctggatccgc 120

cagccccag ggaaggggct ggagtggatt gggagtatct attatagtgg gagcacctac 180

tacaacccgt ccctcaagag tcgagtcacc atatccgtag acacgtccaa gaaccacttc 240

tccctgaagc tgagctctgt gaccgccgca gacacggctg tgtattactg tgcgagaga 299

<210> 648

<211> 290

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-39*03

<400> 648

cagctgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60

acctgcactg tctctggtgg ctccatcagc agtagtagtt actactgggg ctggatccgc 120

cagccccag ggaaggggct ggagtggatt gggagtatct attatagtgg gagcacctac 180

tacaacccgt ccctcaagag tcgagtcacc atatccgtag acacgtccaa gaaccagttc 240

tccctgaagc tgagctctgt gaccgccgca gacacggccg tgtattactg 290

<210> 649

<211> 196

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-39*04

<400> 649

gctccatcag cagtagtagt tactactggg gctggatccg ccagccccca gggaaggggc 60

tggagtggat tgggagtatc tattatagtg ggagcacctac tacaacccg tccctcaaga 120

gtcgagtcac catatccgta gacacgtcca agaaccagtt ctccctgaag ctgagctctg 180

tgaccgccgc ggacac 196

<210> 650

<211> 294

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-39*05

<400> 650

cagctgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cccgtccctc 60

acctgcactg tctctggtgg ctccatcagc agtagtagtt actactgggg ctggatccgc 120
cagcccccag ggaaggggct ggagtggatt gggagtatct attatagtgg gagcacctac 180
tacaacccgt ccctcaagag tcgagtcacc atatccgtag acacgtccaa gaaccagttc 240
tccctgaagc tgagctctgt gaccgccgca gacacggctg tgtattactg tgcg 294

<210> 651
<211> 299
<212> DNA
<213> Homo sapiens

<220>
<223> IGHV4-39*06

<400> 651
cggctgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60
acctgcactg tctctggtgg ctccatcagc agtagtagtt actactgggg ctggatccgc 120
cagcccccag ggaaggggct ggagtggatt gggagtatct attatagtgg gagcacctac 180
tacaacccgt ccctcaagag tcgagtcacc atatcagtag acacgtccaa gaaccagttc 240
ccccctgaagc tgagctctgt gaccgccgcg gacacggccg tgtattactg tgcgagaga 299

<210> 652
<211> 299
<212> DNA
<213> Homo sapiens

<220>
<223> IGHV4-39*07

<400> 652
cagctgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60
acctgcactg tctctggtgg ctccatcagc agtagtagtt actactgggg ctggatccgc 120
cagcccccag ggaaggggct ggagtggatt gggagtatct attatagtgg gagcacctac 180
tacaacccgt ccctcaagag tcgagtcacc atatcagtag acacgtccaa gaaccagttc 240
tccctgaagc tgagctctgt gaccgccgcg gacacggccg tgtattactg tgcgagaga 299

<210> 653

<211> 296

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-4*01

<400> 653

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc ctccggggac cctgtccctc 60

acctgcgctg tctctggtgg ctccatcagc agtagtaact ggtggagttg ggtccgccag 120

cccccaggga aggggctgga gtggattggg gaaatctatc atagtgggag caccaactac 180

aacccgtccc tcaagagtcg agtcaccata tcagtagaca agtccaagaa ccagttctcc 240

ctgaagctga gctctgtgac cgccgcggac acggccgtgt attactgtgc gagaga 296

<210> 654

<211> 296

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-4*02

<400> 654

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggggac cctgtccctc 60

acctgcgctg tctctggtgg ctccatcagc agtagtaact ggtggagttg ggtccgccag 120

cccccaggga aggggctgga gtggattggg gaaatctatc atagtgggag caccaactac 180

aacccgtccc tcaagagtcg agtcaccata tcagtagaca agtccaagaa ccagttctcc 240

ctgaagctga gctctgtgac cgccgcggac acggccgtgt attactgtgc gagaga 296

<210> 655

<211> 287

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-4*03

<400> 655

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc ctccggggac cctgtccctc 60

acctgcgctg tctctggtgg ctccatcagc agtagtaact ggtggagttg ggtccgccag 120

ccccccaggga aggggctgga gtggattggg gaaatctatc atagtgggag caccaactac 180

aacccgtccc tcaagagtcg agtcaccata tcagtagaca agtccaagaa ccagttctcc 240

ctgaagctga gctctgtgac cgccgcggac acggccgtgt attactg 287

<210> 656

<211> 287

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-4*04

<400> 656

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc ctccggggac cctgtccctc 60

acctgcgcta tctctggtgg ctccatcagc agtagtaact ggtggagttg ggtccgccag 120

ccccccaggga aggggctgga gtggattggg gaaatctatc atagtgggag caccaactac 180

aacccgtccc tcaagagtcg agtcaccata tcagtagaca agtccaagaa ccagttctcc 240

ctgaagctga gctctgtgac cgccgcggac acggccgtgt attactg 287

<210> 657

<211> 287

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-4*05

<400> 657
caggtgcagc tgcaggagtc gggcccagga ctggtgaagc ctccggggac cctgtccctc 60
acctgcgctg tctctggtgg ctccatcagc agtagtaact ggtggagtgg ggtccgccag 120
cccccaggga aggggctgga gtggattggg gaaatctatc atagtgggag caccaactac 180
aacccgtccc tcaagagtcg agtcaccata tcagtagaca agtccaagaa ccagttctcc 240
ctgaagctga gctctgtgac cgccgcggac acggccgtgt attactg 287

<210> 658
<211> 224
<212> DNA
<213> Homo sapiens

<220>
<223> IGHV4-4*06

<220>
<221> misc_feature
<222> 59-61
<223> N = a or g or c or t

<400> 658
tctggtggct ccatcagcag tagtaactgg tggagttggg tccgccagcc cccagggann 60
nggctggagt ggattgggga atctatcat agtgggagca ccaactacaa cccgtccctc 120
aagagtcgag tcaccatgtc agtagacacg tccaagaacc agttctccct gaagctgagc 180
tctgtgaccg ccgcggacac ggccgtgtat tactgtgcga gaga 224

<210> 659
<211> 293
<212> DNA
<213> Homo sapiens

<220>
<223> IGHV4-4*07

<400> 659
caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60
acctgcactg tctctggtgg ctccatcagt agttactact ggagctggat ccggcagccc 120
gccgggaagg gactggagtg gattgggcgt atctatacca gtgggagcac caactacaac 180
ccctccctca agagtcgagt caccatgtca gtagacacgt ccaagaacca gttctccctg 240
aagctgagct ctgtgaccgc cgcggacacg gccgtgtatt actgtgcgag aga 293

<210> 660
<211> 293
<212> DNA
<213> Homo sapiens

<220>
<223> IGHV4-59*01

<400> 660
caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60
acctgcactg tctctggtgg ctccatcagt agttactact ggagctggat ccggcagccc 120
ccagggaagg gactggagtg gattgggtat atctattaca gtgggagcac caactacaac 180
ccctccctca agagtcgagt caccatatca gtagacacgt ccaagaacca gttctccctg 240
aagctgagct ctgtgaccgc tgcggacacg gccgtgtatt actgtgcgag aga 293

<210> 661
<211> 293
<212> DNA
<213> Homo sapiens

<220>
<223> IGHV4-59*02

<400> 661
caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60
acctgcactg tctctggtgg ctccgtcagt agttactact ggagctggat ccggcagccc 120

ccagggaagg gactggagtg gattgggtat atctattaca gtgggagcac caactacaac 180

ccctccctca agagtcgagt caccatatca gtagacacgt ccaagaacca gttctccctg 240

aagctgagct ctgtgaccgc tgcggacacg gccgtgtatt actgtgcgag aga 293

<210> 662

<211> 288

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-59*03

<400> 662

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60

acctgcactg tctctggtgg ctccatcagt agttactact ggagctggat ccggcagccc 120

ccagggaagg gactggagtg gattgggtat atctattaca gtgggagcac caactacaac 180

ccctccctca agagtcgagt caccatatca gtagacacgt ccaagaacca attctccctg 240

aagctgagct ctgtgaccgc tgcggacacg gccgtgtatt actgtgcg 288

<210> 663

<211> 288

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-59*04

<400> 663

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60

acctgcactg tctctggtgg ctccatcagt agttactact ggagctggat ccggcagccc 120

ccagggaagg gactggagtg gattgggtat atctattata gtgggagcac ctactacaac 180

ccgtccctca agagtcgagt caccatgtca gtagacacgt ccaagaacca gttctccctg 240

aagctgagct ctgtgaccgc cgcagacacg gctgtgtatt actgtgcg 288

<210> 664

<211> 288

<212> DNA

<213> Homo sapi ens

<220>

<223> I GHV4- 59* 05

<400> 664

caggt gcagc t gcaggagt c gggcccagga ct ggt gaagc ct t cggagac cct gt ccct c 60

acct gcact g t ct ct ggt gg ct ccat cagt agt t act act ggagct ggat ccggcagccg 120

ccggggaagg gact ggagt g gat t gggcgt at ct at t at a gt gggagcac ct act acaac 180

ccgt ccct ca agagt cgagt caccat at cc gt agacacgt ccaagaacca gt t ct ccct g 240

aagct gagct ct gt gaccgc cgcagacacg gct gt gt at t act gt gcg 288

<210> 665

<211> 288

<212> DNA

<213> Homo sapi ens

<220>

<223> I GHV4- 59* 06

<400> 665

caggt gcagc t gcaggagt c gggcccagga ct ggt gaagc ct t cggagac cct gt ccct c 60

acct gcact g t cact ggt gg ct ccat cagt agt t act act ggagct ggat ccggcagccc 120

gct gggaagg gcct ggagt g gat t gggt ac at ct at t aca gt gggagcac ct act acaac 180

ccgt ccct ca agagt cgagt t accat at ca gt agacacgt ct aagaacca gt t ct ccct g 240

aagct gagct ct gt gact gc cgcggacacg gccgt gt at t act gt gcg 288

<210> 666

<211> 291

<212> DNA

<213> Homo sapi ens

<220>

<223> IGHV4-59*07

<400> 666

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggacac cctgtccctc 60

acctgcactg tctctggtgg ctccatcagt agttactact ggagctggat ccggcagccc 120

ccagggaagg gactggagtg gattgggtat atctattaca gtgggagcac caactacaac 180

ccctccctca agagtcgagt caccatatca gtagacacgt ccaagaacca gttctccctg 240

aagctgagct ctgtgaccgc tgcggacacg gccgtgtatt actgtgcgag a 291

<210> 667

<211> 237

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-59*08

<220>

<221> misc_feature

<222> 36, 214

<223> N = a or g or c or t

<400> 667

tccctcacct gcactgtctc tggtggctcc atcagnagtt actactggag ctggatccgg 60

cagcccccag ggaagggact ggagtggatt gggtatatct attacagtgg gagcaccaac 120

tacaacccct ccctcaagag tcgagtcacc atatcagtag acacgtccaa gaaccagttc 180

tccctgaagc tgagctctgt gaccgccgca gacncggccg tgtattactg tgcgaga 237

<210> 668

<211> 221

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-59*09

<220>

<221> misc_feature

<222> 54, 56-58

<223> N = a or g or c or t

<400> 668

tctggtggct ccatcagtag ttactactgg agctggatcc ggcagccccc aggnannnga 60

ctggagtgga ttgggtatat ctattacagt gggagcacca actacaaccc ctccctcaag 120

agtcgagtca ccatatcagt agacacgtcc aagaaccagt tctccctgaa gctgagctct 180

gtgaccgctg cggacacggc cgtgtattac tgtgcgagag g 221

<210> 669

<211> 293

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-59*10

<400> 669

caggtgcagc tacagcagtg gggcgcagga ctgttgaagc cttcggagac cctgtccctc 60

acctgcgctg tctatggtgg ctccatcagt agttactact ggagctggat ccggcagccc 120

gccgggaagg ggctggagtg gattgggcgt atctatacca gtgggagcac caactacaac 180

ccctccctca agagtcgagt caccatgtca gtagacacgt ccaagaacca gttctccctg 240

aagctgagct ctgtgaccgc cgcggacacg gccgtgtatt actgtgcgag ata 293

<210> 670

<211> 299

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-61*01

<400> 670

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60

acctgcactg tctctggtgg ctccgtcagc agtggtagtt actactggag ctggatccgg 120

cagccccag ggaagggact ggagtggatt gggtatatct attacagtgg gagcaccaac 180

tacaaccct ccctcaagag tcgagtcacc atatcagtag acacgtccaa gaaccagttc 240

tccctgaagc tgagctctgt gaccgctgcg gacacggccg tgtattactg tgcgagaga 299

<210> 671

<211> 299

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-61*02

<400> 671

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcacagac cctgtccctc 60

acctgcactg tctctggtgg ctccatcagc agtggtagtt actactggag ctggatccgg 120

cagcccgccg ggaagggact ggagtggatt gggcgtatct atatccagtg gagcaccaac 180

tacaaccct ccctcaagag tcgagtcacc atatcagtag acacgtccaa gaaccagttc 240

tccctgaagc tgagctctgt gaccgccgca gacacggccg tgtattactg tgcgagaga 299

<210> 672

<211> 299

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-61*03

<400> 672

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60
acctgcactg tctctggtgg ctccgtcagc agtggtagtt actactggag ctggatccgg 120
cagccccag ggaagggact ggagtggatt gggtatatct attacagtgg gagcaccaac 180
tacaaccct ccctcaagag tcgagtcacc atatcagtag acacgtccaa gaaccacttc 240
tccctgaagc tgagctctgt gaccgctgcg gacacggccg tgtattactg tgcgagaga 299

<210> 673
<211> 287
<212> DNA
<213> Homo sapiens

<220>
<223> IGHV4-61*04

<400> 673

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60
acctgcactg tctctggtgg ctccgtcagc agtggtagtt actactggag ctggatccgg 120
cagccccag ggaagggact ggagtggatt ggatatatct attacagtgg gagcaccaac 180
tacaaccct ccctcaagag tcgagtcacc atatcagtag acacgtccaa gaaccagttc 240
tccctgaagc tgagctctgt gaccgctgac acggccgtgt attactg 287

<210> 674
<211> 297
<212> DNA
<213> Homo sapiens

<220>
<223> IGHV4-61*05

<400> 674

cagctgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60
acctgcactg tctctggtgg ctccatcagc agtagtagtt actactgggg ctggatccgg 120
cagccccag ggaagggact ggagtggatt gggtatatct attacagtgg gagcaccaac 180

tacaacccct ccctcaagag tcgagtcacc atatcagtag acaagtccaa gaaccagttc 240
tccctgaagc tgagctctgt gaccgccgcg gacacggccg tgtattactg tgcgaga 297

<210> 675
<211> 227
<212> DNA
<213> Homo sapiens

<220>
<223> IGHV4-61*06

<400> 675
tctggtggct ccgtcagcag tggtagttac tactggagct ggatccggca gccccaggg 60
aagggactgg agtggattgg gtatatctat tacagtggga gcaccaacta caacccctcc 120
tcaagagtcg agtcaccat atcagtagac acgtccaaga accagttctc cctgaagctg 180
agctctgtga ccgccgcgga cacggccgtg tattactgtg ccagaga 227

<210> 676
<211> 227
<212> DNA
<213> Homo sapiens

<220>
<223> IGHV4-61*07

<400> 676
tctggtggct ccgtcagcag tggtagttac tactggagct ggatccggca gccccaggg 60
aagggactgg agtggattgg gtatatctat tacagtggga gcaccaacta caacccctcc 120
tcaagagtcg agtcaccat atcagtagac acgtccaaga accagttctc cctgaagctg 180
agctctgtga ccgctgcgga cacggccgtg tattactgtg cgagaca 227

<210> 677
<211> 299
<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-61*08

<400> 677

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60

acctgcactg tctctggtgg ctccgtcagc agtggtggtt actactggag ctggatccgg 120

cagccccag ggaagggact ggagtggatt gggtatatct attacagtgg gagcaccaac 180

tacaaccct ccctcaagag tcgagtcacc atatcagtag acacgtccaa gaaccagttc 240

tccctgaagc tgagctctgt gaccgctgcg gacacggccg tgtattactg tgcgagaga 299

<210> 678

<211> 294

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-b*01

<400> 678

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60

acctgcgctg tctctggtta ctccatcagc agtggttact actggggctg gatccggcag 120

cccccaggga aggggctgga gtggattggg agtatctatc atagtgggag cacctactac 180

aacccgtccc tcaagagtcg agtcaccata tcagtagaca cgtccaagaa ccagttctcc 240

ctgaagctga gctctgtgac cgccgcagac acggccgtgt attactgtgc gaga 294

<210> 679

<211> 294

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV4-b*02

<400> 679
caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60
acctgcactg tctctggtta ctccatcagc agtggttact actggggctg gatccggcag 120
cccccaggga aggggctgga gtggattggg agtatctatc atagtgggag cacctactac 180
aacccgtccc tcaagagtcg agtcaccata tcagtagaca cgtccaagaa ccagttctcc 240
ctgaagctga gctctgtgac cgccgcagac acggccgtgt attactgtgc gaga 294

<210> 680
<211> 296
<212> DNA
<213> Homo sapiens

<220>
<223> IGHV5-51*01

<400> 680
gaggtgcagc tggtgcagtc tggagcagag gtgaaaaagc ccggggagtc tctgaagatc 60
tcctgtaagg gttctggata cagctttacc agctactgga tcggctgggt gcgccagatg 120
cccgggaaag cctggagtgg gatggggatc atctatcctg gtgactctga taccagatac 180
agcccgtcct tccaaggcca ggtcaccatc tcagccgaca agtccatcag caccgcctac 240
ctgcagtgga gcagcctgaa ggcctcggac accgccatgt attactgtgc gagaca 296

<210> 681
<211> 296
<212> DNA
<213> Homo sapiens

<220>
<223> IGHV5-51*02

<400> 681
gaggtgcagc tggtgcagtc tggagcagag gtgaaaaagc ccggggagtc tctgaagatc 60
tcctgtaagg gttctggata cagctttacc agctactgga ccggctgggt gcgccagatg 120

cccgggaaag gcttggagtg gatggggatc atctatcctg gtgactctga taccagatac 180
agcccgtcct tccaaggcca ggtcaccatc tcagccgaca agtccatcag caccgcctac 240
ctgcagtgga gcagcctgaa ggcctcggac accgccatgt attactgtgc gagaca 296

<210> 682
<211> 294
<212> DNA
<213> Homo sapiens

<220>
<223> IGHV5-51*03

<400> 682
gaggtgcagc tggtgcagtc tggagcagag gtgaaaaagc cgggggagtc tctgaagatc 60
tcctgtaagg gttctggata cagctttacc agctactgga tcggctgggt gcgccagatg 120
cccgggaaag gcctggagtg gatggggatc atctatcctg gtgactctga taccagatac 180
agcccgtcct tccaaggcca ggtcaccatc tcagccgaca agtccatcag caccgcctac 240
ctgcagtgga gcagcctgaa ggcctcggac accgccatgt attactgtgc gaga 294

<210> 683
<211> 294
<212> DNA
<213> Homo sapiens

<220>
<223> IGHV5-51*04

<400> 683
gaggtgcagc tggtgcagtc tggagcagag gtgaaaaagc cgggggagtc tctgaagatc 60
tcctgtaagg gttctggata cagctttacc agctactgga tcggctgggt gcgccagatg 120
cccgggaaag gcctggagtg gatggggatc atctatcctg gtgactctga taccagatac 180
agcccgtcct tccaaggcca ggtcaccatc tcagccgaca agcccatcag caccgcctac 240
ctgcagtgga gcagcctgaa ggcctcggac accgccatgt attactgtgc gaga 294

