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ANTI-CD3 ANTIBODIES AND USES THEREOF

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said
5 ASCII copy, created on May 3, 2019, is named JBI5135WOPCT1_Sequence_listing.txt and is 588 KB in size.

TECHNICAL FIELD

The disclosure provided herein relates to anti-cluster of differentiation 3 (CD3)-
antibodies, and antigen-binding fragments thereof, capable of specifically binding to human and
10 non-human CD3, and in particular to anti-CD3 antibodies and antigen-binding fragments that are cross-reactive with CD3 of a non-human mammal (e.g., a cynomolgus monkey); prostate specific membrane antigen (PSMA)-antibodies, and antigen-binding fragments thereof, capable of specifically binding to human and non-human PSMA; IL1RAP antibodies, and antigen-binding fragments thereof, capable of specifically binding to human and non-human IL1RAP;
15 CD33 antibodies, and antigen-binding fragments thereof, capable of specifically binding to human and non-human CD33; and bispecific antibodies that are capable of specifically binding CD3; PSMA; IL1RAP; CD33; CD3 and PSMA; CD3 and IL1RAP; or CD3 and CD33. The disclosure also pertains to uses of such antibodies and antigen-binding fragments in the treatment of cancer, autoimmune and/or inflammatory diseases and other conditions.

20 BACKGROUND

Bispecific antibodies and antibody fragments have been explored as a means to recruit cytolytic T cells to kill tumor cells. However, the clinical use of many T cell-recruiting bispecific antibodies has been limited by challenges including unfavorable pharmacokinetics, potential immunogenicity, and manufacturing issues. There thus exists a considerable need for bispecific
25 antibodies that recruit cytolytic T cells to kill tumor cells that exhibit reduced toxicity and favorable manufacturing profiles.

The human CD3 T cell antigen receptor protein complex is composed of six distinct chains: a CD3 γ chain (SwissProt P09693), a CD3 δ chain (SwissProt P04234), two CD3 ϵ chains

(SwissProt P07766), and one CD3 ζ chain homodimer (SwissProt P20963) ($\epsilon \gamma: \epsilon \delta: \zeta \zeta$), which is associated with the T cell receptor α and β chain. This complex plays an important role in coupling antigen recognition to several intracellular signal-transduction pathways. The CD3 complex mediates signal transduction, resulting in T cell activation and proliferation. CD3 is
 5 required for immune response.

SUMMARY

Provided herein are isolated recombinant anti-CD3 antibodies, or antigen-binding fragments thereof, comprising: a heavy chain comprising a heavy chain complementarity determining region (HCDR) 1 comprising SEQ ID NO: 662; a HCDR2 comprising SEQ ID NO:
 10 663; and a HCDR3 comprising SEQ ID NO: 664 and a light chain comprising a light chain complementarity determining region (LCDR) 1 comprising SEQ ID NO: 671, a LCDR2 comprising SEQ ID NO: 673, and a LCDR3 comprising SEQ ID NO: 690; a heavy chain variable region comprising SEQ ID NO: 652 and a light chain variable region comprising SEQ ID NO: 661; a heavy chain comprising SEQ ID NO: 640 and a light chain comprising SEQ ID
 15 NO: 676; or comprising: a heavy chain comprising a HCDR1 comprising SEQ ID NO: 662; a HCDR2 comprising SEQ ID NO: 663; and a HCDR3 comprising SEQ ID NO: 664 and a light chain comprising a LCDR1 comprising SEQ ID NO: 773, a LCDR2 comprising SEQ ID NO: 673, and a LCDR3 comprising SEQ ID NO: 690; a heavy chain variable region comprising SEQ ID NO: 657 and a light chain variable region comprising SEQ ID NO: 678; or a heavy chain
 20 comprising SEQ ID NO: 675 and a light chain comprising SEQ ID NO: 678.

Also provided are isolated recombinant anti-CD3 antibodies or antigen-binding fragments thereof, that specifically bind *Macaca fascicularis* or human CD3d, or CD3e, or CD3e and CD3d with a binding affinity of about 300 nM or less.

In some embodiments, the isolated recombinant anti-CD3 antibodies or antigen-binding
 25 fragments thereof have one, two, three, or four, of the following properties:

- bind human and *Macaca fascicularis* CD3⁺ T lymphocytes with a calculated EC₅₀ of 20 nM or less and bind *Macaca fascicularis* CD3-expressing HEK cells with a calculated EC₅₀ of 40 nM or less, wherein the difference in calculated EC₅₀ between binding CD3⁺ T lymphocytes and binding *Macaca fascicularis* CD3-

expressing HEK cells is less than 5-fold, and wherein the calculated EC₅₀ is measured in a whole cell binding assay at 0 °C using flow cytometry;

- bind recombinant CD3d from human (SEQ ID NO:691), or bind recombinant CD3e from human (SEQ ID NO:636), or recombinant CD3d from *Macaca fascicularis* (SEQ ID NO:692), with an equilibrium dissociation constant (K_D) of 12 nM or less, wherein the K_D is measured using Proteon surface plasmon resonance assay ProteOn XPR36 system at +25°C;
- bind residues 1-6 of CD3e as determined by X-ray crystallography; or
- activate T cells or induces CD69 expression to a similar degree as cOKT3 or SP34-2 as determined by fluorescence-activated cell sorting assay.

In some embodiments, the antibodies or antigen-binding fragments thereof described herein comprise the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2, and the LCDR3 of SEQ ID NOs:662, 663, 664, 671, 673, and 690, respectively; a VH and a VL of SEQ ID NOs:652 and 661, respectively; or a HC and a LC of SEQ ID NOs:640 and 676, respectively.

In some embodiments, the antibodies or antigen-binding fragments thereof described herein comprise the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2, and the LCDR3 of SEQ ID NOs:662, 663, 664, 773, 673, and 690, respectively; a VH and a VL of SEQ ID NOs:657 and 678, respectively or a HC and a LC of SEQ ID NOs:675 and 677, respectively.

Further described herein are bispecific antibodies comprising a first domain that specifically binds CD3 and a second domain that specifically binds a second antigen, wherein the first domain comprises an antibody or antigen-binding fragment thereof described herein.

The bispecific antibodies described herein can comprise a first domain that comprises the HCDR1, HCDR2, the HCDR3, the LCDR1, the LCDR2, and the LCDR3 of SEQ ID NOs:662, 663, 664, 671, 673, and 670, respectively; and a second domain that comprises the the HCDR1, HCDR2, the HCDR3, the LCDR1, the LCDR2, and the LCDR3 of SEQ ID NOs:697, 683, 698, 699, 792, and 686, respectively;

The bispecific antibodies described herein can comprise a first domain that comprises the VH and VL of SEQ ID NOs:652 and 661, respectively; and a second domain that comprises the VH and VL of SEQ ID NOs:681 and 682, respectively.

The bispecific antibodies described herein can comprise a first domain that comprises the HC and LC of SEQ ID NOs:640 and 676, respectively; and a second domain that comprises the HC and LC of SEQ ID NOs:679 and 680, respectively.