<210> 684

<211> 245

<212> DNA

<213> Homo sapi ens

<220>

<223> I GHV5- 51* 05

<400> 684

aaaagcccgg ggagt ct ct g aagat ct cct gt aagggt t c t ggat acagc t t t accagct 60

act ggat cgg ct gggt gcgc cagat gccca ggaaaggcct ggagt ggat g gggat cat ct 120

at cct ggt ga ct ct gat acc agat acagcc cgt cct t cca aggccaggt c accat ct cag 180

ccgacaagt c cat cagcacc gcct acct gc agt ggagcag cct gaaggcc t cggacaccg 240

ccat g 245

<210> 685

<211> 294

<212> DNA

<213> Homo sapi ens

<220>

<223> I GHV5- a* 01

<400> 685

gaagt gcagc t ggt gcagt c t ggagcagag gt gaaaaagc ccggggagt c t ct gaggat c 60

t cct gt aagg gt t ct ggat a cagct t t acc agct act gga t cagct gggt gcgccagat g 120

cccgggaaag gcct ggagt g gat ggggagg at t gat cct a gt gact ct t a t accaact ac 180

agcccgt cct t ccaaggcca cgt caccat c t cagct gaca agt ccat cag cact gcct ac 240

ct gcagt gga gcagcct gaa ggcct cggac accgccat gt at t act gt gc gaga 294

<210> 686

<211> 294

<212> DNA

<213> Homo sapi ens

<220>

<223> IGHV5-a*03

<400> 686

gaagtgcagc tggtgcagtc cggagcagag gtgaaaaagc ccggggagtc tctgaggatc 60

tcctgtaagg gttctggata cagctttacc agctactgga tcagctgggt gcgccagatg 120

cccgggaaag gcctggagtg gatggggagg attgatccta gtgactctta taccaactac 180

agcccgtcct tccaaggcca cgtcaccatc tcagctgaca agtccatcag cactgcctac 240

ctgcagtgga gcagcctgaa ggcctcggac accgccatgt attactgtgc gaga 294

<210> 687

<211> 294

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV5-a*04

<400> 687

gaagtgcagc tggtgcagtc tggagcagag gtgaaaaagc ccggggagtc tctgaggatc 60

tcctgtaagg gttctggata cagctttacc agctactgga tcagctgggt gcgccagatg 120

cccgggaaag gcctggagtg gatggggagg attgatccta gtgactctta taccaactac 180

agcccgtcct tccaaggcca ggtcaccatc tcagctgaca agtccatcag cactgcctac 240

ctgcagtgga gcagcctgaa ggcctcggac accgccatgt attactgtgc gaga 294

<210> 688

<211> 305

<212> DNA

<213> Homo sapiens

<220>

<223> IGHV6-1*01

<400> 688

caggtacagc tgcagcagtc aggtccagga ctggtgaagc cctcgcagac cctctcactc 60
acctgtgcca tctccgggga cagtgtctct agcaacagtg gctggtggaa ctggatcagg 120
cagtccccat cgagaggcct tgagtggctg ggaaggacat actacaggtc caagtggtat 180
aatgattatg cagtatctgt gaaaagtcga ataaccatca acccagacac atccaagaac 240
cagttctccc tgcagctgaa ctctgtgact cccgaggaca cggctgtgta ttactgtgca 300
agaga 305

<210> 689
<211> 305
<212> DNA
<213> Homo sapiens

<220>
<223> IGHV6-1*02

<400> 689

caggtacagc tgcagcagtc aggtccggga ctggtgaagc cctcgcagac cctctcactc 60
acctgtgcca tctccgggga cagtgtctct agcaacagtg gctggtggaa ctggatcagg 120
cagtccccat cgagaggcct tgagtggctg ggaaggacat actacaggtc caagtggtat 180
aatgattatg cagtatctgt gaaaagtcga ataaccatca acccagacac atccaagaac 240
cagttctccc tgcagctgaa ctctgtgact cccgaggaca cggctgtgta ttactgtgca 300
agaga 305

<210> 690
<211> 31
<212> DNA
<213> Homo sapiens

<220>
<223> IGHD2-15*01

<400> 690

aggatattgt agtggtggta gctgctactc c 31

<210> 691

<211> 31

<212> DNA

<213> Homo sapiens

<220>

<223> IGHD2-2*01

<400> 691

aggatattgt agtagtacca gctgctatgc c 31

<210> 692

<211> 31

<212> DNA

<213> Homo sapiens

<220>

<223> IGHD2-2*02

<400> 692

aggatattgt agtagtacca gctgctatac c 31

<210> 693

<211> 31

<212> DNA

<213> Homo sapiens

<220>

<223> IGHD2-2*03

<400> 693

tggatattgt agtagtacca gctgctatgc c 31

<210> 694

<211> 28

<212> DNA

<213> Homo sapiens

<220>

<223> IGHD2-21*01

<400> 694

agcattgtggtggtgattgctattcc 28

<210> 695

<211> 28

<212> DNA

<213> Homo sapiens

<220>

<223> IGHD2-21*02

<400> 695

agcattgtggtggtgactgctattcc 28

<210> 696

<211> 31

<212> DNA

<213> Homo sapiens

<220>

<223> IGHD2-8*01

<400> 696

aggattgtactaatggtgtatgctatacc 31

<210> 697

<211> 31

<212> DNA

<213> Homo sapiens

<220>

<223> IGHD2-8*02

<400> 697

aggatattgt actggtggtg tatgctatac c 31

<210> 698

<211> 31

<212> DNA

<213> Homo sapiens

<220>

<223> IGHD3-10*01

<400> 698

gtattactat ggttcggggagttattataac 31

<210> 699

<211> 30

<212> DNA

<213> Homo sapiens

<220>

<223> IGHD3-10*02

<400> 699

gtattactat gttcggggagttattataac 30

<210> 700

<211> 37

<212> DNA

<213> Homo sapiens

<220>

<223> IGHD3-16*01

<400> 700

gtattatgat tacgtttggg ggagttatgc ttatacc 37

<210> 701

<211> 37

<212> DNA

<213> Homo sapiens

<220>

<223> IGHD3-16*02

<400> 701

gtattatgat tacgtttggg ggagttatcg ttatacc 37

<210> 702

<211> 31

<212> DNA

<213> Homo sapiens

<220>

<223> IGHD3-22*01

<400> 702

gtattactat gatagtagtg gttattacta c 31

<210> 703

<211> 31

<212> DNA

<213> Homo sapiens

<220>

<223> IGHD3-3*01

<400> 703

gtattacgat ttttggagtg gttattatac c 31

<210> 704

<211> 31

<212> DNA

<213> Homo sapiens

<220>

<223> IGHD3-3*02

<400> 704

gtattagcat ttttggagtg gttattatac c 31

<210> 705

<211> 31

<212> DNA

<213> Homo sapiens

<220>

<223> IGHD3-9*01

<400> 705

gtattacgat attttgactg gttattataa c 31

<210> 706

<211> 16

<212> DNA

<213> Homo sapiens

<220>

<223> IGHD4-11*01

<400> 706

tgactacagtaactac 16

<210> 707

<211> 16

<212> DNA

<213> Homo sapiens

<220>

<223> IGHD4-17*01

<400> 707

tgactacggtgactac 16

<210> 708

<211> 19

<212> DNA

<213> Homo sapiens

<220>

<223> IGHD4-23*01

<400> 708

tgactacggtggtaactcc 19

<210> 709

<211> 16

<212> DNA

<213> Homo sapiens

<220>

<223> IGHD4-4*01

<400> 709

tgactacagt aactac 16

<210> 710

<211> 23

<212> DNA

<213> Homo sapiens

<220>

<223> IGHD5-12*01

<400> 710

gtggatatag tggctacgat tac 23

<210> 711

<211> 20

<212> DNA

<213> Homo sapiens

<220>

<223> IGHD5-18*01

<400> 711

gtggatacag ctatggtt ac 20

<210> 712

<211> 20

<212> DNA

<213> Homo sapiens

<220>

<223> IGHD5-24*01

<400> 712

gtagagatggctacaattac 20

<210> 713

<211> 20

<212> DNA

<213> Homo sapiens

<220>

<223> IGHD5-5*01

<400> 713

gtggatacagctatggttac 20

<210> 714

<211> 21

<212> DNA

<213> Homo sapiens

<220>

<223> IGHD6-13*01

<400> 714

gggtatagcagcagctggtac 21

<210> 715

<211> 21

<212> DNA

<213> Homo sapiens

<220>

<223> IGHD6-19*01

<400> 715

gggtatagca gtggctggta c 21

<210> 716

<211> 18

<212> DNA

<213> Homo sapiens

<220>

<223> IGHD6-25*01

<400> 716

gggtatagca gcggctac 18

<210> 717

<211> 18

<212> DNA

<213> Homo sapiens

<220>

<223> IGHD6-6*01

<400> 717

gagtatagca gctcgtcc 18

<210> 718

<211> 11

<212> DNA

<213> Homo sapiens

<220>

<223> IGHD7-27*01

<400> 718

ctaactgggg a 11

<210> 719

<211> 52

<212> DNA

<213> Homo sapiens

<220>

<223> IGHJ1*01

<400> 719

gctgaatact tccagcactg gggccagggc accctggtca ccgtctcctc ag 52

<210> 720

<211> 53

<212> DNA

<213> Homo sapiens

<220>

<223> IGHJ2*01

<400> 720

ctactggtac ttcgatctct ggggccgtgg caccctggtc actgtctcct cag 53

<210> 721

<211> 50

<212> DNA

<213> Homo sapiens

<220>

<223> IGHJ3*01

<400> 721

tgatgctttt gatgtctggg gccaagggac aatggtcacc gtctcttcag 50

<210> 722
<211> 48
<212> DNA
<213> Homo sapiens

<220>
<223> IGHJ4*01

<400> 722
actactttga ctactggggc caaggaaccc tggtcaccgt ctcctcag 48

<210> 723
<211> 48
<212> DNA
<213> Homo sapiens

<220>
<223> IGHJ4*02

<400> 723
actactttga ctactggggc cagggaaccc tggtcaccgt ctcctcag 48

<210> 724
<211> 48
<212> DNA
<213> Homo sapiens

<220>
<223> IGHJ4*03

<400> 724
gctactttga ctactggggc caagggaccc tggtcaccgt ctcctcag 48

<210> 725

<211> 63

<212> DNA

<213> Homo sapiens

<220>

<223> IGHJ6*01

<400> 725

attactactactactacggtatggacgtctggggcaaggaccacggtcaccgtctcct 60

cag 63

<210> 726

<211> 62

<212> DNA

<213> Homo sapiens

<220>

<223> IGHJ6*02

<400> 726

attactactactactacggtatggacgtctggggccaaggaccacggtcaccgtctcct 60

ca 62

<210> 727

<211> 62

<212> DNA

<213> Homo sapiens

<220>

<223> IGHJ6*03

<400> 727

attactactactactactacatggacgtctggggcaaaggaccacggtcaccgtctcct 60
ca 62

<210> 728
<211> 63
<212> DNA
<213> Homo sapiens

<220>
<223> IGHJ6*04

<400> 728
attactactactactacggtatggacgtctggggcaaaggaccacggtcaccgtctcct 60
cag 63

<210> 729
<211> 287
<212> DNA
<213> Homo sapiens

<220>
<223> IGKV1-12*01

<400> 729
gacatccagatgacccagtctccatctccgtgtctgcatctgtaggagacagagtcacc 60
atcacttgtcgggcgagtcagggtattagcagctggttagcctggtatcagcagaaacca 120
gggaaagcccctaagctcctgatctatgctgcatccagttttgcaaagtgggtcccatca 180
aggttcagcggcagtggatctgggacagatttcactctcaccatcagcagcctgcagcct 240
gaagattttgcaacttactattgtcaacaggctaacagttttccctcc 287

<210> 730
<211> 287
<212> DNA
<213> Homo sapiens

<220>

<223> IGKV1-12*02

<400> 730

gacatccaga tgacccagtc tccatctcc gtgtctgcat ctgtaggaga cagagtcacc 60

atcacttgtc gggcgagtca gggtattagc agctggttag cctggtatca gcagaaacca 120

gggaaagccc ctaagcctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240

gaagattttg caacttactat tgtcaacag gctaacagtt tccctc 287

<210> 731

<211> 287

<212> DNA

<213> Homo sapiens

<220>

<223> IGKV1-13*02

<400> 731

gccatccagt tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcaagtca gggcattagc agtgcttttag cctggtatca gcagaaacca 120

gggaaagctc ctaagcctcct gatctatgat gcctccagtt tggaaagtgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240

gaagattttg caacttattatta ctgtcaacag tttaatagtt accctca 287

<210> 732

<211> 287

<212> DNA

<213> Homo sapiens

<220>

<223> IGKV1-16*01

<400> 732

gacatccaga tgacccagtc tccatcctca ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgtc gggcgagtca gggcattagc aattatttag cctggttcca gcagaaacca 120

gggaaagccc ctaagtccct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240

gaagattttg caacttatta ctgccaacag tataatagtt acccctcc 287

<210> 733

<211> 287

<212> DNA

<213> Homo sapiens

<220>

<223> IGKV1-17*01

<400> 733

gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcaagtca gggcattaga aatgatttag gctggtatca gcagaaacca 120

gggaaagccc ctaagcgcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240

gaagattttg caacttatta ctgtctacag catagtaatt acccctcc 287

<210> 734

<211> 287

<212> DNA

<213> Homo sapiens

<220>

<223> IGKV1-17*02

<400> 734

gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcaagtca gggcattaga aatgatttag gctggtatca gcagaaacca 120

gggaaagccc ctaagcgcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcaa cctgcagcct 240
gaagatttg caacttattac tgtctacag cataatagtt accctcc 287

<210> 735
<211> 287
<212> DNA
<213> Homo sapiens

<220>
<223> IGKV1-27*01

<400> 735
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcgagtca gggcattagc aattattttag cctggtatca gcagaaacca 120
gggaaagttc ctaagctcct gatctatgct gcatccactt tgcaatcagg ggtcccatct 180
cggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
gaagatgttg caacttattac tgtcaaaag tataacagtg cccctcc 287

<210> 736
<211> 287
<212> DNA
<213> Homo sapiens

<220>
<223> IGKV1-33*01

<400> 736
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc aggcgagtca ggacattagc aactatttaa attggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctacgat gcatccaatt tggaaacagg ggtcccatca 180
aggttcagtg gaagtggatc tgggacagat tttactttca ccatcagcag cctgcagcct 240
gaagatattg caacattacta tgtcaacag tatgatgata atctccctcc 287

<210> 737

<211> 287

<212> DNA

<213> Homo sapiens

<220>

<223> IGKV1-37*01

<400> 737

gacatccagt tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggtgagtca gggcattagc agttatttaa attggtatcg gcagaaacca 120

gggaaagttc ctaagcctcc tgatctatagt gcatccaatt tgcaatctgg agtcccatct 180

cggttcagtg gcagtggatc tgggacagat ttcactctca ctatcagcag cctgcagcct 240

gaagatgttg caacttatta cggtcaacgg actttacaat gccctcc 287

<210> 738

<211> 287

<212> DNA

<213> Homo sapiens

<220>

<223> IGKV1-39*01

<400> 738

gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcaagtca gagcattagc agctatttaa attggtatca gcagaaacca 120

gggaaagccc ctaagcctcc tgatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180

aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240

gaagattttg caacttacta ctgtcaacag agttacagta cccctcc 287

<210> 739

<211> 287

<212> DNA

<213> Homo sapiens

<220>

<223> IGKV1-39*02

<400> 739

gacatccaga tgacccagtc tccatcctc tctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcaagtca gagcattagc agctatttaa attggtatca gcagaaacca 120

gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180

aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240

gaagattttg caacttattac tgtcagtgt ggttacagta cacctcc 287

<210> 740

<211> 287

<212> DNA

<213> Homo sapiens

<220>

<223> IGKV1-5*01

<400> 740

gacatccaga tgacccagtc tcctccacc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggccagtca gagttattagt agctggttgg cctggtatca gcagaaacca 120

gggaaagccc ctaagctcct gatctatgat gcctccagtt tggaaagtgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagaa ttcactctca ccatcagcag cctgcagcct 240

gatgattttg caacttattac tgccaacag tatagttagt tattctcc 287

<210> 741

<211> 287

<212> DNA

<213> Homo sapiens

<220>

<223> IGKV1-5*02

<400> 741

gacatccaga tgacccagtc tcctgccacc ctgtctgcat ctgtaggaga cagagtcacc 60

atcatttgcc gggccagtca gagtattagt agctggttgg cctggtatca gcagaaacca 120

gggaaagccc ctaagcttct gatctatgat gcctccagtt tggaaagtgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagaa ttcactctca ccatcagcag cctgcagcct 240

gatgattttg caacttatta ctgccaacag tataatagtt attctcc 287

<210> 742

<211> 287

<212> DNA

<213> Homo sapiens

<220>

<223> IGKV1-5*03

<400> 742

gacatccaga tgacccagtc tcctgccacc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggccagtca gagtattagt agctggttgg cctggtatca gcagaaacca 120

gggaaagccc ctaagcttct gatctataag gcgtctagtt tagaaagtgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagaa ttcactctca ccatcagcag cctgcagcct 240

gatgattttg caacttatta ctgccaacag tataatagtt attctcc 287

<210> 743

<211> 287

<212> DNA

<213> Homo sapiens

<220>

<223> IGKV1-6*01

<400> 743

gccatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcaagtca gggcattaga aatgatttag gctggtatca gcagaaacca 120

gggaaagccc ctaagcttct gatctatgct gcatccagtt tacaaagtgg ggtcccatca 180

aggttcagcg gcagtggatc tggcacagat ttcactctca ccatcagcag cctgcagcct 240

gaagatttg caacttattа ctgtctacaa gattacaatt accctcc 287

<210> 744
<211> 287
<212> DNA
<213> Homo sapiens

<220>
<223> IGKV1-8*01

<400> 744
gccatccgga tgacccagtc tccatcctca ttctctgcat ctacaggaga cagagtcacc 60
atcacttgtc gggcgagtca gggtattagc agttatttag cctggtatca gcaaaaacca 120
gggaaagccc ctaagctcct gatctatgct gcatccactt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagctg cctgcagtct 240
gaagatttg caacttattа ctgtcaacag tattatagtt accctcc 287

<210> 745
<211> 287
<212> DNA
<213> Homo sapiens

<220>
<223> IGKV1-9*01

<400> 745
gacatccagt tgacccagtc tccatcctтc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggccagtca gggcattagc agttatttag cctggtatca gcaaaaacca 120
gggaaagccc ctaagctcct gatctatgct gcatccactt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240
gaagatttg caacttattа ctgtcaacag cttaatagtt accctcc 287

<210> 746
<211> 287

<212> DNA

<213> Homo sapiens

<220>

<223> IGKV1-NL1*01

<400> 746

gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcgagtca gggcattagc aattctttag cctggtatca gcagaaacca 120

gggaaagccc ctaagctcct gctctatgct gcatccagat tggaaagtgg ggtcccatcc 180

aggttcagtg gcagtggatc tgggacggat tcactctca ccatcagcag cctgcagcct 240

gaagattttg caacttatta ctgtcaacag tattatagt a ccccctcc 287

<210> 747

<211> 287

<212> DNA

<213> Homo sapiens

<220>

<223> IGKV1/OR2-0*01

<400> 747

gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcgagtca gggcattagc aataattttaa attggtatca gcagaaacca 120

gggaaaactc ctaagctcct gatctatgct gcacccagtc tgcaaagtgg gattcccct 180

cggttcagtg acagtggatc tggggcagat tcactctca ccatccgcag cctgcagcct 240

gaagattttg caacttatta ctgtcaacag agtgacagt a ccccctcc 287

<210> 748

<211> 287

<212> DNA

<213> Homo sapiens

<220>

<223> IGKV1/OR2-108*01

<400> 748

gacatccagg tgacccagtc tccatcttcc ctgtctgcgt ctgtaggaga cagagtcacc 60

atcacctgcc gggcaagtca gggcattagc aatgggttat cctggtatca gcagaaacca 120

gggcaagccc ctacgcttcct gatctatgct gcatccagtt tgcagtcggg ggtcccatct 180

cggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240

gaagatgttg caacttatta ctgtctacag gattatactt ccccatt 287

<210> 749

<211> 287

<212> DNA

<213> Homo sapiens

<220>

<223> IGKV1D-12*01

<400> 749

gacatccaga tgacccagtc tccatctttct gtgtctgcat ctgtaggaga cagagtcacc 60

atcacttgtc gggcgagtca gggtattagc agctggttag cctggtatca gcagaaacca 120

gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagat ttcactctca ctatcagcag cctgcagcct 240

gaagatttttg caacttactta ttgtcaacag gctaacagtt tccctcc 287

<210> 750

<211> 287

<212> DNA

<213> Homo sapiens

<220>

<223> IGKV1D-12*02

<400> 750

gacatccaga tgacccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc 60

atcacttgtc gggcgagtca gggtattagc agctggttag cctggtatca gcagaaacca 120
gggaaagccc ctaagcttcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
gaagattttg caacttacta ttgtcaacag gctaacagtt tccctttc 287

<210> 751
<211> 287
<212> DNA
<213> Homo sapiens

<220>
<223> IGKV1D-13*01

<400> 751
gccatccagt tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca gggcattagc agtgcttlag cctggtatca gcagaaacca 120
gggaaagctc ctaagcttcct gatctatgat gcctccagtt tggaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
gaagattttg caacttattac tgtcaacag tttaataatt accctca 287

<210> 752
<211> 287
<212> DNA
<213> Homo sapiens

<220>
<223> IGKV1D-16*01

<400> 752
gacatccaga tgacccagtc tccatcctca ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgtc gggcgagtca gggtattagc agctggttag cctggtatca gcagaaacca 120
gagaaagccc ctaagtccct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
gaagattttg caacttattac tgccaacag tatagtagtt accctcc 287

<210> 753

<211> 287

<212> DNA

<213> Homo sapiens

<220>

<223> IGKV1D-16*02

<400> 753

gacatccaga tgacccagtc tccatcctca ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgtc gggcgaggca gggtattagc agctggttag cctggtatca gcagaaacca 120

gagaaagccc ctaagtccct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240

gaagattttg caacttatta ctgccaacag tataatagtt accctcc 287

<210> 754

<211> 287

<212> DNA

<213> Homo sapiens

<220>

<223> IGKV1D-17*01

<400> 754

aacatccaga tgacccagtc tccatctgcc atgtctgcat ctgtaggaga cagagtcacc 60

atcacttgtc gggcgaggca gggcattagc aattattttag cctggtttca gcagaaacca 120

gggaaagtcc ctaagcacct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagaa tttcactctca caatcagcag cctgcagcct 240

gaagattttg caacttatta ctgtctacag catagtaatt accctcc 287

<210> 755

<211> 287

<212> DNA

<213> Homo sapiens

<220>

<223> IGKV1D-33*01

<400> 755

gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc aggcgagtca ggacattagc aactatttaa attggtatca gcagaaacca 120

gggaaagccc ctaagcctcc tgatctacga tgcatccaat ttggaaacagg ggtcccatca 180

aggttcagtg gaagtggatc tgggacagat tttactttca ccatcagcag cctgcagcct 240

gaagatattg caacattact gtcaacagtatgatgatctc tccctcc 287

<210> 756

<211> 287

<212> DNA

<213> Homo sapiens

<220>

<223> IGKV1D-37*01

<400> 756

gacatccagt tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggtgagtca gggcattagc agttattttaa attggtatcg gcagaaacca 120

gggaaagttc ctaagctcct gatctatagt gcatccaatt tgcaatctgg agtcccatct 180

cggttcagtg gcagtggatc tgggacagat ttcactctca ctatcagcag cctgcagcct 240

gaagatgttg caacttatta tcggcaacgg acttacaatg ccccctcc 287

<210> 757

<211> 287

<212> DNA

<213> Homo sapiens

<220>

<223> IGKV1D-39*01

<400> 757
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca gagcattagc agctatttaa attggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240
gaagattttg caacttactg tcaacagagt tacagtaccc cctcc 287

<210> 758
<211> 287
<212> DNA
<213> Homo sapiens

<220>
<223> IGKV1D-42*01

<400> 758
gacatccaga tgatccagtc tccatctttc ctgtctgcat ctgtaggaga cagagtcagt 60
atcatttgct gggcaagtga gggcattagc agtaatttag cctggtatct gcagaaacca 120
gggaaatccc ctaagcctct cctctatgat gcaaaagatt tgcaccctgg ggtctcatcg 180
aggttcagtg gcaggggatc tgggacggat ttcactctca ccatcatcag cctgaagcct 240
gaagatttcg cagcttatta ctgtaaacag gacttcagtt accctcc 287

<210> 759
<211> 287
<212> DNA
<213> Homo sapiens

<220>
<223> IGKV1D-43*01

<400> 759
gccatccgga tgacccagtc tccattctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgct gggccagtca gggcattagc agttatttag cctggtatca gcaaaaacca 120

gcaaaagccc ctaagctctt catctattat gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacggat tacactctca ccatcagcag cctgcagcct 240
gaagatttg caacttattac tgtcaacag tattatagta cccctcc 287

<210> 760
<211> 287
<212> DNA
<213> Homo sapiens

<220>
<223> IGKV1D-8*01

<400> 760
gtcatctgga tgacccagtc tccatcctta ctctctgcat ctacaggaga cagagtcacc 60
atcagttgtc ggatgagtca gggcattagc agttatttag cctggtatca gcaaaaacca 120
gggaaagccc ctgagctcct gatctatgct gcatccactt tgcaaagtgg ggtcccatca 180
aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagttg cctgcagtct 240
gaagatttg caacttattac tgtcaacag tattatagtt tccctcc 287

<210> 761
<211> 302
<212> DNA
<213> Homo sapiens

<220>
<223> IGKV2-24*01

<400> 761
gatattgtga tgacccagac tccactctcc tcacctgtca ccctggaca gccggcctcc 60
atctcctgca ggtctagtca aagcctcgta cacagtgatg gaaacacctac ttgagttgg 120
cttcagcaga ggccaggcca gcctccaaga ctcctaattt ataagatttc taaccggttc 180
tctggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgaaaatc 240
agcagggtgg aagctgagga tgtcggggtt tattactgca tgcaagctac acaatttcct 300
ca 302

<210> 762

<211> 302

<212> DNA

<213> Homo sapiens

<220>

<223> IGKV2-28*01

<400> 762

gatattgtgatgactcagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc 60

atctcctgca ggtctagtca gagcctcctg catagtaatg gatacaactatttggattgg 120

tacctgcaga agccagggca gtctccacag ctcctgatct attttgggtt tctaatcggg 180

tccggggtcc ctgacaggtt cagtggcagt ggatcaggca cagattttac actgaaaatc 240

agcagagtgg aggctgagga tgttggggtt tattactgca tgcaagctct acaaactcct 300

cc 302

<210> 763

<211> 302

<212> DNA

<213> Homo sapiens

<220>

<223> IGKV2-29*02

<400> 763

gatattgtgatgacccagac tccactctct ctgtccgtca cccctggaca gccggcctcc 60

atctcctgca agtctagtca gagcctcctg catagtgatg gaaagacctatttgtattgg 120

tacctgcaga agccaggcca gtctccacag ctcctaatct atgaagtttc cagccggttc 180

tctggagtgc cagataggtt cagtggcagc gggtcaggga cagattttcac actgaaaatc 240

agccgggtgg aggctgagga tgttggggtt tattactgca tgcaaggtat acacctttcct 300

cc 302

<210> 764

<211> 302

<212> DNA

<213> Homo sapiens

<220>

<223> IGKV2-29*03

<400> 764

gatattgtgatgacccagactccactctct ctgtccgtca cccctggaca gccggcctcc 60

atctcctgca agtctagtca gagcctcctg catagtgatg gaaagacctat ttgtattgg 120

tacctgcaga agccaggcca gtctccacag ctcctgatct atgaagtttc cagccggttc 180

tctggagtgc cagataggtt cagtggcagc gggtcaggga cagatttcac actgaaaatc 240

agccgggtgg aggctgagga tgttggggtt tattactgca tgcaaggtat acacctttcc 300

cc 302

<210> 765

<211> 302

<212> DNA

<213> Homo sapiens

<220>

<223> IGKV2-30*01

<400> 765

gatgttgtga tgactcagtc tccactctcc ctgcccgtca ccctt ggaca gccggcctcc 60

atctcctgca ggtctagtca aagcctcgta tacagtgatg gaaacacctat cttgaattgg 120

ttt tcagcaga ggccaggcca atctccaagg cgcctaattt ataaggtttc taaccgggac 180

tctggggtcc cagacagatt cagcggcagt gggtcaggca ctgatttcac actgaaaatc 240

agcagggtgg aggctgagga tgttggggtt tattactgca tgcaaggtac acactggcct 300

cc 302

<210> 766

<211> 305

<212> DNA

<213> Homo sapiens

<220>

<223> IGKV2-40*01

<400> 766

gatattgtgatgacccagactccactctccctgcccgtcacccctggagagccggcctcc 60

atctcctgcaggtctagtcagagcctcttgagtagtgatgatggaaacacctatttggac 120

tggtacctgcagaagccagggcagtctccacagctcctgatctatacgctttcctatcgg 180

gcctctggagtcccagacaggttcagtggcagtgggtcaggcactgatttcacactgaaa 240

atcagcagggtggaggctgaggatgttggagttattactgcatgcaacgtatagagttt 300

cctc 305

<210> 767

<211> 251

<212> DNA

<213> Homo sapiens

<220>

<223> IGKV2-40*02

<400> 767

gcctccatcttcctgcaggtctagtcagagcctcttggatagtgatgatggaaacacctat 60

ttggatttgtttacctgcagaagccagggcagtctccacagctcctgatctatacgctttcc 120

tatcgggcctctggagtcccagacaggttcagtgacagtggtcaggcactgatttcaca 180

ctgaaaatcagcagggtggaggctgaggatgttggagtttattactgcatgcaacgtata 240

gagtttcctc 251

<210> 768

<211> 302

<212> DNA

<213> Homo sapiens

<220>

<223> IGKV2D-24*01

<400> 768

gatattgtga tgacccagac tccactctcc tcgcctgtca ccctt ggaca gccggcctcc 60

atctcctt ca ggtctagtca aagcctcgta cacagtgatg gaaacacctt ctt gagttgg 120

ctt cagcaga ggccaggcca gcctccaaga ctcctaattt ataaggttt c taaccggttc 180

tctggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgaaaatc 240

agcagggtgg aagctgagga tgtcggggtt tattactgca cgcaagctac acaatttcct 300

ca 302

<210> 769

<211> 302

<212> DNA

<213> Homo sapiens

<220>

<223> IGKV2D-26*01

<400> 769

gagattgtga tgacccagac tccactctcc ttgtctatca cccctggaga gcaggcctcc 60

atctcctgca ggtctagtca gagcctcctg catagtgatg gatacacctt tttgtattgg 120

ttt ctgcaga aagccaggcc agtctccaca ctcctgatct atgaagttt c caaccggttc 180

tctggagtgc cagataggtt cagtggcagc gggtcaggga cagatttcac actgaaaatc 240

agccgggtgg aggctgagga ttttggagtt tattactgca tgcaagatgc acaagatcct 300

cc 302

<210> 770

<211> 300

<212> DNA

<213> Homo sapiens

<220>

<223> IGKV2D-26*02

<400> 770

gagattgtga tgacccagac tccactctcc ttgtctatca ccccctggaga gcaggcctcc 60
atgtcctgca ggtctagtca gagcctcctg catagtgatg gatacacctat ttgtattgg 120
ttttctgcaga aagccaggcc agtctccacg ctcctgatct gtgaagtttc caaccggttc 180
tctggagtgc cagataggtt cagtggcagc gggtcaggga cagatttcac actgaaaatc 240
agccgggtgg aggctgagga ttttggagtt tatttactgca tgcaagatgc acaagatcct 300

<210> 771
<211> 302
<212> DNA
<213> Homo sapiens

<220>
<223> IGKV2D-28*01

<400> 771

gatattgtga tgactcagtc tccactctcc ctgcccgtca ccccctggaga gccggcctcc 60
atctcctgca ggtctagtca gagcctcctg catagtaatg gatacaacta tttggattgg 120
tacctgcaga agccagggca gtctccacag ctcctgatct attttgggtt tctaatcggg cc 180
tccggggtcc ctgacaggtt cagtggcagt ggatcaggca cagattttac actgaaaatc 240
agcagagtgg aggctgagga tgttggggtt tattactgca tgcaagctct acaaactcct 300
cc 302

<210> 772
<211> 302
<212> DNA
<213> Homo sapiens

<220>
<223> IGKV2D-29*01

<400> 772

gatattgtga tgacccagac tccactctct ctgtccgtca ccccctggaca gccggcctcc 60

atctcctgca agtctagtca gagcctcctg catagtgatg gaaagacctat ttgtattgg 120
tacctgcaga agccaggcca gcctccacag ctcctgatct atgaagtttc caaccggttc 180
tctggagtgc cagataggtt cagtggcagc gggtcaggga cagatttcac actgaaaatc 240
agccgggtgg aggctgagga tgttggggtt tatttactgca tgcaaagtat acagcttcct 300
cc 302

<210> 773
<211> 302
<212> DNA
<213> Homo sapiens

<220>
<223> IGKV2D-29*02

<400> 773
gatattgtga tgacccagac tccactctct ctgtccgtca cccctggaca gccggcctcc 60
atctcctgca agtctagtca gagcctcctg catagtgatg gaaagacctat ttgtattgg 120
tacctgcaga agccaggcca gtctccacag ctcctgatct atgaagtttc caaccggttc 180
tctggagtgc cagataggtt cagtggcagc gggtcaggga cagatttcac actgaaaatc 240
agccgggtgg aggctgagga tgttggggtt tatttactgca tgcaaagtat acagcttcct 300
cc 302

<210> 774
<211> 302
<212> DNA
<213> Homo sapiens

<220>
<223> IGKV2D-30*01

<400> 774
gatgttgtga tgactcagtc tccactctcc ctgcccgtca ccctiggaca gccggcctcc 60
atctcctgca ggtctagtca agcctcgtta tacagtgatg gaaacacctat cttgaattgg 120
ttttcagcaga ggccaggcca atctccaagg cgcctaatttt ataaggtttc taactgggac 180

tctggggtcc cagacagatt cagcggcagt gggtcaggca ctgatttcac actgaaaatc 240

agcagggtgg aggctgagga tgttggggtt tattactgca tgcaaggtac acactggcct 300

cc 302

<210> 775

<211> 305

<212> DNA

<213> Homo sapiens

<220>

<223> IGKV2D-40*01

<400> 775

gatattgtga tgacccagac tccactctcc ctgcccgtca ccccttggaga gccggcctcc 60

atctcctgca ggtctagtca gagcctcttg gatagtgatg atggaaacac ctatttggac 120

tggtacctgc agaagccagg gcagtctcca cagctcctga tctatacgct ttcctatcgg 180

gcctctggag tcccagacag gttcagtggc agtgggtcag gcactgattt cacactgaaa 240

atcagcaggg tggaggctga ggatgttgga gtttattact gcatgcaacg tatagagttt 300

cctttc 305

<210> 776

<211> 287

<212> DNA

<213> Homo sapiens

<220>

<223> IGKV3-11*01

<400> 776

gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccagggga aagagccacc 60

ctctcctgca gggccagtca gagtgttagc agcttactag cctggtacca acagaaacct 120

ggccaggctc ccaggctcct catctatgat gcatccaaca gggccactgg catcccagcc 180

aggttcagtg gcagtgggtc tgggacagac ttcactctca ccatcagcag cctagagcct 240

gaagattttg cagtttatta ctgtcagcag cgtagcaact ggcctcc 287

<210> 777

<211> 287

<212> DNA

<213> Homo sapiens

<220>

<223> IGKV3-11*02

<400> 777

gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccagggga aagagccacc 60

ctctcctgca gggccagtca gagtgttagc agcttagcct ggtaccaaca gaaacctggc 120

caggctccag gctcctcatc tatgatgcat ccaacagggc cactggcatc ccagccaggt 180

tcagtggcag tgggtctggg agacacttca ctctcaccat cagcagcctg gagcctgaag 240

attttgcagt ttattactgt cagcagcgta gcaactggcc tcc 287

<210> 778

<211> 287

<212> DNA

<213> Homo sapiens

<220>

<223> IGKV3-15*01

<400> 778

gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc 60

ctctcctgca gggccagtca gagttttagc agcaacttag cctggtacca gcagaaacct 120

ggccaggctc caggctccat catctatggt gcatccacca gggccactgg tatcccagcc 180

aggttcagtg gcagtgggtc tgggacagag ttcactctca ccatcagcag cctgcagtct 240

gaagattttg cagtttatta ctgtcagcag tataataact ggcctcc 287

<210> 779

<211> 290

<212> DNA

<213> Homo sapiens

<220>

<223> IGKV3-20*01

<400> 779

gaaattgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc 60

ctctcctgca gggccagtca gagtgttagc agcagcttac tagcctggta ccagcagaaa 120

cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca 180

gacaggttca gtggcagtgg gtctgggaca gacttcactc tcaccatcag cagactggag 240

cctgaagatt ttgcagtgta ttactgtcag cagtatggta gctcacctcc 290

<210> 780

<211> 271

<212> DNA

<213> Homo sapiens

<220>

<223> IGKV3-20*02

<400> 780

gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccagggga aagagccacc 60

ctctcctgca gggccagtca gagtgttagc agcagcttac tagcctggta ccagcagaaa 120

cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca 180

gcaaggttca gtggcagtgg gtctgggaca gacttcactc tcaccatcag cagactggag 240

cctgaagatt ttgcagttta ttactgtcag c 271

<210> 781

<211> 290

<212> DNA

<213> Homo sapiens

<220>

<223> IGKV3-7*01

<400> 781
gaaattgtaa tgacacagtc tccacccacc ctgtctttgt ctccagggga aagagtcacc 60
ctctcctgca gggccagtca gagtgttagc agcagctact taacctggta tcagcagaaa 120
cctggccagg cgcccaggct cctcatctat ggtgcatcca ccagggccac tagcatccca 180
gccaggttca gtggcagtgg gtctgggaca gacttcactc tcaccatcag cagcctgcag 240
cctgaagatt ttgcagttta ttactgtcag caggatcata acttacctcc 290

<210> 782
<211> 290
<212> DNA
<213> Homo sapiens

<220>
<223> IGKV3-7*02

<400> 782
gaaattgtaa tgacacagtc tccacccacc ctgtctttgt ctccagggga aagagtcacc 60
ctctcctgca gggccagtca gagtgttagc agcagctact tatcctggta ccagcagaaa 120
cctgggcagg ctcccaggct cctcatctat ggtgcatcca ccagggccac tggcatccca 180
gccaggttca gtggcagtgg gtctgggaca gacttcactc tcaccatcag cagcctgcag 240
cctgaagatt ttgcagttta ttactgtcag caggattata acttacctcc 290