The bispecific antibodies described herein can comprise a first domain that comprises the
5 HCDR1, HCDR2, the HCDR3, the LCDR1, the LCDR2, and the LCDR3 of SEQ ID NOs:662, 663, 664, 671, 673, and 670, respectively; and a second domain that comprises the the HCDR1, HCDR2, the HCDR3, the LCDR1, the LCDR2, and the LCDR3 of SEQ ID NOs:704, 705, 706, 707, 708, and 709, respectively.

The bispecific antibodies described herein can comprise a first domain that comprises the
10 VH and VL of SEQ ID NOs:652 and 661, respectively; and a second domain that comprises the VH and VL of SEQ ID NOs:702 and 703, respectively.

The bispecific antibodies described herein can comprise a first domain that comprises the HC and LC of SEQ ID NOs:640 and 676, respectively; and a second domain that comprises the HC and LC of SEQ ID NOs:700 and 701, respectively.

15 The disclosure further provides isolated bispecific CD3×PSMA antibodies comprising a first domain that binds to cells expressing recombinant *Macaca fascicularis* or human CD3d or CD3e with an affinity of 300 nM or less, wherein the binding to cells is measured by flow cytometry, and a second domain that specifically bind PSMA.

In some embodiments, the bispecific CD3×PSMA antibody comprises a first domain
20 that:

- binds human and *Macaca fascicularis* CD3+ T lymphocytes with a calculated EC50 of 20 nM or less and binds *Macaca fascicularis* CD3-expressing HEK cells with a calculated EC50 of 40 nM or less, wherein the difference in calculated EC50 between binding CD3+ T lymphocytes and binding *Macaca fascicularis* CD3-expressing HEK cells is less than 5-fold, and wherein the calculated EC50 is
25 measured in a whole cell binding assay at 0 °C using flow cytometry;
- binds recombinant CD3d from human (SEQ ID NO:691), or binds recombinant CD3e from human (SEQ ID NO:636), or binds recombinant CD3d from *Macaca fascicularis* (SEQ ID NO:692), or binds recombinant CD3e from *Macaca fascicularis* (SEQ ID NO:693) with an equilibrium dissociation constant (KD) of
30

12 nM or less, wherein the KD is measured using Proteon surface plasmon resonance assay ProteOn XPR36 system at +25°C;

- displays no methionine or tryptophan oxidation, or displays no asparagine deamidation, or displays no asparagine isomerization as detected by peptide mapping analysis;
- binds residues 1-6 of CD3e as determined by X-ray crystallography; or
- activates T cells or induces CD69 expression to a similar degree as cOKT3 or SP34-2 as determined by fluorescence-activated cell sorting assay.

Also described are pharmaceutical compositions comprising the antibodies described herein and a pharmaceutically acceptable carrier.

The disclosure further provides methods of producing the antibodies described herein, comprising culturing a host cell comprising a vector comprising a polynucleotide encoding the antibodies or antigen-binding fragments thereof described herein in conditions that the antibody is expressed, and recovering the antibody produced by the host cell. The methods of producing the bispecific CD3×PSMA antibody can comprise combining a monospecific bivalent CD3 antibody having two identical HC1 and two identical LC1 and a monospecific bivalent PSMA antibody having two identical HC2 and two identical LC2 in a mixture of about 1:1 molar ratio; introducing a reducing agent into the mixture; incubating the mixture about ninety minutes to about six hours; removing the reducing agent; and purifying the bispecific CD3×PSMA antibody that comprises the HC1, the LC1, the HC2 and the LC2.

Further described are methods of treating a cancer in a subject, comprising administering a therapeutically effective amount of the isolated antibodies described to the subject in need thereof for a time sufficient to treat the cancer.

The disclosure also provides kits comprising the antibodies described herein. The kits can further comprise reagents for detecting the antibodies and instructions of use.

BRIEF DESCRIPTIONS OF THE DRAWINGS

The summary, as well as the following detailed description, is further understood when read in conjunction with the appended drawings. For the purpose of illustrating the disclosed antibodies and methods, there are shown in the drawings exemplary embodiments of the

antibodies and methods; however, antibodies and methods are not limited to the specific embodiments disclosed. In the drawings:

Figs. 1A and 1B show anti-CD3 antibodies produced in OmniRat. VH (Fig. 1A) and VL (Fig. 1B) sequences of active anti-CD3 mAbs produced in OmniRat were aligned with human germline sequences from IMGT. CDR regions are underlined. Sequence divergence is shown in bold. Fig. 1A discloses SEQ ID NOS 651, 651, 653, 656, 655, 20, 654 and 717 and Fig. 1B discloses SEQ ID NOS 658, 688, 660, 659, 659, 659, 659 and 718, all respectively, in order of appearance.

Fig. 2 shows a cell-based binding assay to assess the binding capacity of individual rat hybridoma supernatants to human purified CD3+ T lymphocytes.

Fig. 3 shows a cell-based binding assay to assess the binding capacity of individual rat hybridoma supernatants to cynomolgus purified CD3+ T lymphocytes.

Fig. 4 shows competition assay results of hybridoma supernatants assessed for their ability to compete with commercial anti-human CD3 antibody SP34-2, which has a known epitope and is cross-reactive with cynomolgus CD3.

Fig. 5 shows representative binding curves of anti-CD3 antibodies on primary human T cells.

Fig. 6 shows representative competition binding curves of anti-CD3 antibodies with AlexaFluor 488 conjugated SP34-2 on primary human T cells.

Fig. 7 shows binding of light chain (LC) engineered BLW-2E6 mAbs to primary human T cells.

Fig. 8 shows binding of heavy chain (HC) engineered BLW-2E6 to primary human T cells.

Fig. 9 shows AlexaFluor™ (AF) 488 CD3 Saturation in Human T Cells by FACS analysis. Acquired mean fluorescence intensity values were plotted as a function of the antibody molecule concentration. K_d values were derived for each donor, and the mean value obtained. The Saturation Binding Constant (K_dT) for human T-Cells was derived to be 5.6 ± 1.0 nM (n=4) and was used herein to determine K_d binding affinities. One human donor was excluded as it failed the viability criteria of being at least 60% during analysis. “LS” identifiers in figure legend refer to individual human T cell donors.

Fig. 10 shows inhibition curves for the bivalent anti CD3 antibodies, CD3B376 and CD3B450, for competing for binding against the AlexaFluor488 SP-34 anti CD3 antibody. IC50 values were derived to be 29 and 60 nM respectively.

Fig. 11 shows sensorgrams of BLW-2E6 variants binding to hCD3 ϵ (1-27)-Tn25.

5 **Figs. 12A-12E** shows thermal stability of anti-CD3 antibodies CD3B376 (Fig. 12A), CD3B450 (Fig. 12B), CD3B389 (Fig. 12C), CD3B467 by DSC (Fig. 12D), and overlay of the thermograms for all the candidates (Fig. 12E).

Figs. 13A-13C show comparisons of the thermal stability of anti-CD3 antibodies overlay of thermograms for CD3B376 and CD3B389 (Fig. 13A); overlay of thermograms for CD3B450 and CD3B467 (Fig. 13B); and overlay of thermograms for CD3B376, CD3B450 and CD3B219 (Fig. 13C).

Fig. 14 shows LNCAP cell binding of a subset of affinity-matured PSMA $\times$ CD3 bispecific antibodies.