<210> 783
<211> 290
<212> DNA
<213> Homo sapiens

<220>
<223> IGKV3-7*03

<400> 783
gaaattgtaa tgacacagtc tccacccacc ctgtctttgt ctccagggga aagagtcacc 60
ctctcctgca gggccagtca gagtgttagc agcagctact taacctggta tcagcagaaa 120

cctggccagg cgcccaggct cctcatctat ggtgcatcca ccagggccac tagcatccca 180
gccaggttca gtggcagtgg gtctgggaga gacttcactc tcaccatcag cagcctgcag 240
cctgaagatt ttgcagttta ttactgtcag caggatcata acttacctcc 290

<210> 784
<211> 268
<212> DNA
<213> Homo sapiens

<220>
<223> IGKV3-NL1*01

<400> 784
gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccagggga aagagccacc 60
ctctcctgca gggccagtca gagtgttagc agcttacttag cctggtacca acagaaacct 120
ggccaggctc ccaggctcct catctatggt gcatccacca gggccactgg catcccagcc 180
aggttcagtg gcagtgggtc tgggacagag ttcactctca ccatcagcag cctgcagtct 240
gaagattttg cagtttatta ctgtcagc 268

<210> 785
<211> 268
<212> DNA
<213> Homo sapiens

<220>
<223> IGKV3-NL2*01

<400> 785
gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccagggga aagagccacc 60
ctctcctgca gggccagtca gggtgttagc agcttacttag cctggtacca gcagaaacct 120
ggccaggctc ccaggctcct catctatgat gcatccagca gggccactgg catcccagcc 180
aggttcagtg gcagtgggcc tgggacagac ttcactctca ccatcagcag cctagagcct 240
gaagattttg cagtttatta ctgtcagc 268

<210> 786

<211> 271

<212> DNA

<213> Homo sapiens

<220>

<223> IGKV3-NL3*01

<400> 786

gaaattgtgt tgacacagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc 60

ctctcctgca gggccagtca gagtgttagc agcagctact tagcctggta ccagcagaaa 120

cctggcctgg cgcccaggct cctcatctat ggtgcatcca ccagggccac tggtatccca 180

gccaggttca gtggcagtgg gtctgggaca gagttcactc tcaccatcag cagactgcag 240

tctgaagatt ttgcagttta ttactgtcag c 271

<210> 787

<211> 285

<212> DNA

<213> Homo sapiens

<220>

<223> IGKV3-NL4*01

<400> 787

gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccagggga aagagccacc 60

ctctcctgca gggccagtca gggtgttagc agcaacttag cctggtacca gcagaaacct 120

ggccaggctc ccaggctcct catctatgat gcatccaaca gggccactgg catcccagcc 180

aggttcagtg gcagtgggcc tgggacagac ttcactctca ccatcagcag cctagagcct 240

gaagattttg cagtgtatta ctgtcagcag cgtagcaact ggcat 285

<210> 788

<211> 288

<212> DNA

<213> Homo sapiens

<220>

<223> IGKV3-NL5*01

<400> 788

gaaattgtgt tgacgcagtc tccagccacc ctgtctttgt ctccagggga aagagccacc 60

ctctcctgca gggccagtca gagtgttagc agcagcttac tagcctggta ccagcagaaa 120

cctggccagg ctcccaggct cctcatctat gatgcatcca gcagggccac tggcatccca 180

gacaggttca gtggcagtgg gtctgggaca gacttcactc tcaccatcag cagactggag 240

cctgaagatt ttgcagttta ttactgtcag cagcgtagca actggcat 288

<210> 789

<211> 290

<212> DNA

<213> Homo sapiens

<220>

<223> IGKV3/OR2-268*01

<400> 789

gaaattgtaa tgacacagtc tccagccacc ctgtctttgt ctccagggga aagagccacc 60

ctctcctgca gggccagtca gagtgttagc agcagcttac tatcctggta ccagcagaaa 120

cctgggcagg ctcccaggct cctcatctat ggtgcatcca ccagggccac tggcatccca 180

gccaggttca gtggtagtgg gtctgggaca gacttcactc tcaccatcag cagcctgcag 240

cctgaagatt ttgcagttta ttactgtcag caggatatta acttacctcc 290

<210> 790

<211> 290

<212> DNA

<213> Homo sapiens

<220>

<223> IGKV3/OR2-268*02

<400> 790

gaaattgtaa tgacacagtc tccagccacc ctgtctttgt ctccagggga aagagccacc 60

ctctcctgca gggccagtca gagtgttagc agcagcttact tatcctggta ccagcagaaa 120

cctgggcagg ctcccaggct cctcatctat ggtgcatcca ccagggccac tggcatccca 180

gccaggttca gtggcagtgg gtctgggaca gacttcactc tcaccatcag cagcctgcag 240

cctgaagatt ttgcagttta ttactgtcag caggatatta acttacctcc 290

<210> 791

<211> 287

<212> DNA

<213> Homo sapiens

<220>

<223> IGKV3D-11*01

<400> 791

gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccagggga aagagccacc 60

ctctcctgca gggccagtca gggtgttagc agctacttag cctggtacca gcagaaacct 120

ggccaggctc ccaggctcct catctatgat gcatccaaca gggccactgg catcccagcc 180

aggttcagtg gcagtgggcc tgggacagac ttcactctca ccatcagcag cctagagcct 240

gaagattttg cagtttatta ctgtcagcag cgtagcaact ggcatcc 287

<210> 792

<211> 287

<212> DNA

<213> Homo sapiens

<220>

<223> IGKV3D-15*01

<400> 792

gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc 60

ctctcctgca gggccagtca gagtgttagc agcaacttag cctggtacca gcagaaacct 120

ggccaggctc ccaggctcct catctatggt gcatccacca gggccactgg catcccagcc 180

aggttcagtg gcagtgggtc tgggacagag ttcactctca ccatcagcag cctgcagtct 240
gaagatttg cagttattac tgtcagcag tataataact ggcctcc 287

<210> 793
<211> 290
<212> DNA
<213> Homo sapiens

<220>
<223> IGKV3D-20*01

<400> 793
gaaattgtgt tgacgcagtc tccagccacc ctgtctttgt ctccagggga aagagccacc 60
ctctcctgcg gggccagtca gagtgttagc agcagctact tagcctggta ccagcagaaa 120
cctggcctgg cgcccaggct cctcatctat gatgcatcca gcagggccac tggcatccca 180
gacaggttca gtggcagtgg gtctgggaca gacttcactc tcaccatcag cagactggag 240
cctgaagatt ttgcagtgta ttactgtcag cagtatggta gctcacctcc 290

<210> 794
<211> 290
<212> DNA
<213> Homo sapiens

<220>
<223> IGKV3D-7*01

<400> 794
gaaattgtaa tgacacagtc tccagccacc ctgtctttgt ctccagggga aagagccacc 60
ctctcctgca gggccagtca gagtgttagc agcagctact tatcctggta ccagcagaaa 120
cctgggcagg ctcccaggct cctcatctat ggtgcatcca ccagggccac tggcatccca 180
gccaggttca gtggcagtgg gtctgggaca gacttcactc tcaccatcag cagcctgcag 240
cctgaagatt ttgcagttta ttactgtcag caggatttat actttacctc c 290

<210> 795

<211> 38

<212> DNA

<213> Homo sapiens

<220>

<223> IGKJ1*01

<400> 795

gtggacgttc ggccaaggga ccaaggtgga aatcaaac 38

<210> 796

<211> 297

<212> DNA

<213> Homo sapiens

<220>

<223> IGLV2-11*01

<400> 796

cagtctgccc tgactcagcc tcgctcagtg tccgggtctc ctggacagtc agtcaccatc 60

tcctgcactg gaaccagcag tgattgttggt ggttatAact atgtctcctg gtaccaacag 120

cacccaggca aagcccccaa actcatgatt tatgatgtca gtaagcggcc ctcaggggtc 180

cctgatcgct tctctggctc caagtctggc aacacggcct ccctgaccat ctctgggctc 240

caggctgagg atgaggctga ttattactgc tgctcatatg caggcagcta cacttttc 297

<210> 797

<211> 297

<212> DNA

<213> Homo sapiens

<220>

<223> IGLV2-11*02

<400> 797

cagtctgccc tgactcagcc tcgctcagtg tccgggtctc ctggacagtc agtcaccatc 60
tcctgcactg gaaccagcag tgatgttggt gggtataact atgtctcctg gtaccaacag 120
cacccaggca aagcccccaa actcatgatt tatgatgtca gtaagcggcc tcaggggtc 180
cctgatcgct tctctggctc caagtctggc aacacggcct ccctgaccat ctctgggctc 240
caggctgagg atgaggctga ttattactgc tgcatatgca caggcagcta cacttttc 297

<210> 798
<211> 274
<212> DNA
<213> Homo sapiens

<220>
<223> IGLV2-11*03

<400> 798
ctcagtgtcc gggtctcctg gacagtcagt caccatctcc tgcactggaa ccagcagtga 60
tgttggtggt tataactatg tctcctggta ccaacaacac ccaggcaaag cccccaaact 120
catgatttat gatgtcagta agcggccctc aggggtccct gatcgcttct ctggctccaa 180
gtctggcaac acggcctccc tgaccatctc tgggctccag gctgaggatg aggctgatta 240
ttactgctgc tcatatgcag gcagctacac tttc 274

<210> 799
<211> 297
<212> DNA
<213> Homo sapiens

<220>
<223> IGLV2-14*01

<400> 799
cagtctgccc tgactcagcc tgcctccgtg tctgggtctc ctggacagtc gatcaccatc 60
tcctgcactg gaaccagcag tgacgttggt ggttatAact atgtctcctg gtaccaacag 120
cacccaggca aagcccccaa actcatgatt tatgaggtca gtaatcggcc tcaggggtt 180
tctaatcgct tctctggctc caagtctggc aacacggcct ccctgaccat ctctgggctc 240

caggctgagg acgaggctga ttattactgc agctcatata caagcagcag cactctc 297

<210> 800
<211> 297
<212> DNA
<213> Homo sapiens

<220>
<223> IGLV2-14*02

<400> 800
cagtctgccc tgactcagcc tgcctccgtg tctgggtctc ctggacagtc gatcaccatc 60
tcctgcactg gaaccagcag tgatgttggg agttataacc ttgtctcctg gtaccaacag 120
cacccaggca aagcccccaa actcatgatt tatgagggca gtaagcggcc tcaggggt 180
tctaatcgct tctctggctc caagtctggc aacacggcct ccctgaccat ctctgggct c 240
caggctgagg acgaggctga ttattactgc agctcatata caagcagcag cactctc 297

<210> 801
<211> 274
<212> DNA
<213> Homo sapiens

<220>
<223> IGLV2-14*03

<400> 801
ctccgtgtct gggtctcctg gacagtcgat caccatctcc tgcactggaa ccagcagtga 60
cgttggtggt tataactatg tctcctggta ccaacaacac ccaggcaaag cccccaaact 120
catgatttat gatgtcagta atcggccctc aggggttt ct aatcgctt ct ctggctccaa 180
gtctggcaac acggcctccc tgaccatctc tgggctccag gctgaggacg aggctgatta 240
ttactgcagc tcatatacaa gcagcagcac tctc 274

<210> 802
<211> 274

<212> DNA

<213> Homo sapiens

<220>

<223> IGLV2-14*04

<400> 802

ctccgtgtct gggtctcctg gacagtcgat caccatctcc tgcactggaa ccagcagtga 60

cgttggtggt tatatactat gtctcctggt accaacagcac ccaggcaaag cccccaaact 120

catgattat gatgtcagta atcggccctc aggggttttct aatcgctttct ctggctccaa 180

gtctggcaac acggcctccc tgaccatctc tgggctccag gctgaggacg aggctgatta 240

ttactgcagc tcatatacaa gcagcagcac tctc 274

<210> 803

<211> 297

<212> DNA

<213> Homo sapiens

<220>

<223> IGLV2-18*01

<400> 803

cagtctgccc tgactcagcc tccctccgtg tccgggtctc ctggacagtc agtcaccatc 60

tcctgcactg gaaccagcag tgacgttggt agttatatacc gtgtctcctg gtaccagcag 120

cccccaggca cagccccaa actcatgatt tatgaggtca gtaatcggcc ctcaggggtc 180

cctgatcgct tctctgggtc caagtctggc aacacggcct ccctgaccat ctctgggctc 240

caggctgagg acgaggctga ttattactgc agcttatata caagcagcag cacttttc 297

<210> 804

<211> 297

<212> DNA

<213> Homo sapiens

<220>

<223> IGLV2-18*02

<400> 804

cagtctgccc tgactcagcc tccctccgtg tccgggtctc ctggacagtc agtcaccatc 60

tcctgcactg gaaccagcag tgacgttggt agttatAacc gtgtctcctg gtaccagcag 120

ccccaggca cagccccaa actcatgatt tatgaggtca gtaatcggcc tcaggggtc 180

cctgatcgct tctctgggtc caagtctggc aacacggcct ccctgaccat ctctgggct c 240

caggctgagg acgaggctga ttattactgc agctcatata caagcagcag cacttttc 297

<210> 805

<211> 297

<212> DNA

<213> Homo sapiens

<220>

<223> IGLV2-18*03

<400> 805

cagtctgccc tgactcagcc tccctccgtg tccgggtctc ctggacagtc agtcaccatc 60

tcctgcactg gaaccagcag tgacgttggt agttatAacc gtgtctcctg gtaccagcag 120

ccccaggca cagccccaa actcatgatt tatgaggtca gtaatcggcc tcaggggtc 180

cctgatcgct tctctgggtc caagtctggc aacacggcct ccctgaccac ctctgggct c 240

caggctgagg acgaggctga ttattactgc agctcatata caagcagcag cacttttc 297

<210> 806

<211> 297

<212> DNA

<213> Homo sapiens

<220>

<223> IGLV2-18*04

<400> 806

cagtctgccc tgactcagcc tccctccgtg tccgggtctc ctggacagtc agtcaccatc 60

tcctgcactg gaaccagcag tgacgttggt agttataacc gtgtctcctg gtaccagcag 120
ccccaggca cagccccaa actcatgatt tatgaggtca gtaatcggcc ctcaggggtc 180
cctgatcgct cctctgggtc caagtccggc aacacggcct ccctgaccat ctctgggctc 240
aggctgagg acgaggctga ttattactgc agctcatata caagcagcag cacttttc 297

<210> 807
<211> 298
<212> DNA
<213> Homo sapiens

<220>
<223> IGLV2-23*01

<400> 807
cagtctgccc tgactcagcc tgcctccgtg tctgggtctc ctggacagtc gatcaccatc 60
tcctgcactg gaaccagcag tgatgttggg agttatAacc ttgtctcctg gtaccaacag 120
cacccaggca aagccccaa actcatgatt tatgagggca gtaagcggcc ctcaggggtt 180
tctaatcgct tctctggctc caagtctggc aacacggcct ccctgacaat ctctgggctc 240
aggctgagg acgaggctga ttattactgc tgctcatatg caggtagtag cacttttac 298

<210> 808
<211> 297
<212> DNA
<213> Homo sapiens

<220>
<223> IGLV2-23*02

<400> 808
cagtctgccc tgactcagcc tgcctccgtg tctgggtctc ctggacagtc gatcaccatc 60
tcctgcactg gaaccagcag tgatgttggg agttatAacc ttgtctcctg gtaccaacag 120
cacccaggca aagccccaa actcatgatt tatgaggtca gtaagcggcc ctcaggggtt 180
tctaatcgct tctctggctc caagtctggc aacacggcct ccctgacaat ctctgggctc 240
aggctgagg acgaggctga ttattactgc tgctcatatg caggtagtag cacttttc 297

<210> 809

<211> 297

<212> DNA

<213> Homo sapiens

<220>

<223> IGLV2-23*03

<400> 809

cagtctgccc tgactcagcc tgcctccgtg tctgggtctc ctggacagtc gatcaccatc 60

tcctgcactg gaaccagcag tgatgttggg agttatAacc ttgtctcctg gtaccaacag 120

cacccaggca aagcccccaa actcatgatt tatgagggca gtaagcggcc tcaggggtct 180

tctaatcgct tctctggctc caagtctggc aacacggcct ccctgacaat ctctgggctc 240

caggctgagg acgaggctga ttattactgc tgctcatatg caggtagtag cacttttc 297

<210> 810

<211> 297

<212> DNA

<213> Homo sapiens

<220>

<223> IGLV2-33*01

<400> 810

caatctgccc tgactcagcc tcctttttgt tccggggctc ctggacagtc ggtcaccatc 60

tcctgcactg gaaccagcag tgacgttggg gattatgatc atgtctttct gtaccaaaag 120

cgtctcagca ctacctccag actcctgatt tacaatgtca atactcggcc ttcagggatc 180

tctgacctct tctctaggct ccaagtctgg aacatggctt ccctgaccat ctctgggctc 240

aagtccgagg ttgaggctaa ttatcactgc agcttatatt caagtagtta cacttttc 297

<210> 811

<211> 297

<212> DNA

<213> Homo sapiens

<220>

<223> IGLV2-33*02

<400> 811

cagtctgccc tgactcagcc tcctttgtg tccggggctc ctggacagtc ggtcaccatc 60

tcctgcactg gaaccagcag tgacgttggg gattatgatc atgtcttctg gtaccaaaag 120

cgtctcagca ctacctccag actcctgatt tacaatgtca atactcggcc ttcagggatc 180

tctgacctct tctcaggctc caagtctggc aacatggctt ccctgaccat ctctgggctc 240

aagtccgagg ttgaggctaa ttatcactgc agcttatatt caagtagtta cacttttc 297

<210> 812

<211> 297

<212> DNA

<213> Homo sapiens

<220>

<223> IGLV2-33*03

<400> 812

caatctgccc tgactcagcc tcctttgtg tccggggctc ctggacagtc ggtcaccatc 60

tcctgcactg gaaccagcag tgacgttggg gactatgatc atgtcttctg gtaccaaaag 120

cgtctcagca ctacctccag actcctgatt tacaatgtca atactcggcc ttcagggatc 180

tctgacctct tctcaggctc caagtctggc aacgtggctt ccctgaccat ctctgggctc 240

aagtccgagg ttgaggctaa ttatcactgc agcttatatt caagtagtta cacttttc 297

<210> 813

<211> 297

<212> DNA

<213> Homo sapiens

<220>

<223> IGLV2-8*01

<400> 813
cagtctgccc tgactcagcc tccctccgcg tccgggtctc ctggacagtc agtcaccatc 60
tcctgcactg gaaccagcag tgacgttggt ggttataact atgtctcctg gtaccaacag 120
cacccaggca aagcccccaa actcatgatt tatgaggtca gtaagcggcc ctcaggggtc 180
cctgatcgct tctctggctc caagtctggc aacacggcct ccctgaccgt ctctgggctc 240
caggctgagg atgaggctga ttattactgc agctcatatg caggcagcaa caatttc 297

<210> 814
<211> 297
<212> DNA
<213> Homo sapiens

<220>
<223> IGLV2-8*02

<400> 814
cagtctgccc tgactcagcc tccctccgcg tccaggtctc ctggacagtc agtcaccatc 60
tcctgcactg gaaccagcag tgacgttggt ggttataact atgtctcctg gtaccaacag 120
cacccaggca aagcccccaa actcatgatt tatgaggtca gtaagcggcc ctcaggggtc 180
cctgatcgct tctctggctc caagtctggc aacacggcct ccctgaccgt ctctgggctc 240
caggctgagg atgaggctga ttattactgc agctcatatg caggcagcaa caatttc 297

<210> 815
<211> 274
<212> DNA
<213> Homo sapiens

<220>
<223> IGLV2-8*03

<400> 815
ctccgcgtcc gggtctcctg gacagtcagt caccatctcc tgcactggaa ccagcagtga 60
cgttggtggt tataactatg tctcctggta ccaacagcac ccaggcaaag cccccaaact 120

cat gat t t at gaggt cagt a agcggccct c aggggt ccct gat cgct t ct t t ggct ccaa 180

gt ct ggcaac acggcct ccc t gaccgt ct c t gggct ccag gct gaggat g aggct gat t a 240

t t act gcagc t cat at gcag gcagcaacaa t t t c 274

<210> 816

<211> 312

<212> DNA

<213> Homo sapi ens

<220>

<223> I GLV5- 37* 01

<400> 816

cagcct gt gc t gact cagcc acct t cct cc t ccgcat ct c ct ggagaat c cgccagact c 60

acct gcacct t gcccagt ga cat caat gt t ggt agct aca acat at act g gt accagcag 120

aagccaggga gccct cccag gt at ct cct g t act act act cagact caga t aagggccag 180

ggct ct ggag t ccccagccg ct t ct ct gga t ccaaagat g ct t cagccaa t acagggat t 240

t t act cat ct ccgggct cca gt ct gaggat gaggct gact at t act gt at gat t t ggcca 300

agcaat gct t ct 312

<210> 817

<211> 312

<212> DNA

<213> Homo sapi ens

<220>

<223> I GLV5- 39* 01

<400> 817

cagcct gt gc t gact cagcc aacct ccct c t cagcat ct c ct ggagcat c agccagat t c 60

acct gcacct t gcgcagt gg cat caat gt t ggt acct aca ggat at act g gt accagcag 120

aagccaggga gt ct t ccccg gt at ct cct g aggt acaaat cagact caga t aagcagcag 180

ggct ct ggag t ccccagccg ct t ct ct gga t ccaaagat g ct t caaccaa t gcaggcct t 240

t t act cat ct ct gggct cca gt ct gaagat gaggct gact at t act gt gc cat t t ggt ac 300

agcagcactt ct 312

<210> 818
<211> 312
<212> DNA
<213> Homo sapiens

<220>
<223> IGLV5-39*02

<400> 818
cagcctgtgc tgactcagcc aacctccctc tcagcatctc ctggagcatc agccagattc 60
acctgcacct tgcgcagcgg catcaatgtt ggtacctaca ggatatactg gtaccagcag 120
aatccaggga gtcttccccg gtatctcctg aggtacaaat cagactcaga taagcagcag 180
ggctctggag tccccagccg cttctctctg gatccaaagat gcttcaaccaa tgcaggcctt 240
ttactcatct ctgggctcca gtctgaagat gaggctgact attactgtgc catttggtac 300
agcagcactt ct 312

<210> 819
<211> 312
<212> DNA
<213> Homo sapiens

<220>
<223> IGLV5-45*01

<400> 819
caggctgtgc tgactcagcc ggcttccctc tctgcatctc ctggagcatc agccagtctc 60
acctgcacct tgcgcagtgg catcaatgtt ggtacctaca ggatatactg gtaccagcag 120
aagccaggga gtcctcccca gtatctcctg aggtacaaat cagactcaga taagcagcag 180
ggctctggag tccccagccg cttctctctg gatccaaagat gcttcggccaa tgcagggatt 240
ttactcatct ctgggctcca gtctgaggat gaggctgact attactgtat gatttggcac 300
agcagcgctt ct 312

<210> 820

<211> 312

<212> DNA

<213> Homo sapiens

<220>

<223> IGLV5-45*02

<400> 820

caggctgtgc tgactcagcc gtctttccct ctctgcatct cctggagcat cagccagtct c 60

acctgcacct tacgcagtgg catcaatgtt ggtacctaca ggatatactg gtaccagcag 120

aagccaggga gtcctcccca gtatctcctg aggtacaaat cagactcaga taagcagcag 180

ggctctggag tccccagccg cttctctgga tccaaagatg cttcggccaa tgcagggatt 240

ttactcatct ctgggctcca gtctgaggat gaggctgact attactgtat gatttggcac 300

agcagcgctt ct 312

<210> 821

<211> 312

<212> DNA

<213> Homo sapiens

<220>

<223> IGLV5-45*03

<400> 821

caggctgtgc tgactcagcc gtctttccct ctctgcatct cctggagcat cagccagtct c 60

acctgcacct tgcgcagtgg catcaatgtt ggtacctaca ggatatactg gtaccagcag 120

aagccaggga gtcctcccca gtatctcctg aggtacaaat cagactcaga taagcagcag 180

ggctctggag tccccagccg cttctctgga tccaaagatg cttcggccaa tgcagggatt 240

ttactcatct ctgggctcca gtctgaggat gaggctgact attactgtat gatttggcac 300

agcagcgctt ct 312

<210> 822

<211> 312

<212> DNA

<213> Homo sapiens

<220>

<223> IGLV5-48*01

<400> 822

cagcctgtgc tgactcagcc aacttccctc tcagcatctc ctggagcatc agccagactc 60

acctgcacct tgcgcagtgg catcaatctt ggtagctaca ggatattctg gtaccagcag 120

aagccagaga gccctccccg gtatctcctg agctactact cagactcaag taagcatcag 180

ggctctggag tccccagccg cttctctcga tccaaagatg cttcgagcaa tgcagggatt 240

ttagtcatct ctgggctcca gtctgaggat gaggctgact attactgtat gatttggcac 300

agcagtgctt ct 312

<210> 823

<211> 317

<212> DNA

<213> Homo sapiens

<220>

<223> IGLV5-52*01

<400> 823

cagcctgtgc tgactcagcc atcttcccat tctgcatctt ctggagcatc agtcagactc 60

acctgcatgc tgagcagtgg cttcagtgtt ggggactttc ggatcaaggt gtaccaacaa 120

aagccaggga accctccccg gtatctcctg tactaccact cagactccaa taagggccaa 180

ggctctggag ttcccagccg cttctctcga tccaacgatg catcagccaa tgcagggatt 240

ctgcgtatct ctgggctcca gcctgaggat gaggctgact attactgtgg tacatggcac 300

agcaactcta gactca 317

<210> 824

<211> 296

<212> DNA

<213> Homo sapiens

<220>

<223> IGLV8-61*01

<400> 824

cagactgtgg tgacccagga gccatcgttc tcagtgtccc ctggagggac agtcacactc 60

acttgtggct tgagctctgg ctcagtctct actagttact accccagctg gtaccagcag 120

accccaggcc aggctccacg cacgctcatc tacagcacaa acactcgctc ttctggggtc 180

cctgatcgct tctctggctc catcctttgg aacaaagctg ccctcaccat cacgggggcc 240

caggcagatg atgaatctga ttattactgt gtgctgtata tgggtagtgg catttc 296

<210> 825

<211> 296

<212> DNA

<213> Homo sapiens

<220>

<223> IGLV8-61*02

<400> 825

cagactgtgg tgacccagga gccatcgttc tcagtgtccc ctggagggac agtcacactc 60

acttgtggct tgagctctgg ctcagtctct actagttact accccagctg gtaccagcag 120

accccaggcc aggctccacg cacgctcatc tacagcacaa acactcgctc ttctggggtc 180

cctgattgct tctctggctc catcctttgg aacaaagctg ccctcaccat cacgggggcc 240

caggcagatg atgaatctga ttattactgt gtgctgtata tgggtagtgg catttc 296

<210> 826

<211> 247

<212> DNA

<213> Homo sapiens

<220>

<223> IGLV8-61*03

<400> 826

ggtgacccag gagccatcgt tctcagtgtc ccctggaggg acagtcacac tcacttgtgg 60
cttgagctct ggctcagtct ctactagttta ctaccccagc tggtaccagc agaccccagg 120
ccaggctcca cgcacgctca tctacagcac aaacactcgc tcttctggcg tccctgatcg 180
cttctctggc tccatcctg ggaacaaagc tgccctcacc atcacggggg cccaggcaga 240
tgatgaa 247

<210> 827

<211> 312

<212> DNA

<213> Homo sapiens

<220>

<223> IGLV11-55*01

<400> 827

cggcccgtgc tgactcagcc gccctctctg tctgcatccc cgggagcaac agccagactc 60
ccctgcaccc tgagcagtga cctcagtgtt ggtggtaaaa acatgttctg gtaccagcag 120
aagccaggga gctcccag gttattcctg tatcactact cagactcaga caagcagct g 180
ggacctgggg tccccagtcg agtctctggc tccaaggaga cctcaagtaa cacagcgttt 240
ttgctcatct ctgggctcca gcctgaggac gaggccgatt attactgcca ggtgtgacgaa 300
agtagtgcta at 312

<210> 828

<211> 38

<212> DNA

<213> Homo sapiens

<220>

<223> IGLJ1*01

<400> 828

ttatgtcttc ggaactggga ccaaggtcac cgtcctag 38

<210> 829

<211> 38

<212> DNA

<213> Homo sapiens

<220>

<223> IGLJ4*01

<400> 829

ttttgtattt ggtggaggaa cccagctgat cattttag 38

<210> 830

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH1

<400> 830

Gly Tyr Thr Phe Thr Ser Tyr Tyr Met His

1 5 10

<210> 831

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH1

<400> 831

Gly Tyr Ser Phe Thr Ser Tyr Trp Ile Gly

1 5 10

<210> 832

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH1

<400> 832

Gly Asp Ser Val Ser Ser Asn Ser Ala Ala

1 5 10

<210> 833

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH1

<400> 833

Gly Gly Ser Phe Ser Gly Tyr Tyr Trp Ser

1 5 10

<210> 834

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH1

<400> 834

Gly Tyr Thr Phe Thr Ser Tyr Ala Met His
1 5 10

<210> 835

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH1

<400> 835

Gly Tyr Thr Phe Thr Ser Tyr Ala Ile Asn
1 5 10

<210> 836

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH1

<400> 836

Gly Gly Ser Ile Ser Ser Gly Gly Tyr Tyr
1 5 10

<210> 837

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH1

<400> 837

Ser Tyr Tyr Met His

1 5

<210> 838

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH1

<400> 838

Ser Tyr Trp Ile Gly

1 5

<210> 839

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH1

<400> 839

Ser Asn Ser Ala Ala
1 5

<210> 840

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH1

<400> 840

Gly Tyr Tyr Trp Ser
1 5

<210> 841

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH1

<400> 841

Ser Tyr Ala Met His
1 5

<210> 842

<211> 5

<212> PRT

<213> Artificial Sequence

<220>
<223> CDRH1

<400> 842
Ser Tyr Ala Ile Asn
1 5

<210> 843
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRH1

<400> 843
Ser Gly Gly Tyr Tyr
1 5

<210> 844
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRH2

<400> 844
Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 845

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH2

<400> 845

Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe Gln
1 5 10 15

Gly

<210> 846

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH2

<400> 846

Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala Val Ser Val
1 5 10 15

Lys Ser

<210> 847

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH2

<400> 847

Glu Ile Asn His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> 848

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH2

<400> 848

Ile Asn Ser Asn Ala Gly Asn Gly Asn Thr Lys Tyr Ser Gln Glu Phe
1 5 10 15

Gln Gly

<210> 849

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH2

<400> 849

Trp Met Asn Pro Asn Ser Gly Asn Thr Gly Tyr Ala Gln Lys Phe Gln
1 5 10 15
Gly

<210> 850

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH2

<400> 850

Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> 851

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH3

<400> 851

Glu Glu Tyr Ser Ser Ser Ser Ala Glu Tyr Lys Gln His
1 5 10

<210> 852

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH3

<400> 852

Arg Gly Tyr Ser Tyr Gly Tyr Asp Tyr Phe Asp Tyr

1 5 10

<210> 853

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH3

<400> 853

Glu Tyr Tyr Asp Phe Trp Ser Gly Tyr Tyr Thr Asp Tyr Phe Asp Tyr

1 5 10 15

<210> 854

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH3

<400> 854

Glu Gly Tyr Ser Ser Ser Trp Tyr Asp Tyr Phe Asp Tyr

1 5 10

<210> 855

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH3

<400> 855

Ala Asn Trp Gly Asp Tyr Phe Asp Tyr

1 5

<210> 856

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH3

<400> 856

Asp Asp Tyr Gly Gly Asn Ser Asp Tyr Phe Asp Tyr

1 5 10

<210> 857

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH3

<400> 857

Glu Gly Tyr Cys Ser Gly Gly Ser Cys Tyr Ser
1 5 10

<210> 858

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH3

<400> 858

Glu Tyr Tyr Tyr Gly Ser Gly Ser Tyr Tyr Asn Asp Tyr Phe Asp Tyr
1 5 10 15

<210> 859

<211> 21

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH3

<400> 859

Gly Cys Tyr Cys Ser Ser Thr Ser Cys Tyr Ala Asp Tyr Tyr Tyr Tyr

1 5 10 15

Tyr Gly Met Asp Val
20

<210> 860
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRH3

<400> 860
Gly Ser Cys Tyr Ser Tyr Trp Tyr Phe Asp Leu
1 5 10

<210> 861
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL1

<400> 861
Arg Ala Ser Gln Ser Val Ser Ser Tyr Leu Ala
1 5 10

<210> 862
<211> 14
<212> PRT

<213> Artificial Sequence

<220>
<223> CDRL1

<400> 862
Gly Leu Ser Ser Gly Ser Val Ser Thr Ser Tyr Tyr Pro Ser
 1   5   10

<210> 863
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL1

<400> 863
Thr Leu Arg Ser Gly Ile Asn Leu Gly Ser Tyr Arg Ile Phe
 1   5   10

<210> 864
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL1

<400> 864
Arg Ala Ser Gln Ser Val Ser Ser Asn Leu Ala
 1   5   10

<210> 865

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL1

<400> 865

Arg Ala Ser Gln Gly Ile Ser Ser Trp Leu Ala

1 5 10

<210> 866

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL1

<400> 866

Arg Ala Ser Gln Val Ser Ser Ser Tyr Leu Ala

1 5 10

<210> 867

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL1

<400> 867

Arg Ala Ser Gln Ser Ile Ser Ser Trp Leu Ala
1 5 10

<210> 868

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL1

<400> 868

Arg Ser Ser Gln Ser Leu Leu Asp Ser Asp Asp Gly Asn Thr Tyr Leu
1 5 10 15

Asp

<210> 869

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL1

<400> 869

Thr Gly Thr Ser Ser Asp Val Gly Gly Thr Asn Tyr Val Ser
1 5 10

<210> 870

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL1

<400> 870

Thr Leu Ser Ser Asp Leu Ser Val Gly Gly Lys Asn Met Phe

1 5 10

<210> 871

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL2

<400> 871

Asp Ala Ser Asn Arg Ala Thr

1 5

<210> 872

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL2

<400> 872

Ser Thr Asn Thr Arg Ser Ser

1 5

<210> 873

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL2

<400> 873

Tyr Tyr Ser Asp Ser Ser Lys

1 5

<210> 874

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL2

<400> 874

Gly Ala Ser Thr Arg Ala Thr

1 5

<210> 875

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL2

<400> 875

Ala Ala Ser Ser Leu Gln Ser

1 5

<210> 876

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL2

<400> 876

Gly Ala Ser Ser Arg Ala Thr

1 5

<210> 877

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL2

<400> 877

Asp Ala Ser Ser Leu Gly Ser

1 5

<210> 878
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL2

<400> 878
Thr Leu Ser Tyr Arg Ala Ser
1 5

<210> 879
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL2

<400> 879
Glu Val Ser Asn Arg Pro Ser
1 5

<210> 880
<211> 7
<212> PRT
<213> Artificial Sequence

<220>

<223> CDRL2

<400> 880

His Tyr Ser Asp Ser Asp Lys

1 5

<210> 881

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL3

<400> 881

Gln Gln Arg Ser Asn Trp Pro Pro Trp Thr

1 5 10

<210> 882

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL3

<400> 882

Val Leu Tyr Met Gly Ser Gly Ile Ser Tyr Val

1 5 10

<210> 883

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL3

<400> 883

Met Ile Trp His Ser Ser Ala Ser Phe Val
1 5 10

<210> 884

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL3

<400> 884

Gln Gln Tyr Asn Asn Trp Pro Pro Trp Thr
1 5 10

<210> 885

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL3

<400> 885

Gln Ala Asn Ser Phe Pro Pro Trp Thr
1 5

<210> 886

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL3

<400> 886

Gln Gln Tyr Gly Ser Ser Pro Pro Trp Thr
1 5 10

<210> 887

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL3

<400> 887

Gln Gln Tyr Asn Ser Tyr Ser Pro Trp Thr
1 5 10

<210> 888

<211> 10

<212> PRT

<213> Artificial Sequence

<220>
<223> CDRL3

<400> 888
Met Gln Arg Ile Glu Phe Pro Ser Trp Thr
 1   5   10

<210> 889
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL3

<400> 889
Ser Ser Tyr Thr Ser Ser Ser Thr Leu Phe Val
 1   5   10

<210> 890
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL3

<400> 890
Gln Val Tyr Glu Ser Ser Ala Asn Phe Val
 1   5   10

<210> 891

<211> 330

<212> PRT

<213> Artificial Sequence

<220>

<223> IgG1 CH1-hinge-CH2-CH3

<400> 891

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu

180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn

195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly

210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu

225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr

245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn

260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe

275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn

290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr

305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys

325 330

<210> 892

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> CL Kappa

<400> 892

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu

1 5 10 15

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe

20 25 30

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
35 40 45
Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
50 55 60
Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
65 70 75 80
Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
85 90 95
Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
100 105

<210> 893
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> CL Lambda

<400> 893
Gly Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser
1 5 10 15
Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp
20 25 30
Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro
35 40 45
Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn
50 55 60
Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys
65 70 75 80
Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val
85 90 95
Glu Lys Thr Val Ala Pro Thr Glu Cys Ser

100 105

<210> 894

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T Y27A

<400> 894

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Ala Ser Phe Thr Ser Tyr
20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

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

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Arg Lys Tyr Ser Tyr Thr Tyr Asp Tyr Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 895

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T S31A

<400> 895

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ala Tyr
20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

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

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Arg Lys Tyr Ser Tyr Thr Tyr Asp Tyr Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 896

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T Y32A

<400> 896

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Ala
20 25 30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Arg Lys Tyr Ser Tyr Thr Tyr Asp Tyr Phe Asp Tyr Trp Gly
100 105 110
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 897
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T G54A

<400> 897
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30
Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Tyr Pro Ala Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr

65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Arg Lys Tyr Ser Tyr Thr Tyr Asp Tyr Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 898

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T S56A

<400> 898

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ala Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

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

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Arg Lys Tyr Ser Tyr Thr Tyr Asp Tyr Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120

<210> 899

<211> 2555

<212> PRT

<213> Homo sapiens

<220>

<223> Notch-1 (P46531)