15 **Fig. 15** shows LNCAP cell binding of a subset of affinity-matured PSMA $\times$ CD3 bispecific antibodies.

Fig. 16 shows PSMA-negative PC3 cell binding results of affinity-matured PSMA $\times$ CD3 bispecific antibodies.

Fig. 17 shows results of PSMA $\times$ CD3 Affinity Matured Bispecific Abs in a Functional Cell Killing Assay.

20 **Fig. 19** shows antibody-antigen interactions in the CD3B334:CD3 complex. CD3 residues are in ellipses, CD3B334 residues are in boxes.

Fig. 20 shows a primary human and cynomolgus monkey T cell based assay used to determine the capacity of the hybridoma hits to activate T cells as measured by CD69 activation.

25 **Fig. 21** shows anti-tumor efficacy of PS3B79 in LnCAP AR.TB human prostate xenografts in T cell humanized NSG mice. Subcutaneous LnCAP AR.TB tumors were measured twice weekly and the results presented as the mean tumor volume, expressed in mm³ $\pm$ SEM (*, p<0.0001).

30 **Fig. 22** shows anti-tumor efficacy of PS3B90 in LnCAP AR.TB human prostate xenografts in T cell humanized NSG mice. Subcutaneous LnCAP AR.TB tumors were measured twice weekly and the results presented as the mean tumor volume, expressed in mm³ $\pm$ SEM (*, p<0.001).

Figs. 23A-23D show titration curves for Anti-PSMA phage panning hits binding to human LNCaP cells. **Fig. 23A** shows titration curves for hits G9-PSM M18, M25, M50, M52, M56, M57, and M59; **Fig. 23B** shows M52 and M110; **Fig. 23C** shows M85, M87, and M81; and **Fig. 23D** shows M52 and M84. In **Fig. 23D**, Mammalian-expressed supernatants were
5 normalized for Fab expression via octet, and titrated against either human LNCAP, PSMG5 (Cyno-PSMA HEK), or PSMG9 (chimp-PSMA HEK) cells using flowcytometry. Geometric mean fluorescence intensity (GeoMFI) was plotted vs. Fab concentration using GraphPad Prism.

Figs. 24A-24D show titration curves for Anti-PSMA phage panning hits binding to Chimpanzee-PSMA expressing HEK cells shows. (Mammalian Fab Supernatant Titration Curves
10 for Anti-PSMA Phage Panning Hits vs Chimp-PSMA HEK). **Fig. 24A** shows titration curves for hits G9-PSM M18, M25, M50, M52, M56, M57, and M59; **Fig. 24B** shows M52 and M110; **Fig. 24C** shows M81, M52, M85, and M87; and **Fig. 24D** shows M52 and M84. In **Fig. 24D**, Mammalian-expressed supernatants were normalized for Fab expression via octet, and titrated against either human LNCAP, PSMG5 (Cyno-PSMA HEK), or PSMG9 (chimp-PSMA HEK)
15 cells using flowcytometry. Geometric mean fluorescence intensity (GeoMFI) was plotted vs. Fab concentration using GraphPad Prism.

Figs. 25A-25D show titration curves for Anti-PSMA phage panning hits binding to Cynomolgus monkey PSMA-expressing HEK cells. (Mammalian Fab Supernatant Titration Curves for Anti-PSMA Phage Panning Hits vs Cyno PSMA HEK). **Fig. 25A** shows titration
20 curves for hits G9-PSM M18, M25, M50, M52, M56, M57, and M59; **Fig. 25B** shows M52 and M110; **Fig. 25C** shows M81, M52, M85, and M87; and **Fig. 25D** shows M52 and M84. In **Fig. 25D**, Mammalian-expressed supernatants were normalized for Fab expression via octet, and titrated against either human LNCAP, PSMG5 (Cyno-PSMA HEK), or PSMG9 (chimp-PSMA HEK) cells using flow cytometry. Geometric mean fluorescence intensity (GeoMFI) was plotted
25 vs. Fab concentration using GraphPad Prism.

Fig. 26 shows the overall structure of PSMM84 Fab bound to human PSMA ECD homodimer.

Fig. 27 shows a close view of PSMA main interactions with the PSMB83 Light Chain.

Fig. 28 shows a close view of PSMA main interactions with the PSMB83 Heavy Chain.

Fig. 29 shows the comparison of epitope residues of PSMB83 within the sequences of human (SEQ ID NO: 719), mouse (SEQ ID NO: 720) and cynomolgus monkey (cyno) (SEQ ID NO: 721) PSMA. Epitope residues are shaded and sequence divergence is shown by underline.

Fig. 30 shows the paratope residues of PSMB83. CDRs are underlined and paratope residues are shaded. Fig. 30 discloses SEQ ID NOS 722-727, respectively, in order of appearance.

Fig. 31 shows an interaction map with direct contacts made between PSMA and PSMM84. Van der Waals interactions are shown as dashed lines and H-bonds are solid lines with arrows pointing to the backbone atoms.

10 **Fig. 32** shows expression levels of anti-PSMA Fab clones derived from PSMM84 as compared to expression of parent PSMB83. Raw luminescence numbers were plotted against the log concentration

Fig. 33 shows binding to human PSMA of anti-PSMA Fab clones derived from PSMB83 as compared to binding of parent PSMM84. Raw luminescence numbers were plotted against
15 the log concentration.

Fig. 34 shows binding to cyno PSMA of anti-PSMA Fab clones derived from PSMB83 as compared to binding of parent PSMB83. Raw luminescence numbers were plotted against the log concentration.

Fig. 35 shows IC3B19 and IC3B34 Ex Vivo Mediated T cell Cytotoxicity of LAMA-84
20 cells in Whole Blood after 48 hours. The concentration of IC3B19 and IC3B34 is provided in the table in the lower part of the figure.

Fig. 36 shows IC3B19 and IC3B34 Ex Vivo Mediated T-cell Activation in Whole Blood after 48 hours. The concentration of IC3B19 and IC3B34 is provided in the table in the lower part of the figure.

25 **Figs. 37-56** show IC3B19 and IC3B34 mediated engagement of T cells and IL1RAP+ target cell line LAMA-84 (endogenous and exogenously added tumor cells). Supernatants were evaluated for 10 pro-inflammatory cytokines from whole blood (n=15 donors) cytotoxicity and T-cell activation assays with exogenous LAMA-84 IL1RAP+ tumor cell line added. For these figures, statistically significant differences are shown in bold text.

30 **Figs. 37A-37B** show T cell IL-1beta release mediated by IC3B19 and IC3B34 (Fig. 37A) and corresponding 4PL regression parameter estimates (Fig. 37B) after 24 hours.

Figs. 38A-38B show T cell IL-1beta release mediated by IC3B19 and IC3B34 (Fig. 38A) and corresponding 4PL regression parameter estimates (Fig. 38B) after 48 hours.

Figs. 39A-39B show T cell IL-2 release mediated by IC3B19 and IC3B34 (Fig. 39A) and corresponding 4PL regression parameter estimates (Fig. 39B) after 24 hours.

5 **Figs. 40A-40B** show T cell IL-2 release mediated by IC3B19 and IC3B34 (Fig. 40A) and corresponding 4PL regression parameter estimates (Fig. 40B) after 48 hours.