<400> 899

Met Pro Pro Leu Leu Ala Pro Leu Leu Cys Leu Ala Leu Leu Pro Ala
1 5 10 15

Leu Ala Ala Arg Gly Pro Arg Cys Ser Gln Pro Gly Glu Thr Cys Leu
20 25 30

Asn Gly Gly Lys Cys Glu Ala Ala Asn Gly Thr Glu Ala Cys Val Cys
35 40 45

Gly Gly Ala Phe Val Gly Pro Arg Cys Gln Asp Pro Asn Pro Cys Leu
50 55 60

Ser Thr Pro Cys Lys Asn Ala Gly Thr Cys His Val Val Asp Arg Arg
65 70 75 80

Gly Val Ala Asp Tyr Ala Cys Ser Cys Ala Leu Gly Phe Ser Gly Pro
85 90 95

Leu Cys Leu Thr Pro Leu Asp Asn Ala Cys Leu Thr Asn Pro Cys Arg
100 105 110

Asn Gly Gly Thr Cys Asp Leu Leu Thr Leu Thr Glu Tyr Lys Cys Arg
115 120 125

Cys Pro Pro Gly Trp Ser Gly Lys Ser Cys Gln Gln Ala Asp Pro Cys
130 135 140

Ala Ser Asn Pro Cys Ala Asn Gly Gly Gln Cys Leu Pro Phe Glu Ala
145 150 155 160

Ser Tyr Ile Cys His Cys Pro Pro Ser Phe His Gly Pro Thr Cys Arg
165 170 175

Gln Asp Val Asn Glu Cys Gly Gln Lys Pro Gly Leu Cys Arg His Gly

180 185 190

Gly Thr Cys His Asn Glu Val Gly Ser Tyr Arg Cys Val Cys Arg Ala

195 200 205

Thr His Thr Gly Pro Asn Cys Glu Arg Pro Tyr Val Pro Cys Ser Pro

210 215 220

Ser Pro Cys Gln Asn Gly Gly Thr Cys Arg Pro Thr Gly Asp Val Thr

225 230 235 240

His Glu Cys Ala Cys Leu Pro Gly Phe Thr Gly Gln Asn Cys Glu Glu

245 250 255

Asn Ile Asp Asp Cys Pro Gly Asn Asn Cys Lys Asn Gly Gly Ala Cys

260 265 270

Val Asp Gly Val Asn Thr Tyr Asn Cys Arg Cys Pro Pro Glu Trp Thr

275 280 285

Gly Gln Tyr Cys Thr Glu Asp Val Asp Glu Cys Gln Leu Met Pro Asn

290 295 300

Ala Cys Gln Asn Gly Gly Thr Cys His Asn Thr His Gly Gly Tyr Asn

305 310 315 320

Cys Val Cys Val Asn Gly Trp Thr Gly Glu Asp Cys Ser Glu Asn Ile

325 330 335

Asp Asp Cys Ala Ser Ala Ala Cys Phe His Gly Ala Thr Cys His Asp

340 345 350

Arg Val Ala Ser Phe Tyr Cys Glu Cys Pro His Gly Arg Thr Gly Leu

355 360 365

Leu Cys His Leu Asn Asp Ala Cys Ile Ser Asn Pro Cys Asn Glu Gly

370 375 380

Ser Asn Cys Asp Thr Asn Pro Val Asn Gly Lys Ala Ile Cys Thr Cys

385 390 395 400

Pro Ser Gly Tyr Thr Gly Pro Ala Cys Ser Gln Asp Val Asp Glu Cys

405 410 415

Ser Leu Gly Ala Asn Pro Cys Glu His Ala Gly Lys Cys Ile Asn Thr

420 425 430

Leu Gly Ser Phe Glu Cys Gln Cys Leu Gln Gly Tyr Thr Gly Pro Arg

435 440 445

Cys Glu Ile Asp Val Asn Glu Cys Val Ser Asn Pro Cys Gln Asn Asp

450 455 460

Ala Thr Cys Leu Asp Gln Ile Gly Glu Phe Gln Cys Ile Cys Met Pro
465 470 475 480

Gly Tyr Glu Gly Val His Cys Glu Val Asn Thr Asp Glu Cys Ala Ser
485 490 495

Ser Pro Cys Leu His Asn Gly Arg Cys Leu Asp Lys Ile Asn Glu Phe
500 505 510

Gln Cys Glu Cys Pro Thr Gly Phe Thr Gly His Leu Cys Gln Tyr Asp
515 520 525

Val Asp Glu Cys Ala Ser Thr Pro Cys Lys Asn Gly Ala Lys Cys Leu
530 535 540

Asp Gly Pro Asn Thr Tyr Thr Cys Val Cys Thr Glu Gly Tyr Thr Gly
545 550 555 560

Thr His Cys Glu Val Asp Ile Asp Glu Cys Asp Pro Asp Pro Cys His
565 570 575

Tyr Gly Ser Cys Lys Asp Gly Val Ala Thr Phe Thr Cys Leu Cys Arg
580 585 590

Pro Gly Tyr Thr Gly His His Cys Glu Thr Asn Ile Asn Glu Cys Ser
595 600 605

Ser Gln Pro Cys Arg His Gly Gly Thr Cys Gln Asp Arg Asp Asn Ala
610 615 620

Tyr Leu Cys Phe Cys Leu Lys Gly Thr Thr Gly Pro Asn Cys Glu Ile
625 630 635 640

Asn Leu Asp Asp Cys Ala Ser Ser Pro Cys Asp Ser Gly Thr Cys Leu
645 650 655

Asp Lys Ile Asp Gly Tyr Glu Cys Ala Cys Glu Pro Gly Tyr Thr Gly
660 665 670

Ser Met Cys Asn Ile Asn Ile Asp Glu Cys Ala Gly Asn Pro Cys His
675 680 685

Asn Gly Gly Thr Cys Glu Asp Gly Ile Asn Gly Phe Thr Cys Arg Cys
690 695 700

Pro Glu Gly Tyr His Asp Pro Thr Cys Leu Ser Glu Val Asn Glu Cys
705 710 715 720

Asn Ser Asn Pro Cys Val His Gly Ala Cys Arg Asp Ser Leu Asn Gly

725 730 735

Tyr Lys Cys Asp Cys Asp Pro Gly Trp Ser Gly Thr Asn Cys Asp Ile

740 745 750

Asn Asn Asn Glu Cys Glu Ser Asn Pro Cys Val Asn Gly Gly Thr Cys

755 760 765

Lys Asp Met Thr Ser Gly Tyr Val Cys Thr Cys Arg Glu Gly Phe Ser

770 775 780

Gly Pro Asn Cys Gln Thr Asn Ile Asn Glu Cys Ala Ser Asn Pro Cys

785 790 795 800

Leu Asn Gln Gly Thr Cys Ile Asp Asp Val Ala Gly Tyr Lys Cys Asn

805 810 815

Cys Leu Leu Pro Tyr Thr Gly Ala Thr Cys Glu Val Val Leu Ala Pro

820 825 830

Cys Ala Pro Ser Pro Cys Arg Asn Gly Gly Glu Cys Arg Gln Ser Glu

835 840 845

Asp Tyr Glu Ser Phe Ser Cys Val Cys Pro Thr Gly Trp Gln Gly Gln

850 855 860

Thr Cys Glu Val Asp Ile Asn Glu Cys Val Leu Ser Pro Cys Arg His

865 870 875 880

Gly Ala Ser Cys Gln Asn Thr His Gly Gly Tyr Arg Cys His Cys Gln

885 890 895

Ala Gly Tyr Ser Gly Arg Asn Cys Glu Thr Asp Ile Asp Asp Cys Arg

900 905 910

Pro Asn Pro Cys His Asn Gly Gly Ser Cys Thr Asp Gly Ile Asn Thr

915 920 925

Ala Phe Cys Asp Cys Leu Pro Gly Phe Arg Gly Thr Phe Cys Glu Glu

930 935 940

Asp Ile Asn Glu Cys Ala Ser Asp Pro Cys Arg Asn Gly Ala Asn Cys

945 950 955 960

Thr Asp Cys Val Asp Ser Tyr Thr Cys Thr Cys Pro Ala Gly Phe Ser

965 970 975

Gly Ile His Cys Glu Asn Asn Thr Pro Asp Cys Thr Glu Ser Ser Cys

980 985 990

Phe Asn Gly Gly Thr Cys Val Asp Gly Ile Asn Ser Phe Thr Cys Leu

995 1000 1005

Cys Pro Pro Gly Phe Thr Gly Ser Tyr Cys Gln His Asp Val Asn Glu
1010 1015 1020

Cys Asp Ser Gln Pro Cys Leu His Gly Gly Thr Cys Gln Asp Gly Cys
1025 1030 1035 1040

Gly Ser Tyr Arg Cys Thr Cys Pro Gln Gly Tyr Thr Gly Pro Asn Cys
1045 1050 1055

Gln Asn Leu Val His Trp Cys Asp Ser Ser Pro Cys Lys Asn Gly Gly
1060 1065 1070

Lys Cys Trp Gln Thr His Thr Gln Tyr Arg Cys Glu Cys Pro Ser Gly
1075 1080 1085

Trp Thr Gly Leu Tyr Cys Asp Val Pro Ser Val Ser Cys Glu Val Ala
1090 1095 1100

Ala Gln Arg Gln Gly Val Asp Val Ala Arg Leu Cys Gln His Gly Gly
1105 1110 1115 1120

Leu Cys Val Asp Ala Gly Asn Thr His His Cys Arg Cys Gln Ala Gly
1125 1130 1135

Tyr Thr Gly Ser Tyr Cys Glu Asp Leu Val Asp Glu Cys Ser Pro Ser
1140 1145 1150

Pro Cys Gln Asn Gly Ala Thr Cys Thr Asp Tyr Leu Gly Gly Tyr Ser
1155 1160 1165

Cys Lys Cys Val Ala Gly Tyr His Gly Val Asn Cys Ser Glu Glu Ile
1170 1175 1180

Asp Glu Cys Leu Ser His Pro Cys Gln Asn Gly Gly Thr Cys Leu Asp
1185 1190 1195 1200

Leu Pro Asn Thr Tyr Lys Cys Ser Cys Pro Arg Gly Thr Gln Gly Val
1205 1210 1215

His Cys Glu Ile Asn Val Asp Asp Cys Asn Pro Pro Val Asp Pro Val
1220 1225 1230

Ser Arg Ser Pro Lys Cys Phe Asn Asn Gly Thr Cys Val Asp Gln Val
1235 1240 1245

Gly Gly Tyr Ser Cys Thr Cys Pro Pro Gly Phe Val Gly Glu Arg Cys
1250 1255 1260

Glu Gly Asp Val Asn Glu Cys Leu Ser Asn Pro Cys Asp Ala Arg Gly

1265 1270 1275 1280

Thr Gln Asn Cys Val Gln Arg Val Asn Asp Phe His Cys Glu Cys Arg
1285 1290 1295

Ala Gly His Thr Gly Arg Arg Cys Glu Ser Val Ile Asn Gly Cys Lys
1300 1305 1310

Gly Lys Pro Cys Lys Asn Gly Gly Thr Cys Ala Val Ala Ser Asn Thr
1315 1320 1325

Ala Arg Gly Phe Ile Cys Lys Cys Pro Ala Gly Phe Glu Gly Ala Thr
1330 1335 1340

Cys Glu Asn Asp Ala Arg Thr Cys Gly Ser Leu Arg Cys Leu Asn Gly
1345 1350 1355 1360

Gly Thr Cys Ile Ser Gly Pro Arg Ser Pro Thr Cys Leu Cys Leu Gly
1365 1370 1375

Pro Phe Thr Gly Pro Glu Cys Gln Phe Pro Ala Ser Ser Pro Cys Leu
1380 1385 1390

Gly Gly Asn Pro Cys Tyr Asn Gln Gly Thr Cys Glu Pro Thr Ser Glu
1395 1400 1405

Ser Pro Phe Tyr Arg Cys Leu Cys Pro Ala Lys Phe Asn Gly Leu Leu
1410 1415 1420

Cys His Ile Leu Asp Tyr Ser Phe Gly Gly Gly Ala Gly Arg Asp Ile
1425 1430 1435 1440

Pro Pro Pro Leu Ile Glu Glu Ala Cys Glu Leu Pro Glu Cys Gln Glu
1445 1450 1455

Asp Ala Gly Asn Lys Val Cys Ser Leu Gln Cys Asn Asn His Ala Cys
1460 1465 1470

Gly Trp Asp Gly Gly Asp Cys Ser Leu Asn Phe Asn Asp Pro Trp Lys
1475 1480 1485

Asn Cys Thr Gln Ser Leu Gln Cys Trp Lys Tyr Phe Ser Asp Gly His
1490 1495 1500

Cys Asp Ser Gln Cys Asn Ser Ala Gly Cys Leu Phe Asp Gly Phe Asp
1505 1510 1515 1520

Cys Gln Arg Ala Glu Gly Gln Cys Asn Pro Leu Tyr Asp Gln Tyr Cys
1525 1530 1535

Lys Asp His Phe Ser Asp Gly His Cys Asp Gln Gly Cys Asn Ser Ala

1540 1545 1550

Glu Cys Glu Trp Asp Gly Leu Asp Cys Ala Glu His Val Pro Glu Arg
1555 1560 1565

Leu Ala Ala Gly Thr Leu Val Val Val Leu Met Pro Pro Glu Gln
1570 1575 1580

Leu Arg Asn Ser Ser Phe His Phe Leu Arg Glu Leu Ser Arg Val Leu
1585 1590 1595 1600

His Thr Asn Val Val Phe Lys Arg Asp Ala His Gly Gln Gln Met Ile
1605 1610 1615

Phe Pro Tyr Tyr Gly Arg Glu Glu Glu Leu Arg Lys His Pro Ile Lys
1620 1625 1630

Arg Ala Ala Glu Gly Trp Ala Ala Pro Asp Ala Leu Leu Gly Gln Val
1635 1640 1645

Lys Ala Ser Leu Leu Pro Gly Gly Ser Glu Gly Gly Arg Arg Arg Arg
1650 1655 1660

Glu Leu Asp Pro Met Asp Val Arg Gly Ser Ile Val Tyr Leu Glu Ile
1665 1670 1675 1680

Asp Asn Arg Gln Cys Val Gln Ala Ser Ser Gln Cys Phe Gln Ser Ala
1685 1690 1695

Thr Asp Val Ala Ala Phe Leu Gly Ala Leu Ala Ser Leu Gly Ser Leu
1700 1705 1710

Asn Ile Pro Tyr Lys Ile Glu Ala Val Gln Ser Glu Thr Val Glu Pro
1715 1720 1725

Pro Pro Pro Ala Gln Leu His Phe Met Tyr Val Ala Ala Ala Ala Phe
1730 1735 1740

Val Leu Leu Phe Phe Val Gly Cys Gly Val Leu Leu Ser Arg Lys Arg
1745 1750 1755 1760

Arg Arg Gln His Gly Gln Leu Trp Phe Pro Glu Gly Phe Lys Val Ser
1765 1770 1775

Glu Ala Ser Lys Lys Lys Arg Arg Glu Pro Leu Gly Glu Asp Ser Val
1780 1785 1790

Gly Leu Lys Pro Leu Lys Asn Ala Ser Asp Gly Ala Leu Met Asp Asp
1795 1800 1805

Asn Gln Asn Glu Trp Gly Asp Glu Asp Leu Glu Thr Lys Lys Phe Arg

1810 1815 1820

Phe Glu Glu Pro Val Val Leu Pro Asp Leu Asp Asp Gln Thr Asp His
1825 1830 1835 1840

Arg Gln Trp Thr Gln Gln His Leu Asp Ala Ala Asp Leu Arg Met Ser
1845 1850 1855

Ala Met Ala Pro Thr Pro Pro Gln Gly Glu Val Asp Ala Asp Cys Met
1860 1865 1870

Asp Val Asn Val Arg Gly Pro Asp Gly Phe Thr Pro Leu Met Ile Ala
1875 1880 1885

Ser Cys Ser Gly Gly Gly Leu Glu Thr Gly Asn Ser Glu Glu Glu Glu
1890 1895 1900

Asp Ala Pro Ala Val Ile Ser Asp Phe Ile Tyr Gln Gly Ala Ser Leu
1905 1910 1915 1920

His Asn Gln Thr Asp Arg Thr Gly Glu Thr Ala Leu His Leu Ala Ala
1925 1930 1935

Arg Tyr Ser Arg Ser Asp Ala Ala Lys Arg Leu Leu Glu Ala Ser Ala
1940 1945 1950

Asp Ala Asn Ile Gln Asp Asn Met Gly Arg Thr Pro Leu His Ala Ala
1955 1960 1965

Val Ser Ala Asp Ala Gln Gly Val Phe Gln Ile Leu Ile Arg Asn Arg
1970 1975 1980

Ala Thr Asp Leu Asp Ala Arg Met His Asp Gly Thr Thr Pro Leu Ile
1985 1990 1995 2000

Leu Ala Ala Arg Leu Ala Val Glu Gly Met Leu Glu Asp Leu Ile Asn
2005 2010 2015

Ser His Ala Asp Val Asn Ala Val Asp Asp Leu Gly Lys Ser Ala Leu
2020 2025 2030

His Trp Ala Ala Ala Val Asn Asn Val Asp Ala Ala Val Val Leu Leu
2035 2040 2045

Lys Asn Gly Ala Asn Lys Asp Met Gln Asn Asn Arg Glu Glu Thr Pro
2050 2055 2060

Leu Phe Leu Ala Ala Arg Glu Gly Ser Tyr Glu Thr Ala Lys Val Leu
2065 2070 2075 2080

Leu Asp His Phe Ala Asn Arg Asp Ile Thr Asp His Met Asp Arg Leu

2085 2090 2095

Pro Arg Asp Ile Ala Gln Glu Arg Met His His Asp Ile Val Arg Leu
2100 2105 2110

Leu Asp Glu Tyr Asn Leu Val Arg Ser Pro Gln Leu His Gly Ala Pro
2115 2120 2125

Leu Gly Gly Thr Pro Thr Leu Ser Pro Pro Leu Cys Ser Pro Asn Gly
2130 2135 2140

Tyr Leu Gly Ser Leu Lys Pro Gly Val Gln Gly Lys Lys Val Arg Lys
2145 2150 2155 2160

Pro Ser Ser Lys Gly Leu Ala Cys Gly Ser Lys Glu Ala Lys Asp Leu
2165 2170 2175

Lys Ala Arg Arg Lys Lys Ser Gln Asp Gly Lys Gly Cys Leu Leu Asp
2180 2185 2190

Ser Ser Gly Met Leu Ser Pro Val Asp Ser Leu Glu Ser Pro His Gly
2195 2200 2205

Tyr Leu Ser Asp Val Ala Ser Pro Pro Leu Leu Pro Ser Pro Phe Gln
2210 2215 2220

Gln Ser Pro Ser Val Pro Leu Asn His Leu Pro Gly Met Pro Asp Thr
2225 2230 2235 2240

His Leu Gly Ile Gly His Leu Asn Val Ala Ala Lys Pro Glu Met Ala
2245 2250 2255

Ala Leu Gly Gly Gly Gly Arg Leu Ala Phe Glu Thr Gly Pro Pro Arg
2260 2265 2270

Leu Ser His Leu Pro Val Ala Ser Gly Thr Ser Thr Val Leu Gly Ser
2275 2280 2285

Ser Ser Gly Gly Ala Leu Asn Phe Thr Val Gly Gly Ser Thr Ser Leu
2290 2295 2300

Asn Gly Gln Cys Glu Trp Leu Ser Arg Leu Gln Ser Gly Met Val Pro
2305 2310 2315 2320

Asn Gln Tyr Asn Pro Leu Arg Gly Ser Val Ala Pro Gly Pro Leu Ser
2325 2330 2335

Thr Gln Ala Pro Ser Leu Gln His Gly Met Val Gly Pro Leu His Ser
2340 2345 2350

Ser Leu Ala Ala Ser Ala Leu Ser Gln Met Met Ser Tyr Gln Gly Leu

2355 2360 2365

Pro Ser Thr Arg Leu Ala Thr Gln Pro His Leu Val Gln Thr Gln Gln

2370 2375 2380

Val Gln Pro Gln Asn Leu Gln Met Gln Gln Gln Asn Leu Gln Pro Ala

2385 2390 2395 2400

Asn Ile Gln Gln Gln Gln Ser Leu Gln Pro Pro Pro Pro Pro Pro Gln

2405 2410 2415

Pro His Leu Gly Val Ser Ser Ala Ala Ser Gly His Leu Gly Arg Ser

2420 2425 2430

Phe Leu Ser Gly Glu Pro Ser Gln Ala Asp Val Gln Pro Leu Gly Pro

2435 2440 2445

Ser Ser Leu Ala Val His Thr Ile Leu Pro Gln Glu Ser Pro Ala Leu

2450 2455 2460

Pro Thr Ser Leu Pro Ser Ser Leu Val Pro Pro Val Thr Ala Ala Gln

2465 2470 2475 2480

Phe Leu Thr Pro Pro Ser Gln His Ser Tyr Ser Ser Pro Val Asp Asn

2485 2490 2495

Thr Pro Ser His Gln Leu Gln Val Pro Glu His Pro Phe Leu Thr Pro

2500 2505 2510

Ser Pro Glu Ser Pro Asp Gln Trp Ser Ser Ser Ser Pro His Ser Asn

2515 2520 2525

Val Ser Asp Trp Ser Glu Gly Val Ser Ser Pro Pro Thr Ser Met Gln

2530 2535 2540

Ser Gln Ile Ala Arg Ile Pro Glu Ala Phe Lys

2545 2550 2555

<210> 900

<211> 2003

<212> PRT

<213> Homo sapiens

<220>

<223> Notch-4 (Q99466)

<400> 900

Met Gln Pro Pro Ser Leu Leu Leu Leu Leu Leu Leu Leu Leu Leu Leu Leu
1 5 10 15

Cys Val Ser Val Val Arg Pro Arg Gly Leu Leu Cys Gly Ser Phe Pro
20 25 30

Glu Pro Cys Ala Asn Gly Gly Thr Cys Leu Ser Leu Ser Leu Gly Gln
35 40 45

Gly Thr Cys Gln Cys Ala Pro Gly Phe Leu Gly Glu Thr Cys Gln Phe
50 55 60

Pro Asp Pro Cys Gln Asn Ala Gln Leu Cys Gln Asn Gly Gly Ser Cys
65 70 75 80

Gln Ala Leu Leu Pro Ala Pro Leu Gly Leu Pro Ser Ser Pro Ser Pro
85 90 95

Leu Thr Pro Ser Phe Leu Cys Thr Cys Leu Pro Gly Phe Thr Gly Glu
100 105 110

Arg Cys Gln Ala Lys Leu Glu Asp Pro Cys Pro Pro Ser Phe Cys Ser
115 120 125

Lys Arg Gly Arg Cys His Ile Gln Ala Ser Gly Arg Pro Gln Cys Ser
130 135 140

Cys Met Pro Gly Trp Thr Gly Glu Gln Cys Gln Leu Arg Asp Phe Cys
145 150 155 160

Ser Ala Asn Pro Cys Val Asn Gly Gly Val Cys Leu Ala Thr Tyr Pro
165 170 175

Gln Ile Gln Cys His Cys Pro Pro Gly Phe Glu Gly His Ala Cys Glu
180 185 190

Arg Asp Val Asn Glu Cys Phe Gln Asp Pro Gly Pro Cys Pro Lys Gly
195 200 205

Thr Ser Cys His Asn Thr Leu Gly Ser Phe Gln Cys Leu Cys Pro Val
210 215 220

Gly Gln Glu Gly Pro Arg Cys Glu Leu Arg Ala Gly Pro Cys Pro Pro
225 230 235 240

Arg Gly Cys Ser Asn Gly Gly Thr Cys Gln Leu Met Pro Glu Lys Asp
245 250 255

Ser Thr Phe His Leu Cys Leu Cys Pro Pro Gly Phe Ile Gly Pro Asp
260 265 270

Cys Glu Val Asn Pro Asp Asn Cys Val Ser His Gln Cys Gln Asn Gly
275 280 285

Gly Thr Cys Gln Asp Gly Leu Asp Thr Tyr Thr Cys Leu Cys Pro Glu
290 295 300

Thr Trp Thr Gly Trp Asp Cys Ser Glu Asp Val Asp Glu Cys Glu Thr
305 310 315 320

Gln Gly Pro Pro His Cys Arg Asn Gly Gly Thr Cys Gln Asn Ser Ala
325 330 335

Gly Ser Phe His Cys Val Cys Val Ser Gly Trp Gly Gly Thr Ser Cys
340 345 350

Glu Glu Asn Leu Asp Asp Cys Ile Ala Ala Thr Cys Ala Pro Gly Ser
355 360 365

Thr Cys Ile Asp Arg Val Gly Ser Phe Ser Cys Leu Cys Pro Pro Gly
370 375 380

Arg Thr Gly Leu Leu Cys His Leu Glu Asp Met Cys Leu Ser Gln Pro
385 390 395 400

Cys His Gly Asp Ala Gln Cys Ser Thr Asn Pro Leu Thr Gly Ser Thr
405 410 415

Leu Cys Leu Cys Gln Pro Gly Tyr Ser Gly Pro Thr Cys His Gln Asp
420 425 430

Leu Asp Glu Cys Leu Met Ala Gln Gln Gly Pro Ser Pro Cys Glu His
435 440 445

Gly Gly Ser Cys Leu Asn Thr Pro Gly Ser Phe Asn Cys Leu Cys Pro
450 455 460

Pro Gly Tyr Thr Gly Ser Arg Cys Glu Ala Asp His Asn Glu Cys Leu
465 470 475 480

Ser Gln Pro Cys His Pro Gly Ser Thr Cys Leu Asp Leu Leu Ala Thr
485 490 495

Phe His Cys Leu Cys Pro Pro Gly Leu Glu Gly Gln Leu Cys Glu Val
500 505 510

Glu Thr Asn Glu Cys Ala Ser Ala Pro Cys Leu Asn His Ala Asp Cys
515 520 525

```
His Asp Leu Leu Asn Gly Phe Gln Cys Ile Cys Leu Pro Gly Phe Ser
    530                 535                 540
Gly Thr Arg Cys Glu Glu Asp Ile Asp Glu Cys Arg Ser Ser Pro Cys
545                 550                 555                 560
Ala Asn Gly Gly Gln Cys Gln Asp Gln Pro Gly Ala Phe His Cys Lys
                565                 570                 575
Cys Leu Pro Gly Phe Glu Gly Pro Arg Cys Gln Thr Glu Val Asp Glu
            580                 585                 590
Cys Leu Ser Asp Pro Cys Pro Val Gly Ala Ser Cys Leu Asp Leu Pro
        595                 600                 605
Gly Ala Phe Phe Cys Leu Cys Pro Ser Gly Phe Thr Gly Gln Leu Cys
    610                 615                 620
Glu Val Pro Leu Cys Ala Pro Asn Leu Cys Gln Pro Lys Gln Ile Cys
625                 630                 635                 640
Lys Asp Gln Lys Asp Lys Ala Asn Cys Leu Cys Pro Asp Gly Ser Pro
                645                 650                 655
Gly Cys Ala Pro Pro Glu Asp Asn Cys Thr Cys His His Gly His Cys
            660                 665                 670
Gln Arg Ser Ser Cys Val Cys Asp Val Gly Trp Thr Gly Pro Glu Cys
        675                 680                 685
Glu Ala Glu Leu Gly Gly Cys Ile Ser Ala Pro Cys Ala His Gly Gly
    690                 695                 700
Thr Cys Tyr Pro Gln Pro Ser Gly Tyr Asn Cys Thr Cys Pro Thr Gly
705                 710                 715                 720
Tyr Thr Gly Pro Thr Cys Ser Glu Glu Met Thr Ala Cys His Ser Gly
                725                 730                 735
Pro Cys Leu Asn Gly Gly Ser Cys Asn Pro Ser Pro Gly Gly Tyr Tyr
            740                 745                 750
Cys Thr Cys Pro Pro Ser His Thr Gly Pro Gln Cys Gln Thr Ser Thr
        755                 760                 765
Asp Tyr Cys Val Ser Ala Pro Cys Phe Asn Gly Gly Thr Cys Val Asn
    770                 775                 780
Arg Pro Gly Thr Phe Ser Cys Leu Cys Ala Met Gly Phe Gln Gly Pro
785                 790                 795                 800
```

Arg Cys Glu Gly Lys Leu Arg Pro Ser Cys Ala Asp Ser Pro Cys Arg
805 810 815

Asn Arg Ala Thr Cys Gln Asp Ser Pro Gln Gly Pro Arg Cys Leu Cys
820 825 830

Pro Thr Gly Tyr Thr Gly Gly Ser Cys Gln Thr Leu Met Asp Leu Cys
835 840 845

Ala Gln Lys Pro Cys Pro Arg Asn Ser His Cys Leu Gln Thr Gly Pro
850 855 860

Ser Phe His Cys Leu Cys Leu Gln Gly Trp Thr Gly Pro Leu Cys Asn
865 870 875 880

Leu Pro Leu Ser Ser Cys Gln Lys Ala Ala Leu Ser Gln Gly Ile Asp
885 890 895

Val Ser Ser Leu Cys His Asn Gly Gly Leu Cys Val Asp Ser Gly Pro
900 905 910

Ser Tyr Phe Cys His Cys Pro Pro Gly Phe Gln Gly Ser Leu Cys Gln
915 920 925

Asp His Val Asn Pro Cys Glu Ser Arg Pro Cys Gln Asn Gly Ala Thr
930 935 940

Cys Met Ala Gln Pro Ser Gly Tyr Leu Cys Gln Cys Ala Pro Gly Tyr
945 950 955 960

Asp Gly Gln Asn Cys Ser Lys Glu Leu Asp Ala Cys Gln Ser Gln Pro
965 970 975

Cys His Asn His Gly Thr Cys Thr Pro Lys Pro Gly Gly Phe His Cys
980 985 990

Ala Cys Pro Pro Gly Phe Val Gly Leu Arg Cys Glu Gly Asp Val Asp
995 1000 1005

Glu Cys Leu Asp Gln Pro Cys His Pro Thr Gly Thr Ala Ala Cys His
1010 1015 1020

Ser Leu Ala Asn Ala Phe Tyr Cys Gln Cys Leu Pro Gly His Thr Gly
1025 1030 1035 1040

Gln Trp Cys Glu Val Glu Ile Asp Pro Cys His Ser Gln Pro Cys Phe
1045 1050 1055

His Gly Gly Thr Cys Glu Ala Thr Ala Gly Ser Pro Leu Gly Phe Ile
1060 1065 1070

Cys His Cys Pro Lys Gly Phe Glu Gly Pro Thr Cys Ser His Arg Ala
1075 1080 1085

Pro Ser Cys Gly Phe His His Cys His His Gly Gly Leu Cys Leu Pro
1090 1095 1100

Ser Pro Lys Pro Gly Phe Pro Pro Arg Cys Ala Cys Leu Ser Gly Tyr
1105 1110 1115 1120

Gly Gly Pro Asp Cys Leu Thr Pro Pro Ala Pro Lys Gly Cys Gly Pro
1125 1130 1135

Pro Ser Pro Cys Leu Tyr Asn Gly Ser Cys Ser Glu Thr Thr Gly Leu
1140 1145 1150

Gly Gly Pro Gly Phe Arg Cys Ser Cys Pro His Ser Ser Pro Gly Pro
1155 1160 1165

Arg Cys Gln Lys Pro Gly Ala Lys Gly Cys Glu Gly Arg Ser Gly Asp
1170 1175 1180

Gly Ala Cys Asp Ala Gly Cys Ser Gly Pro Gly Gly Asn Trp Asp Gly
1185 1190 1195 1200

Gly Asp Cys Ser Leu Gly Val Pro Asp Pro Trp Lys Gly Cys Pro Ser
1205 1210 1215

His Ser Arg Cys Trp Leu Leu Phe Arg Asp Gly Gln Cys His Pro Gln
1220 1225 1230

Cys Asp Ser Glu Glu Cys Leu Phe Asp Gly Tyr Asp Cys Glu Thr Pro
1235 1240 1245

Pro Ala Cys Thr Pro Ala Tyr Asp Gln Tyr Cys His Asp His Phe His
1250 1255 1260

Asn Gly His Cys Glu Lys Gly Cys Asn Thr Ala Glu Cys Gly Trp Asp
1265 1270 1275 1280

Gly Gly Asp Cys Arg Pro Glu Asp Gly Asp Pro Glu Trp Gly Pro Ser
1285 1290 1295

Leu Ala Leu Leu Val Val Leu Ser Pro Pro Ala Leu Asp Gln Gln Leu
1300 1305 1310

Phe Ala Leu Ala Arg Val Leu Ser Leu Thr Leu Arg Val Gly Leu Trp
1315 1320 1325

Val Arg Lys Asp Arg Asp Gly Arg Asp Met Val Tyr Pro Tyr Pro Gly
1330 1335 1340

Ala Arg Ala Glu Glu Lys Leu Gly Gly Thr Arg Asp Pro Thr Tyr Gln
1345 1350 1355 1360

Glu Arg Ala Ala Pro Gln Thr Gln Pro Leu Gly Lys Glu Thr Asp Ser
1365 1370 1375

Leu Ser Ala Gly Phe Val Val Val Met Gly Val Asp Leu Ser Arg Cys
1380 1385 1390

Gly Pro Asp His Pro Ala Ser Arg Cys Pro Trp Asp Pro Gly Leu Leu
1395 1400 1405

Leu Arg Phe Leu Ala Ala Met Ala Ala Val Gly Ala Leu Glu Pro Leu
1410 1415 1420

Leu Pro Gly Pro Leu Leu Ala Val His Pro His Ala Gly Thr Ala Pro
1425 1430 1435 1440

Pro Ala Asn Gln Leu Pro Trp Pro Val Leu Cys Ser Pro Val Ala Gly
1445 1450 1455

Val Ile Leu Leu Ala Leu Gly Ala Leu Leu Val Leu Gln Leu Ile Arg
1460 1465 1470

Arg Arg Arg Arg Glu His Gly Ala Leu Trp Leu Pro Pro Gly Phe Thr
1475 1480 1485

Arg Arg Pro Arg Thr Gln Ser Ala Pro His Arg Arg Arg Pro Pro Leu
1490 1495 1500

Gly Glu Asp Ser Ile Gly Leu Lys Ala Leu Lys Pro Lys Ala Glu Val
1505 1510 1515 1520

Asp Glu Asp Gly Val Val Met Cys Ser Gly Pro Glu Glu Gly Glu Glu
1525 1530 1535

Val Gly Gln Ala Glu Glu Thr Gly Pro Pro Ser Thr Cys Gln Leu Trp
1540 1545 1550

Ser Leu Ser Gly Gly Cys Gly Ala Leu Pro Gln Ala Ala Met Leu Thr
1555 1560 1565

Pro Pro Gln Glu Ser Glu Met Glu Ala Pro Asp Leu Asp Thr Arg Gly
1570 1575 1580

Pro Asp Gly Val Thr Pro Leu Met Ser Ala Val Cys Cys Gly Glu Val
1585 1590 1595 1600

Gln Ser Gly Thr Phe Gln Gly Ala Trp Leu Gly Cys Pro Glu Pro Trp
1605 1610 1615

Glu Pro Leu Leu Asp Gly Gly Ala Cys Pro Gln Ala His Thr Val Gly
1620 1625 1630

Thr Gly Glu Thr Pro Leu His Leu Ala Ala Arg Phe Ser Arg Pro Thr
1635 1640 1645

Ala Ala Arg Arg Leu Leu Glu Ala Gly Ala Asn Pro Asn Gln Pro Asp
1650 1655 1660

Arg Ala Gly Arg Thr Pro Leu His Ala Ala Val Ala Ala Asp Ala Arg
1665 1670 1675 1680

Glu Val Cys Gln Leu Leu Leu Arg Ser Arg Gln Thr Ala Val Asp Ala
1685 1690 1695

Arg Thr Glu Asp Gly Thr Thr Pro Leu Met Leu Ala Ala Arg Leu Ala
1700 1705 1710

Val Glu Asp Leu Val Glu Glu Leu Ile Ala Ala Gln Ala Asp Val Gly
1715 1720 1725

Ala Arg Asp Lys Trp Gly Lys Thr Ala Leu His Trp Ala Ala Ala Val
1730 1735 1740

Asn Asn Ala Arg Ala Ala Arg Ser Leu Leu Gln Ala Gly Ala Asp Lys
1745 1750 1755 1760

Asp Ala Gln Asp Asn Arg Glu Gln Thr Pro Leu Phe Leu Ala Ala Arg
1765 1770 1775

Glu Gly Ala Val Glu Val Ala Gln Leu Leu Leu Gly Leu Gly Ala Ala
1780 1785 1790

Arg Glu Leu Arg Asp Gln Ala Gly Leu Ala Pro Ala Asp Val Ala His
1795 1800 1805

Gln Arg Asn His Trp Asp Leu Leu Thr Leu Leu Glu Gly Ala Gly Pro
1810 1815 1820

Pro Glu Ala Arg His Lys Ala Thr Pro Gly Arg Glu Ala Gly Pro Phe
1825 1830 1835 1840

Pro Arg Ala Arg Thr Val Ser Val Ser Val Pro Pro His Gly Gly Gly
1845 1850 1855

Ala Leu Pro Arg Cys Arg Thr Leu Ser Ala Gly Ala Gly Pro Arg Gly
1860 1865 1870

Gly Gly Ala Cys Leu Gln Ala Arg Thr Trp Ser Val Asp Leu Ala Ala
1875 1880 1885

Arg Gly Gly Gly Ala Tyr Ser His Cys Arg Ser Leu Ser Gly Val Gly
1890 1895 1900

Ala Gly Gly Gly Pro Thr Pro Arg Gly Arg Arg Phe Ser Ala Gly Met
1905 1910 1915 1920

Arg Gly Pro Arg Pro Asn Pro Ala Ile Met Arg Gly Arg Tyr Gly Val
1925 1930 1935

Ala Ala Gly Arg Gly Gly Arg Val Ser Thr Asp Asp Trp Pro Cys Asp
1940 1945 1950

Trp Val Ala Leu Gly Ala Cys Gly Ser Ala Ser Asn Ile Pro Ile Pro
1955 1960 1965

Pro Pro Cys Leu Thr Pro Ser Pro Glu Arg Gly Ser Pro Gln Leu Asp
1970 1975 1980

Cys Gly Pro Pro Ala Leu Gln Glu Met Pro Ile Asn Gln Gly Gly Glu
1985 1990 1995 2000