Figs. 41A-41B show T cell IL-4 release mediated by IC3B19 and IC3B34 (Fig. 41A) and corresponding 4PL regression parameter estimates (Fig. 41B) after 24 hours.

Fig. 42 shows T cell IL-4 release mediated by IC3B19 and IC3B34 after 48 hours.

10 **Figs. 43A-43B** show T cell IL-6 release mediated by IC3B19 and IC3B34 (Fig. 43A) and corresponding 4PL regression parameter estimates (Fig. 43B) after 24 hours.

Fig. 44 shows T cell IL-6 release mediated by IC3B19 and IC3B34 after 48 hours.

Fig. 45 shows T cell IL-8 release mediated by IC3B19 and IC3B34 after 24 hours.

Fig. 46 shows T cell IL-8 release mediated by IC3B19 and IC3B34 after 48 hours.

15 **Figs. 47A-47B** show T cell IL-10 release mediated by IC3B19 and IC3B34 (Fig. 47A) and corresponding 4PL regression parameter estimates (Fig. 47B) after 24 hours.

Figs. 48A-48B show T cell IL-10 release mediated by IC3B19 and IC3B34 (Fig. 48A) and corresponding 4PL regression parameter estimates (Fig. 48B) after 48 hours.

Fig. 49 shows T cell IL-12p70 release mediated by IC3B19 and IC3B34 after 24 hours.

20 **Fig. 50** shows T cell IL-12p70 release mediated by IC3B19 and IC3B34 after 48 hours.

Fig. 51 shows T cell IL-13 release mediated by IC3B19 and IC3B34 after 24 hours.

Figs. 52A-52B show T cell IL-13 release mediated by IC3B19 and IC3B34 (Fig. 52A) and corresponding 4PL regression parameter estimates (Fig. 52B) after 48 hours.

25 **Figs. 53A-53B** show T cell IFN-gamma release mediated by IC3B19 and IC3B34 (Fig. 53A) and corresponding 4PL regression parameter estimates (Fig. 53B) after 24 hours.

Figs. 54A-54B show T cell IFN-gamma release mediated by IC3B19 and IC3B34 (Fig. 54A) and corresponding 4PL regression parameter estimates (Fig. 54B) after 48 hours.

Figs. 55A-55B show T cell TNF-alpha release mediated by IC3B19 and IC3B34 (Fig. 55A) and corresponding 4PL regression parameter estimates (Fig. 55B) after 24 hours.

30 **Figs. 56A-56B** show T cell TNF-alpha release mediated by IC3B19 and IC3B34 (Fig. 56A) and corresponding 4PL regression parameter estimates (Fig. 56BB) after 48 hours.

Fig. 57 shows IC3B19 and IC3B34, but not the bispecific antibodies with null arms (IAPB57×B23B49 or B23B39×CD3B219), induced target specific cytotoxicity in NCI-H1975 cells. In this assay, the cytotoxicity EC50s vary three-fold between IC3B19 and IC3B34, with values of 0.018 and 0.057 nM, respectively.

5 **Fig. 58** shows Anti-Tumor Efficacy of IAPB57×CD3B376 in H1975 Human NSCLC Xenografts in T cell Humanized NSG Mice. Subcutaneous H1975 tumors were measured twice weekly and the results presented as the average tumor volume, expressed in mm³ ± SEM, *p<0.0001.

Fig. 59 shows a comparison of isoelectric points for various anti-PSMA constructs.

10 **Fig. 60** plots change in wavelength compared to CNTO5825 control molecule. Control CNTO607 shows characteristically strong self-interaction. Error bars represent standard deviations from triplicate measurements.

Fig. 61 shows a comparison of retention times on IgG and control columns in an anti-PSMA cross-interaction assay.

15 **Figs. 62A-62B** show *ex vivo* assessment of CD33×CD3 bispecific antibodies using anti-CD3 arm CD3B219 and CD3B376 cytotoxicity of blasts and T cell activation in fresh AML patient whole blood. FIG. 2A shows the percent of total cell cytotoxicity of AML cells using CD33 bispecific antibodies or the CD3xnull controls. FIG. 2B shows T cell activation induced by CD33 bispecific antibodies or the CD3xnull controls. No Fc blocker was added.

20 **Figs. 63A-63C** show CD33×CD3 T-cell mediated cytotoxicity assays. CD33×CD3 bispecific antibodies using anti-CD3 arm CD3B219 and anti-CD3B376 were incubated with human pan T cells and AML cell lines that are either wildtype (KG1, FIG. 3A), heterozygous (SH2, FIG. 3B) or homozygous (OCIAML3, FIG. 3C) for the CD33 SNP rs12459419 mutation. After 48 hr at 37°C, 5% CO₂, total tumor cell cytotoxicity was measured by flow cytometry.

25 **Figs. 64A-64B** show *ex vivo* assessment of C33B904 antibodies paired with either CD3B219 or CD3B376 on the cytotoxicity of MOLM-13 cells exogenously added to normal healthy human whole blood (N=6 donors): Percent of cytotoxicity of MOLM-13 cells (FIG. 4A) and CD33⁺ CD14⁺ monocytes (FIG. 4B) using CD33×CD3 bispecifics and respective null×CD3 controls at 48 hrs.

30 **Figs. 65A-65B** show *ex vivo* assessment of CD33×CD3 bispecific antibodies using anti-CD3 arm CD3B219 and CD3B376 on the cytotoxicity of monocytes and T cell activation in

fresh whole blood from six normal cynomolgous monkey donors. FIG. 5A shows the percent of total cell cytotoxicity of CD33⁺CD14⁺ cyno monocytes using CD33 bispecific antibodies or their CD3xnull controls. FIG. 5B shows T cell activation induced by CD33 bispecific antibodies or their CD3xnull controls. No Fc blocker was added.

5 **Fig. 66** shows anti-tumor efficacy of C3CB189 in MOLM-13 human AML xenografts in T cell humanized NSG mice. Disseminated MOLM-13 tumors were imaged for bioluminescence (BLI) twice weekly and the results presented as average radiance (p/s/cm²/sr) ± SEM (n=8-10/group). *p≤ 0.0001 for treatment vs. control, calculated by two-way ANOVA with Bonferroni test.

10 **Fig. 67** shows survival of animals treated with C3CB189 in MOLM-13 Human AML xenografts in T cell humanized NSG mice. Survival of MOLM-13 bearing mice is graphically represented using a Kaplan-Meier curve and evaluated by Log-rank (Mantel-Cox) test. *p≤ 0.0001 for treatment vs. control groups.

15 **Fig. 68** shows anti-tumor efficacy of C3CB88 in MOLM-13 human AML xenografts in T cell humanized NSG mice. Disseminated MOLM-13 tumors were imaged for bioluminescence (BLI) twice weekly and the results presented as average radiance (p/s/cm²/sr) ± SEM (n=8-10/group). *p≤ 0.0001 for treatment vs. control, calculated by two-way ANOVA with Bonferroni test.

20 **Fig. 69** shows survival of animals treated with C3CB88 in MOLM-13 human AML xenografts in T cell humanized NSG mice. Survival of MOLM-13 bearing mice is graphically represented using a Kaplan-Meier curve and evaluated by Log-rank (Mantel-Cox) test. *p≤ 0.05 for treatment vs. control groups.

Figure 70 shows the alignment of select anti-TMEFF2 antibody heavy chain variable regions (VH). The VH regions are identified by their SEQ ID NO: at the beginning of each row.

25 **Figure 71** shows the alignment of select anti-TMEFF2 antibody light chain variable regions (VL). The VL regions are identified by their SEQ ID NO: at the beginning of each row.

Figure 72 shows the reduction in mean tumor volume of each mouse treated with 0.5 mg/kg TMCB132 in an *ex vivo* LnCaP prostate cancer model in male NGS mice.

30 **Figure 73** shows efficacy of TMEB762xCD3B376 in established LNCaP Xenografts in T Cell Humanized NSG Mice.

Figure 74 shows T-cell activation in LnCaP prostate cancer cells in response to administration of TMCB132.

Figure 75 shows T cell-mediated cytotoxicity of TMCB132.

Figure 76 shows the antitumor efficacy of TMCB132 in T-cell humanized mice.

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DETAILED DESCRIPTION OF THE INVENTION

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as though fully set forth.

It is to be understood that the terminology used herein is for the purpose of describing
10 particular embodiments only and is not intended to be limiting. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains.

Although any methods and materials similar or equivalent to those described herein may be used in the practice for testing of the present invention, exemplary materials and methods are
15 described herein. In describing and claiming the present invention, the following terminology will be used.

As used in this specification and the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to “a cell” includes a combination of two or more cells, and the like.

20 “Specific binding” or “specifically binds” or “binds” refers to an antibody binding to an antigen or an epitope within the antigen with greater affinity than for other antigens. Typically, the antibody binds to the antigen or the epitope within the antigen with an equilibrium dissociation constant (K_D) of about 5×10^{-8} M or less, for example about 1×10^{-9} M or less, about 1×10^{-10} M or less, about 1×10^{-11} M or less, or about 1×10^{-12} M or less, typically with the K_D that
25 is at least one hundred-fold less than its K_D for binding to a non-specific antigen (e.g., BSA, casein). The dissociation constant may be measured using standard procedures. Antibodies that specifically bind to the antigen or the epitope within the antigen may, however, have cross-reactivity to other related antigens, for example to the same antigen from other species (homologs), such as human or monkey, for example *Macaca fascicularis* (cynomolgus, cyno) or
30 *Pan troglodytes* (chimpanzee, chimp). While a monospecific antibody specifically binds one

antigen or one epitope, a bispecific antibody specifically binds two distinct antigens or two distinct epitopes.

“Antibodies” is meant in a broad sense and includes immunoglobulin molecules including monoclonal antibodies including murine, human, humanized and chimeric monoclonal antibodies, antigen binding fragments, bispecific or multispecific antibodies, dimeric, tetrameric or multimeric antibodies, single chain antibodies, domain antibodies and any other modified configuration of the immunoglobulin molecule that comprises an antigen binding site of the required specificity. “Full length antibody molecules” are comprised of two heavy chains (HC) and two light chains (LC) inter-connected by disulfide bonds as well as multimers thereof (e.g. IgM). Each heavy chain is comprised of a heavy chain variable region (VH) and a heavy chain constant region (comprised of domains CH1, hinge, CH2 and CH3). Each light chain is comprised of a light chain variable region (VL) and a light chain constant region (CL). The VH and the VL regions may be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with framework regions (FR). Each VH and VL is composed of three CDRs and four FR segments, arranged from amino-to-carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4.

“Complementarity determining regions (CDR)” are antibody regions that bind an antigen. CDRs may be defined using various delineations such as Kabat (Wu et al. (1970) J Exp Med 132: 211-50) (Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md., 1991), Chothia (Chothia et al. (1987) J Mol Biol 196: 901-17), IMGT (Lefranc et al. (2003) Dev Comp Immunol 27: 55-77) and AbM (Martin and Thornton (1996) J Biomol Biol 263: 800-15). The correspondence between the various delineations and variable region numbering are described (see e.g. Lefranc et al. (2003) Dev Comp Immunol 27: 55-77; Honegger and Pluckthun, (2001) J Mol Biol 309:657-70; International ImMunoGeneTics (IMGT) database; Web resources, <http://www.imgt.org>). Available programs such as abYsis by UCL Business PLC may be used to delineate CDRs. The term “CDR”, “HCDR1”, “HCDR2”, “HCDR3”, “LCDR1”, “LCDR2” and “LCDR3” as used herein includes CDRs defined by any of the methods described supra, Kabat, Chothia, IMGT or AbM, unless otherwise explicitly stated in the specification.

Immunoglobulins may be assigned to five major classes, IgA, IgD, IgE, IgG and IgM, depending on the heavy chain constant domain amino acid sequence. IgA and IgG are further

sub-classified as the isotypes IgA1, IgA2, IgG1, IgG2, IgG3 and IgG4. Antibody light chains of any vertebrate species may be assigned to one of two clearly distinct types, namely kappa (κ) and lambda (λ), based on the amino acid sequences of their constant domains.

“Antigen binding fragment” refers to a portion of an immunoglobulin molecule that binds an antigen. Antigen binding fragments may be synthetic, enzymatically obtainable or genetically engineered polypeptides and include the VH, the VL, the VH and the VL, Fab, F(ab')₂, Fd and Fv fragments, domain antibodies (dAb) consisting of one VH domain or one VL domain, shark variable IgNAR domains, camelized VH domains, minimal recognition units consisting of the amino acid residues that mimic the CDRs of an antibody, such as FR3-CDR3-FR4 portions, the HCDR1, the HCDR2 and/or the HCDR3 and the LCDR1, the LCDR2 and/or the LCDR3. VH and VL domains may be linked together via a synthetic linker to form various types of single chain antibody designs where the VH/VL domains may pair intramolecularly, or intermolecularly in those cases when the VH and VL domains are expressed by separate single chain antibody constructs, to form a monovalent antigen binding site, such as single chain Fv (scFv) or diabody; described for example in Int. Patent Publ. Nos. WO1998/44001, WO1988/01649, WO1994/13804 and WO1992/01047.

“Monoclonal antibody” refers to an antibody obtained from a substantially homogenous population of antibody molecules, i.e., the individual antibodies comprising the population are identical except for possible well-known alterations such as removal of C-terminal lysine from the antibody heavy chain or post-translational modifications such as amino acid isomerization or deamidation, methionine oxidation or asparagine or glutamine deamidation. Monoclonal antibodies typically bind one antigenic epitope. A bispecific monoclonal antibody binds two distinct antigenic epitopes. Monoclonal antibodies may have heterogeneous glycosylation within the antibody population. Monoclonal antibody may be monospecific or multispecific such as bispecific, monovalent, bivalent or multivalent.

“Isolated antibody” refers to an antibody or antibody fragment that is substantially free of other antibodies having different antigenic specificities (e.g., an isolated antibody specifically binding an antigen is substantially free of antibodies that specifically bind antigens other than the antigen). In the case of bispecific CD3 antibodies, the bispecific antibody specifically binds both CD3 a second antigen. “Isolated antibody” encompasses antibodies that are isolated to a higher

purity, such as antibodies that are 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% pure.