Gly Lys Lys

<210> 901
<211> 52
<212> DNA
<213> Artificial Sequence

<220>
<223> DLL4 Egf2 reverse1

<400> 901
cagatcctct tctgagatga gttttttgttc gttgagatct tggtcacaaa ac 52

<210> 902
<211> 5882
<212> DNA
<213> Artificial Sequence

<220>

<223> pGL4. 26

<400> 902

ggcct aact g gccggt acct gagct cgct a gcct cgagga t at caagat c t ggcct cggc 60

ggccaagct t agacact aga gggt at at aa t ggaagct cg act t ccagct t ggcaat ccg 120

gt act gt t gg t aaagccacc at ggaagat g ccaaaaacat t aagaagggc ccagcgccat 180

t ct acccact cgaagacggg accgccggcg agcagct gca caaagccat g aagcgct acg 240

ccct ggt gcc cggcaccat c gcct t t accg acgcacat at cgaggt ggac at t acct acg 300

ccgagt act t cgagat gagc gt t cggct gg cagaagct at gaagcgct at gggct gaat a 360

caaaccat cg gat cgt ggt g t gcagcgaga at agct t gca gt t ct t cat g cccgt gt t gg 420

gt gccct gt t cat cggt gt g gct gt ggccc cagct aacga cat ct acaac gagcgcgagc 480

t gct gaacag cat gggcat c agccagccca ccgt cgt at t cgt gagcaag aaagggct gc 540

aaaagat cct caacgt gcaa aagaagct ac cgat cat aca aaagat cat c at cat ggat a 600

gcaagaccga ct accagggc t t ccaaagca t gt acacct t cgt gact t cc cat t t gccac 660

ccggct t caa cgagt acgac t t cgt gcccg agagct t cga ccgggacaaa accat cgccc 720

t gat cat gaa cagt agt ggc agt accggat t gcccaaggg cgt agccct a ccgcaccgca 780

ccgct t gt gt ccgat t cagt cat gcccgcg accccat ct t cggcaaccag at cat ccccg 840

acaccgct at cct cagcgt g gt gccat t t c accacggct t cggcat gt t c accacgct gg 900

gct act t gat ct gcggct t t cgggt cgt gc t cat gt accg ct t cgaggag gagct at t ct 960

t gcgcagct t gcaagact at aagat t caat ct gccct gct ggt gcccaca ct at t t agct 1020

t ct t cgct aa gagcact ct c at cgacaagt acgacct aag caact t gcac gagat cgcca 1080

gcggcggggc gccgct cagc aaggaggt ag gt gaggccgt ggccaaacgc t t ccacct ac 1140

caggcat ccg ccagggct ac ggcct gacag aaacaaccag cgccat t ct g at caccccg 1200

aaggggacga caagcct ggc gcagt aggca aggt ggt gcc ct t ct t cgag gct aaggt gg 1260

t ggact t gga caccggt aag acact gggt g t gaaccagcg cggcgagct g t gcgt ccgt g 1320

gccccat gat cat gagcggc t acgt t aaca accccgaggc t acaaacgct ct cat cgaca 1380

aggacggct g gct gcacagc ggcgacat cg cct act ggga cgaggacgag cact t ct t ca 1440

t cgt ggaccg gct gaagagc ct gat caaat acaagggct a ccaggt agcc ccagccgaac 1500

t ggagagcat cct gct gcaa caccccaaca t ct t cgacgc cggggt cgcc ggcct gcccg 1560

acgacgat gc cggcgagct g cccgccgcag t cgt cgt gct ggaacacggt aaaaccat ga 1620

ccgagaagga gat cgt ggac t at gt ggcca gccaggt t ac aaccgccaag aagct gcgcg 1680

gt ggt gt t gt gt t cgt ggac gaggt gcct a aaggact gac cggcaagt t g gacgcccgca 1740

agat ccgcga gat t ct cat t aaggccaaga agggcggcaa gat cgccgt g t aat aat t ct 1800

agagt cgggg cggccggccg ct t cgagcag acat gat aag at acat t gat gagt t t ggac 1860

aaaccacaac t agaat gcag t gaaaaaaat gct t t at t t g t gaaat t t gt gat gct at t g 1920

ct t t at t t gt aaccat t at a agct gcaat a aacaagt t aa caacaacaat t gcat t cat t 1980

t t at gt t t ca ggt t cagggg gaggt gt ggg aggt t t t t t a aagcaagt aa aacct ct aca 2040

aat gt ggt aa aat cgat aag gat ccgt t t g cgt at t gggc gct ct t ccgc t gat ct gcgc 2100

agcaccat gg cct gaaat aa cct ct gaaag aggaact t gg t t agct acct t ct gaggcgg 2160

aaagaaccag ct gt ggaat g t gt gt cagt t agggt gt gga aagt ccccag gct ccccagc 2220

aggcagaagt at gcaaagca t gcat ct caa t t agt cagca accaggt gt g gaaagt cccc 2280

aggct cccca gcaggcagaa gt at gcaaag cat gcat ct c aat t agt cag caaccat agt 2340

cccgcccct a act ccgccca t cccgcccct aact ccgccc agt t ccgccc at t ct ccgcc 2400

ccat ggct ga ct aat t t t t t t t at t t at gc agaggccgag gccgcct ct g cct ct gagct 2460

at t ccagaag t agt gaggag gct t t t t t gg aggcct aggc t t t t gcaaaa agct cgat t c 2520

t t ct gacact agcgccacca t gaagaagcc cgaact cacc gct accagcg t t gaaaaat t 2580

t ct cat cgag aagt t cgaca gt gt gagcga cct gat gcag t t gt cggagg gcgaagagag 2640

ccgagcct t c agct t cgat g t cggcggacg cggct at gt a ct gcgggt ga at agct gcgc 2700

t gat ggct t c t acaaagacc gct acgt gt a ccgccact t c gccagcgct g cact acccat 2760

ccccgaagt g t t ggacat cg gcgagt t cag cgagagcct g acat act gca t cagt agacg 2820

cgcccaaggc gt t act ct cc aagacct ccc cgaaacagag ct gcct gct g t gt t acagcc 2880

t gt cgccgaa gct at ggat g ct at t gccgc cgccgacct c agt caaacca gcggct t cgg 2940

cccat t cggg ccccaaggca t cggccagt a cacaacct gg cgggat t t ca t t t gcgccat 3000

t gct gat ccc cat gt ct acc act ggcagac cgt gat ggac gacaccgt gt ccgccagcgt 3060

agct caagcc ct ggacgaac t gat gct gt g ggccgaagac t gt cccgagg t gcgccacct 3120

cgt ccat gcc gact t cggca gcaacaacgt cct gaccgac aacggccgca t caccgccgt 3180

aat cgact gg t ccgaagct a t gt t cgggga cagt cagt ac gaggt ggcca acat ct t ct t 3240

ct ggcggccc t ggct ggct t gcat ggagca gcagact cgc t act t cgagc gccggcat cc 3300

cgagct ggcc ggcagccct c gt ct gcgagc ct acat gct g cgcat cggcc t ggat cagct 3360

ct accagagc ct cgt ggacg gcaact t cga cgat gct gcc t gggct caag gccgct gcga 3420

t gccat cgt c cgcagcgggg ccggcaccgt cggt cgcaca caaat cgct c gccggagcgc 3480

agccgt at gg accgacggct gcgt cgaggt gct ggccgac agcggcaacc gccggcccag 3540

t acacgaccg cgcgct aagg aggt aggt cg agt t t aaact ct agaaccgg t cat ggccgc 3600

aat aaaat at ct t t at t t t c at t acat ct g t gt gt t ggt t t t t t gt gt gt t cgaact aga 3660

t gct gt cgac cgat gccct t gagagcct t c aacccagt ca gct cct t ccg gt gggcgcgg 3720

ggcat gact a t cgt cgccgc act t at gact gt ct t ct t t a t cat gcaact cgt aggacag 3780

gt gccggcag cgct ct t ccg ct t cct cgct cact gact cg ct gcgct cgg t cgt t cggct 3840

gcggcgagcg gt at cagct c act caaaggc ggt aat acgg t t at ccacag aat cagggga 3900

t aacgcagga aagaacat gt gagcaaaagg ccagcaaaag gccaggaacc gt aaaaaggc 3960

cgcgt t gct g gcgt t t t t cc at aggct ccg ccccct gac gagcat caca aaaat cgacg 4020

ct caagt cag aggt ggcgaa acccgacagg act at aaaga t accaggcgt t t ccccct gg 4080

aagct ccct c gt gcgct ct c ct gt t ccgac cct gccgct t accggat acc t gt ccgcct t 4140

t ct ccct t cg ggaagcgt gg cgct t t ct ca t agct cacgc t gt aggt at c t cagt t cggt 4200

gt aggt cgt t cgct ccaagc t gggct gt gt gcacgaaccc cccgt t cagc ccgaccgct g 4260

cgcct t at cc ggt aact at c gt ct t gagt c caacccggt a agacacgact t at cgccact 4320

ggcagcagcc act ggt aaca ggat t agcag agcgaggt at gt aggcggt g ct acagagt t 4380

ct t gaagt gg t ggcct aact acggct acac t agaagaaca gt at t t ggt a t ct gcgct ct 4440

gct gaagcca gt t acct t cg gaaaaagagt t ggt agct ct t gat ccggca aacaaaccac 4500

cgct ggt agc ggt ggt t t t t t t gt t t gcaa gcagcagat t acgcgcagaa aaaaaggat c 4560

t caagaagat cct t t gat ct t t t ct acggg gt ct gacgct cagt ggaacg aaaact cacg 4620

t t aagggat t t t ggt cat ga gat t at caaa aaggat ct t c acct agat cc t t t t aaat t a 4680

aaaat gaagt t t t aaat caa t ct aaagt at at at gagt aa act t ggt ct g acagcggccg 4740

caaat gct aa accact gcag t ggt t accag t gct t gat ca gt gaggcacc gat ct cagcg 4800

at ct gcct at t t cgt t cgt c cat agt ggcc t gact ccccg t cgt gt agat cact acgat t 4860

cgt gagggct t accat cagg ccccagcgca gcaat gat gc cgcgagagcc gcgt t caccg 4920

gcccccgat t t gt cagcaat gaaccagcca gcagggaggg ccgagcgaag aagt ggt cct 4980

gct act t t gt ccgcct ccat ccagt ct at g agct gct gt c gt gat gct ag agt aagaagt 5040

t cgccagt ga gt agt t t ccg aagagt t gt g gccat t gct a ct ggcat cgt ggt at cacgc 5100

t cgt cgt t cg gt at ggct t c gt t caact ct ggt t cccagc ggt caagccg ggt cacat ga 5160

t cacccat at t at gaagaaa t gcagt cagc t cct t agggc ct ccgat cgt t gt cagaagt 5220

aagt t ggccg cggt gt t gt c gct cat ggt a at ggcagcac t acacaat t c t ct t accgt c 5280

at gccat ccg t aagat gct t t t ccgt gacc ggcgagt act caaccaagt c gt t t t gt gag 5340

t agt gt at ac ggcgaccaag ct gct ct t gc ccggcgt ct a t acgggacaa caccgcgcca 5400

cat agcagt a ct t t gaaagt gct cat cat c gggaat cgt t ct t cggggcg gaaagact ca 5460

aggat ct t gc cgct at t gag at ccagt t cg at at agccca ct ct t gcacc cagt t gat ct 5520

t cagcat ct t t t act t t cac cagcgt t t cg gggt gt gcaa aaacaggcaa gcaaaat gcc 5580

gcaaagaagg gaat gagt gc gacacgaaaa t gt t ggat gc t cat act cgt cct t t t t caa 5640

t at t at t gaa gcat t t at ca gggt t act ag t acgt ct ct c aaggat aagt aagt aat at t 5700

aaggt acggg aggt at t gga caggccgcaa t aaaat at ct t t at t t t cat t acat ct gt g 5760

t gt t ggt t t t t t gt gt gaat cgat agt act aacat acgct ct ccat caaa acaaaacgaa 5820

acaaaacaaa ct agcaaaat aggct gt ccc cagt gcaagt gcaggt gcca gaacat t t ct 5880

<210> 903

<211> 4188

<212> DNA

<213> Artificial Sequence

<220>

<223> pFUSE-hIgG2-Fc2

<400> 903

ggatctgcga tcgctccggt gcccgtcagt gggcagagcg cacatcgccc acagtccccg 60
agaagttggg gggaggggtc ggcaattgaa cgggtgccta gagaaggtgg cgcggggtaa 120
actgggaaag tgatgtcgtg tactggctcc gcctttttcc cgagggtggg ggagaaccgt 180
atataagtgc agtagtcgcc gtgaacgttc ttttttcgcaa cgggttt gcc gccagaacac 240
agctgaagct tcgaggggct cgcatctctc ctt cacgcgc ccgccgccct acctgaggcc 300
gccatccacg ccggttgagt cgcgttctgc cgcctcccgc ctgtggtgcc tcctgaactg 360
cgtccgccgt ctaggtaagt tt aaagctca ggtcgagacc gggcctttgt ccggcgctcc 420
ctt ggagcct acctagactc agccggctct ccacgctttg cctgaccctg ctt gctcaac 480
tctacgtctt tgttt cgttt tctgttctgc gccgttacag atccaagctg tgaccggcgc 540
ctacctgaga tcaccggcga aggagggcca ccatgtacag gatgcaactc ctgtctt gca 600
ttgcactaag tcttgcactt gtcacgaatt cgatatcggc catggttaga tctgtggagt 660
gcccacctt g cccagcacca cctgtggcag gacctt cagt ctt cct ctt c ccccaaaac 720
ccaaggacac cctgatgatc ttccagaaccc ctgaggtcac gtgcgtggtg gtggacgtga 780
gccacgaaga ccccgaggtc cagttcaact ggtacgtgga cggcatggag gtgcataatg 840
ccaagacaaa gccacgggag gagcagttca acagcacgtt ccgtgtggtc agcgtcctca 900
ccgtcgtgca ccaggactgg ctgaacggca aggagtacaa gtgcaaggtc tccaacaaag 960
gcctcccagc ccccatcgag aaaaccatct ccaaaaccaa agggcagccc cgagaaccac 1020
aggtgtacac cctgccccca tcccgggagg agatgaccaa gaaccaggtc agcctgacct 1080
gcctggtcaa aggcttctac cccagcgaca tcgccgtgga gtgggagagc aatgggcagc 1140
cggagaacaa ctacaagacc acacctccca tgctggactc cgacggctcc ttcttcctct 1200
acagcaagct caccgtggac aagagcaggt ggcagcaggg gaacgtcttc tcatgctccg 1260
tgatgcatga ggctctgcac aaccactaca cacagaagag cctctccctg tctccgggta 1320

aat gagt gcc acggct agct ggccagacat gat aagat ac at t gat gagt t t ggacaaac 1380

cacaact aga at gcagt gaa aaaaat gct t t at t t gt gaa at t t gt gat g ct at t gct t t 1440

at t t gt aacc at t at aagct gcaat aaaca agt t aacaac aacaat t gca t t cat t t t at 1500

gt t t caggt t caggggggagg t gt gggaggt t t t t t aaagc aagt aaaacc t ct acaaat g 1560

t ggt at ggaa t t aat t ct aa aat acagcat agcaaaact t t aacct ccaa at caagcct c 1620

t act t gaat c ct t t t ct gag ggat gaat aa ggcat aggca t caggggct g t t gccaat gt 1680

gcat t agct g t t t gcagcct cacct t ct t t cat ggagt t t aagat at agt gt at t t t ccc 1740

aaggt t t gaa ct agct ct t c at t t ct t t at gt t t t aaat g cact gacct c ccacat t ccc 1800

t t t t t agt aa aat at t caga aat aat t t aa at acat cat t gcaat gaaaa t aaat gt t t t 1860

t t at t aggca gaat ccagat gct caaggcc ct t cat aat a t ccccc agt t t agt agt t gg 1920

act t agggaa caaaggaacc t t t aat agaa at t ggacagc aagaaagcga gct t ct agct 1980

t at cct cagt cct gct cct c t gccacaaag t gcacgcagt t gccggccgg gt cgcgcagg 2040

gcgaact ccc gcccccacgg ct gct cgccg at ct cggt ca t ggccggccc ggaggcgt cc 2100

cggaagt t cg t ggacacgac ct ccgaccac t cggcgt aca gct cgt ccag gccgcgcacc 2160

cacacccagg ccagggt gt t gt ccggcacc acct ggt cct ggaccgcgct gat gaacagg 2220

gt cacgt cgt cccggaccac accggcgaag t cgt cct cca cgaagt cccg ggagaacccg 2280

agccggt cgg t ccagaact c gaccgct ccg gcgacgt cgc gcgcggt gag caccggaacg 2340

gcact ggt ca act t ggccat gat ggct cct cct gt cagga gaggaaagag aagaaggt t a 2400

gt acaat t gc t at agt gagt t gt at t at ac t at gcagat a t act at gcca at gat t aat t 2460

gt caaact ag ggct gcaggg t t cat agt gc cact t t t cct gcact gcccc at ct cct gcc 2520

caccct t t cc caggcat aga cagt cagt ga ct t accaaac t cacaggagg gagaaggcag 2580

aagct t gaga cagacccgcg ggaccgccga act gcgaggg gacgt ggct a gggcggct t c 2640

t t t t at ggt g cgccggccct cggaggcagg gcgct cgggg aggcct agcg gccaat ct gc 2700

ggt ggcagga ggcggggccg aaggccgt gc ct gaccaat c cggagcacat aggagt ct ca 2760

gccccccgcc ccaaagcaag gggaagt cac gcgcct gt ag cgccagcgt g t t gt gaaat g 2820

ggggct t ggg ggggt t gggg ccct gact ag t caaaacaaa ct cccat t ga cgt caat ggg 2880

gt ggagact t ggaaat cccc gt gagt caaa ccgct at cca cgcccat t ga t gt act gcca 2940

aaaccgcat c at cat ggt aa t agcgat gac t aat acgt ag at gt act gcc aagt aggaaa 3000

gt cccat aag gt cat gt act gggcat aat g ccaggcgggc cat t t accgt cat t gacgt c 3060

aat agggggc gt act t ggca t at gat acac t t gat gt act gccaagt ggg cagt t t accg 3120

t aaat act cc acccat t gac gt caat ggaa agt ccct at t ggcgt t act a t gggaacat a 3180

cgt cat t at t gacgt caat g ggcgggggt c gt t gggcggt cagccaggcg ggccat t t ac 3240

cgt aagt t at gt aacgcct g caggt t aat t aagaacat gt gagcaaaagg ccagcaaaag 3300

gccaggaacc gt aaaaaggc cgcgt t gct g gcgt t t t t cc at aggct ccg ccccct gac 3360

gagcatcaca aaaatcgacg ctcaagtcag aggtggcgaa acccgacagg actataaaga 3420

taccaggcgt ttcccctgg aagctccctc gtgcgctctc ctgttccgac cctgccgctt 3480

accggatacc tgtccgcctt tctcccttcg ggaagcgtgg cgctttctca tagctcacgc 3540

tgtaggtatc tcagttcggt gtaggtcgtt cgctccaagc tgggctgtgt gcacgaaccc 3600

cccgttcagc ccgaccgctg cgccttatcc ggtaactatc gtcttgagtc caacccggta 3660

agacacgact tatcgccact ggcagcagcc actggtaaca ggattagcag agcgaggtat 3720

gtaggcggtg ctacagagtt cttgaagtgg tggcctaact acggctacac tagaagaaca 3780

gtatttggta tctgcgctct gctgaagcca gttacctteg gaaaaagagt tggtagctct 3840

tgatccggca aacaaaccac cgctggtagc ggtggttttt ttgttgcaa gcagcagatt 3900

acgcgcagaa aaaaaggatc tcaagaagat cctttgatct tttctacggg gtctgacgct 3960

cagtggaacg aaaactcacg ttaagggatt ttggtcatgg ctagttaatt aacatttaaa 4020

tcagcggccg caataaaata tctttatttt cattacatct gtgtgttggt ttttgtgtg 4080

aatcgtaact aacatacgct ctccatcaaa acaaaacgaa acaaaacaaa ctagcaaaat 4140

aggctgtccc cagtgcaagt gcaggtgcca gaacatttct ctatcgaa 4188

<210> 904

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH1

<400> 904

Gly Tyr Thr Phe Thr Ser Tyr Val Ile Asn

1 5 10