“Humanized antibody” refers to an antibody in which at least one CDR is derived from non-human species and at least one framework is derived from human immunoglobulin sequences. Humanized antibody may include substitutions in the frameworks so that the frameworks may not be exact copies of expressed human immunoglobulin or human immunoglobulin germline gene sequences.

“Human antibody” refers to an antibody that is optimized to have minimal immune response when administered to a human subject. Variable regions of human antibody are derived from human immunoglobulin sequences. If human antibody contains a constant region or a portion of the constant region, the constant region is also derived from human immunoglobulin sequences. Human antibody comprises heavy and light chain variable regions that are “derived from” sequences of human origin if the variable regions of the human antibody are obtained from a system that uses human germline immunoglobulin or rearranged immunoglobulin genes. Such exemplary systems are human immunoglobulin gene libraries displayed on phage, and transgenic non-human animals such as mice or rats carrying human immunoglobulin loci. “Human antibody” typically contains amino acid differences when compared to the immunoglobulins expressed in humans due to differences between the systems used to obtain the human antibody and human immunoglobulin loci, introduction of somatic mutations or intentional introduction of substitutions into the frameworks or CDRs, or both. Typically, “human antibody” is at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical in amino acid sequence to an amino acid sequence encoded by human germline immunoglobulin or rearranged immunoglobulin genes. In some cases, “human antibody” may contain consensus framework sequences derived from human framework sequence analyses, for example as described in Knappik et al., (2000) J Mol Biol 296:57-86, or synthetic HCDR3 incorporated into human immunoglobulin gene libraries displayed on phage, for example as described in Shi et al., (2010) J Mol Biol 397:385-96, and in Int. Patent Publ. No. WO2009/085462.

“Percent (%) amino acid sequence identity” with respect to a reference polypeptide sequence is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the reference polypeptide sequence, after aligning the

sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for aligning sequences, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. For purposes herein, however, % amino acid sequence identity values are generated using the sequence comparison computer program ALIGN-2. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc., and the source code has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available from Genentech, Inc., South San Francisco, Calif., or may be compiled from the source code. The ALIGN-2 program should be compiled for use on a UNIX operating system, including digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary. Where ALIGN-2 is employed for amino acid sequence comparisons, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows:

100 times the fraction X/Y ,

where X is the number of amino acid residues scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A. Unless specifically stated otherwise, all % amino acid sequence identity values used herein are obtained as described in the immediately preceding paragraph using the ALIGN-2 computer program.

Antibodies in which antigen binding sites are derived from a non-human species are not included in the definition of "human antibody".

“Recombinant” refers to DNA, antibodies and other proteins that are prepared, expressed, created or isolated by recombinant means when segments from different sources are joined to produce recombinant DNA, antibodies or proteins.

“Epitope” refers to a portion of an antigen to which an antibody specifically binds.

5 Epitopes typically consist of chemically active (such as polar, non-polar or hydrophobic) surface groupings of moieties such as amino acids or polysaccharide side chains and may have specific three-dimensional structural characteristics, as well as specific charge characteristics. An epitope may be composed of contiguous and/or discontinuous amino acids that form a conformational spatial unit. For a discontinuous epitope, amino acids from differing portions of
10 the linear sequence of the antigen come in close proximity in 3-dimensional space through the folding of the protein molecule. Antibody “epitope” depends on the methodology used to identify the epitope.

“Paratope” refers to a portion of an antibody to which an antigen specifically binds. A paratope may be linear in nature or may be discontinuous, formed by a spatial relationship
15 between non-contiguous amino acids of an antibody rather than a linear series of amino acids. A “light chain paratope” and a “heavy chain paratope” or “light chain paratope amino acid residues” and “heavy chain paratope amino acid residues” refer to antibody light chain and heavy chain residues in contact with an antigen, respectively, or in general, “antibody paratope residues” refer to those antibody amino acids that are in contact with antigen.

20 “Bispecific” refers to an antibody that specifically binds two distinct antigens or two distinct epitopes within the same antigen. The bispecific antibody may have cross-reactivity to other related antigens, for example to the same antigen from other species (homologs), such as human or monkey, for example *Macaca fascicularis* (cynomolgus, cyno) or *Pan troglodytes*, or may bind an epitope that is shared between two or more distinct antigens.

25 “Multispecific” refers to an antibody that specifically binds two or more distinct antigens or two or more distinct epitopes within the same antigen. The multispecific antibody may have cross-reactivity to other related antigens, for example to the same antigen from other species (homologs), such as human or monkey, for example *Macaca fascicularis* (cynomolgus, cyno) or *Pan troglodytes*, or may bind an epitope that is shared between two or more distinct antigens.

“Variant” refers to a polypeptide or a polynucleotide that differs from a reference polypeptide or a reference polynucleotide by one or more modifications, for example one or more substitutions, insertions or deletions.

“Vector” refers to a polynucleotide capable of being duplicated within a biological system or that can be moved between such systems. Vector polynucleotides typically contain elements, such as origins of replication, promoter, polyadenylation signal and selection markers, that function to facilitate the duplication or maintenance of these polynucleotides in a biological system, such as a cell, virus, animal, plant, and reconstituted biological systems utilizing biological components capable of duplicating a vector. The vector polynucleotide may be DNA or RNA molecules or a hybrid of these, single stranded or double stranded.

“Expression vector” refers to a vector that can be utilized in a biological system or in a reconstituted biological system to direct the translation of a polypeptide encoded by a polynucleotide sequence present in the expression vector.

“Polynucleotide” refers to a molecule comprising a chain of nucleotides covalently linked by a sugar-phosphate backbone or other equivalent covalent chemistry. Double and single-stranded DNA and RNA are typical examples of polynucleotides. “Polynucleotide” may refer to a synthetic molecule comprising a chain of nucleotides covalently linked by a sugar-phosphate backbone or other equivalent covalent chemistry. cDNA is an exemplary synthetic polynucleotide.

“Polypeptide” or “protein” refers to a molecule that comprises at least two amino acid residues linked by a peptide bond to form a polypeptide. Small polypeptides of less than 50 amino acids may be referred to as “peptides”.

“Flow cytometry” is a technology that is used to analyze the physical and chemical characteristics of particles in a fluid as it passes through at least one laser. Cell components are fluorescently labelled and then excited by the laser to emit light at varying wavelengths (Adan, et al, Critical Reviews in Biotechnology (2016) 1549-7801).

“Anti-idiotypic (anti-Id) antibody” is an antibody that recognizes the antigenic determinants (e.g. the paratope or CDRs) of the antibody. It is generally known in the art the process of producing or preparing an anti-idiotypic antibody. (Lathey, J. et al Immunology 1986 57(1):29-35). The anti-Id antibody may be antigen-blocking or non-blocking. The antigen-blocking anti-Id antibody may be used to detect the free antibody in a sample, e.g. CD3. The

non-blocking anti-Id antibody may be used to detect the total antibody (free, partially bound to antigen, or fully bound to antigen) in a sample. An anti-Id antibody may be prepared by immunizing an animal with the antibody to which an anti-Id antibody is being prepared. In some embodiments described herein, the anti-idiotypic antibody is used for detecting the level of the
5 therapeutic antibodies in a sample.

An anti-Id antibody may also be used as an immunogen to induce an immune response in yet another animal, producing a so-called anti-anti-Id antibody. An anti-anti-Id antibody may be epitopically identical to the original mAb, which induced the anti-Id antibody. Thus, by using antibodies to the idiotypic determinants of a mAb, it is possible to identify other clones
10 expressing antibodies of identical specificity. Anti-Id antibodies may be varied (thereby producing anti-Id antibody variants) and/or derivatized by any suitable technique, such as those described elsewhere herein with respect to the anti-CD3 antibodies.

PSMA refers to Prostate Specific Membrane Antigen. The amino acid sequence of *Pan troglodytes* (also referred to as chimpanzee or chimp) PSMA is shown in SEQ ID NO: 49. The
15 extracellular domain spans residues 44 - 750, the transmembrane domain spans residues 20 - 43 and the cytoplasmic domain spans residues 1 - 19 of SEQ ID NO: 49. The amino acid sequence of the *Macaca fascicularis* (also referred to as cynomolgus monkey, macaque or cyno) PSMA is shown in SEQ ID NO: 50. The extracellular domain spans residues 44 - 750, the transmembrane domain spans residues 20 - 43 and the cytoplasmic domain spans residues 1 - 19 of SEQ ID NO:
20 50. The amino acid sequence of the human PSMA is shown in SEQ ID NO:51. The extracellular domain spans residues 44 - 750, the transmembrane domain spans residues 20 - 43 and the cytoplasmic domain spans residues 1 - 19 of SEQ ID NO:51.

Throughout the specification, “CD3-specific” or “specifically binds CD3” or “anti-CD3 antibody” refers to antibodies that bind specifically to the CD3-epsilon polypeptide (SEQ ID
25 NO:635), including antibodies that bind specifically to the CD3-epsilon extracellular domain (ECD) (SEQ ID NO:636). CD3-epsilon, together with CD3-gamma, -delta and -zeta, and the T-cell receptor alpha/beta and gamma/delta heterodimers, forms the T-cell receptor-CD3 complex. This complex plays an important role in coupling antigen recognition to several intracellular signal-transduction pathways. The CD3 complex mediates signal transduction, resulting in T cell
30 activation and proliferation. CD3 is required for the immune response.

SEQ ID NO:635 (Human CD3 epsilon)

MQSGTHWRVLGLCLLSVGWVGQDGNEEMGGITQTPYKVSISGTTVILTCPQYPG
 SEILWQHNDKNIGGDEDDKNIGSDEDHLSSLKEFSELEQSGYYVCYPRGSKPEDA
 NFYLYLRARVCENCMEMDVMSVATIVIVDICITGGLLLLVYYWSKNRKAKAKPV
 TRGAGAGGRQGRGQNKERPPVNPDPYEPIRKGQRDLYSGLNQRR

SEQ ID NO:636 (Human CD3 epsilon extracellular domain)

DGNEEMGGITQTPYKVSISGTTVILTCPQYPGSEILWQHNDKNIGGDEDDKNIG
 SDEDHLSSLKEFSELEQSGYYVCYPRGSKPEDANFYLYLRARVCENCMEMD

As used herein, the terms “interleukin-1 receptor accessory protein”, “IL1RAP” and “IL1-RAP” specifically include the human IL1RAP protein, for example as described in GenBank Accession No. AAB84059, NCBI Reference Sequence: NP_002173.1 and UniProtKB/Swiss-Prot Accession No. Q9NPH3-1 (see also Huang et al., 1997, Proc. Natl. Acad. Sci. USA. 94 (24), 12829-12832). IL1RAP is also known in the scientific literature as IL1 R3, C3orf13, FLJ37788, IL-1 RAcP and EG3556.

“CD33” refers to cluster of differentiation 33 protein. CD33 is a 67 kilodalton (kD) single pass transmembrane glycoprotein and is a member of the sialic acid-binding immunoglobulin-like lectins (Siglecs) family. CD33 is primarily considered to be a myeloid differentiation antigen, with low expression in myeloid progenitors, neutrophils and macrophages and high expression in circulating monocytes and dendritic cells. Human CD33 extracellular domain (Uniprot P20138) (SEQ ID NO:636) and cynomolgus CD33 (XP_005590138.1) are examples of proteins for use in generating CD33-specific antibodies according to the present disclosure.

“TMEFF2” refers to human transmembrane protein with EGF like and two follistatin like domains 2, also called tomoregulin 2. The amino acid sequence of the full length human TMEFF2 is shown in SEQ ID NO: 77. The extracellular domain of TMEFF2 is shown in SEQ ID NO: 575 and spans residues 40-374 of the full length TMEFF2. TMEFF2 extracellular domain harbors three distinct subdomains, the Kazal-like 1 (residues 85-137), the Kazal-like 2 (residues 176-229) and the EGF domain (residues 261-301). The TMEFF2 EGF domain is shown in SEQ ID NO: 577. The TMEFF2 “membrane proximal region” refers to the TMEFF2

region of **SEQ ID NO: 629**, which encompasses the EGF domain and the N- C-terminal linker regions (e.g. residues 230-320 of full length human TMEFF2 of **SEQ ID NO: 77**). All references to proteins, polypeptides and protein fragments herein are intended to refer to the human version of the respective protein, polypeptide or protein fragment unless explicitly

5 specified as being from a non-human species. Thus, “TMEFF2” means human TMEFF2 unless specified as being from a non-human species, e.g., “mouse TMEFF2” or “monkey TMEFF2” etc.

SEQ ID NO: 77 (full length human TMEFF2)

MVLWESPRQCSSWTLCEGFCWLLLLPVMLLIVARPVKLAAPFSLSDCQTPTGW
NCSGYDDRENDLFLCDTNTCKFDGECLRIGDTVTCVCQFKCNNDYVPVCGSNGESYQN
10 ECYLRQAACKQQSEILVVSEGSCATDAGSGSGDGVHEGSGETSQKETSTCDICQFGAEC
DEDAEDVWCVCNIDCSQTNFNPLCASDGKSYDNACQIKEASCQKQEKIEVMSLGRCQD
NTTTTTSKSEDGHYARTDYAENANKLEESAREHHIPCPEHYNGFCMHGKCEHSINMQEPS
CRCDAGYTGQHCEKKDYSVLYVVPGPVRFQYVLIAAVIGTIQIavicvvvlCITRKCPRS
NRIHRQKQNTGHYSSDNTTRASTRLI

15 **SEQ ID NO: 575** (extracellular domain of human TMEFF2)

FPTSLSDCQTPTGWNCSGYDDRENDLFLCDTNTCKFDGECLRIGDTVTCVCQFK
CNNDYVPVCGSNGESYQNECYLRQAACKQQSEILVVSEGSCATDAGSGSGDGVHEGSG
ETSQKETSTCDICQFGAECDEDAEDVWCVCNIDCSQTNFNPLCASDGKSYDNACQIKEA
SCQKQEKIEVMSLGRCQDNTTTTTSKSEDGHYARTDYAENANKLEESAREHHIPCPEHYN
20 GFCMHGKCEHSINMQEPSCRCDAAGYTGQHCEKKDYSVLYVVPGPVRFQYVLIAAVIGTI
QIavicvvvlCITRKCPRSNRIHRQKQNTGHYSSDNTTRASTRLI

TMEFF2 EGF domain **SEQ ID NO: 577**

HHIPCPEHYNGFCMHGKCEHSINMQEPSCRCDAAGYTGQHCE

TMEFF2 membrane proximal region **SEQ ID NO: 629**

25 NTTTTTSKSEDGHYARTDYAENANKLEESAREHHIPCPEHYNGFCMHGKCEHSIN
MQEPSCRCDAAGYTGQHCEKKDYSVLYVVPGPVRFQYV

“TMEFF2 positive cancer” refers to a cancer tissue or a cancer cell that displays measurable level of TMEFF2 protein. Level of TMEFF2 protein may be measured using well known assays using, for example ELISA, immunofluorescence, flow cytometry or

30 radioimmunoassay on live or lysed cells. “Overexpress”, “overexpressed” and “overexpressing” interchangeably refers to a sample such as a cancer cell, malignant cell or cancer tissue that has

measurably higher levels of tumor antigen when compared to a reference sample. The overexpression may be caused by gene amplification or by increased transcription or translation. Expression and overexpression of protein in the sample may be measured using well-known assays using, for example ELISA, immunofluorescence, flow cytometry or radioimmunoassay
5 on live or lysed cells. Expression and overexpression of a polynucleotide in the sample may be measured, for example, using fluorescent in situ hybridization, Southern blotting, or PCR techniques. A protein or a polynucleotide is overexpressed when the level of the protein or the polynucleotide in the sample is at least 1.5-fold higher when compared to the reference sample. Selection of the reference sample is well known.

10 “Sample” refers to a collection of similar fluids, cells, or tissues isolated from a subject, as well as fluids, cells, or tissues present within a subject. Exemplary samples are biological fluids such as blood, serum and serosal fluids, plasma, lymph, urine, saliva, cystic fluid, tear drops, feces, sputum, mucosal secretions of the secretory tissues and organs, vaginal secretions, ascites fluids such as those associated with non-solid tumors, fluids of the pleural, pericardial,
15 peritoneal, abdominal and other body cavities, fluids collected by bronchial lavage, liquid solutions contacted with a subject or biological source, for example, cell and organ culture medium including cell or organ conditioned medium, lavage fluids and the like, tissue biopsies, fine needle aspirations or surgically resected tumor tissue.

A “cancer cell” or a “tumor cell” as used herein refers to a cancerous, pre-cancerous or
20 transformed cell, either in vivo, ex vivo, or in tissue culture, that has spontaneous or induced phenotypic changes. These changes do not necessarily involve the uptake of new genetic material. Although transformation may arise from infection with a transforming virus and incorporation of new genomic nucleic acid or uptake of exogenous nucleic acid, it can also arise spontaneously or following exposure to a carcinogen, thereby mutating an endogenous gene.
25 Transformation/cancer is exemplified by morphological changes, immortalization of cells, aberrant growth control, foci formation, proliferation, malignancy, modulation of tumor specific marker levels, invasiveness, tumor growth in suitable animal hosts such as nude mice, and the like, in vitro, in vivo, and ex vivo (Freshney, Culture of Animal Cells: A Manual of Basic Technique (3rd ed. 1994)).

30 Unless otherwise stated, any numerical values, such as a concentration or a concentration range described herein, are to be understood as being modified in all instances by the term

“about.” Thus, a numerical value typically includes $\pm 10\%$ of the recited value. For example, a concentration of 1 mg/mL includes 0.9 mg/mL to 1.1 mg/mL. Likewise, a concentration range of 1% to 10% (w/v) includes 0.9% (w/v) to 11% (w/v). As used herein, the use of a numerical range expressly includes all possible subranges, all individual numerical values within that range, including integers within such ranges and fractions of the values unless the context clearly indicates otherwise.

“Effector antigens” are antigens from cells of the immune system that can stimulate or trigger cytotoxicity, phagocytosis, antigen presentation, and/or cytokine release. Such effector antigens are from, for example but not limited to, T cells and natural killer (NK) cells. Examples of suitable specificities for effector antigens include but are not limited to CD3 or CD3 subunits such as CD3 ϵ for T cells and CD16 for NK cells. Such cell surface molecules of effector cells are suitable for mediating cell killing. Effector cells are cells of the immune system that can stimulate or trigger cytotoxicity, phagocytosis, antigen presentation, and/or cytokine release. Such effector cells are, for example but not limited to, T-cells, natural killer (NK) cells, granulocytes, monocytes, macrophages, dendritic cells, and antigen-presenting cells. Examples of suitable specificities for effector cells include but are not limited to CD2, CD3 and CD3 subunits such as CD3 ϵ , CD5, CD28 and other components of the T-cell receptor (TCR) for T cells; CD16, CD16A, CD25, CD38, CD44, CD56, CD69, CD94, CD335 (NKp46), CD336, (NKp44), CD337 (NKp30), NKp80, NKG2C and NKG2D, DNAM, NCRs for NK cells; CD18, CD64 and CD89 for granulocytes; CD18, CD32, CD64, CD89 and mannose receptor for monocytes and macrophages; CD64 and mannose receptor for dendritic cells; as well as CD35. In certain embodiments of the inventions, those specificities, i.e. cell surface molecules, of effector cells are suitable for mediating cell killing upon binding of a bispecific or multispecific molecules to such cell surface molecule and, thereby, inducing cytolysis or apoptosis.

“Bispecific CD3 antibody” refers to a molecule comprising at least one binding domain specifically binding CD3 and at least one binding domain specifically binding a second antigen, such as a bispecific antibody comprising a first domain that specifically binds CD3 and a second domain that specifically binds a second antigen. The domains specifically binding CD3 and a second antigen are typically V_H/V_L pairs. The bispecific CD3 antibody may be monovalent in terms of its binding to either CD3 or the second antigen. In some embodiments, the second, or target, antigen is a cell surface antigen that is expressed on a target cell other than an immune

effector cell. In some embodiments, the second antigen is a tumor associated antigen (TAA). Exemplary TAAs are PSMA, CD33, IL1RAP, and TMEFF2.

“Bispecific PSMA×CD3 antibody”, “PSMA/CD3 antibody”, “bispecific anti-PSMA×CD3 antibody” or “anti-PSMA/CD3 antibody” and the like refer to a molecule comprising at least one binding domain specifically binding PSMA and at least one binding domain specifically binding CD3. The domains specifically binding PSMA and CD3 are typically V_H/V_L pairs. The bispecific anti-PSMA×CD3 antibody may be monovalent in terms of its binding to either PSMA or CD3.

“Bispecific CD33×CD3 antibody”, “CD33/CD3 antibody”, “bispecific anti-CD33×CD3 antibody” or “anti-CD33/CD3 antibody” and the like refer to a molecule comprising at least one binding domain specifically binding CD33 and at least one binding domain specifically binding CD3. The domains specifically binding CD33 and CD3 are typically V_H/V_L pairs. The bispecific anti-CD33×CD3 antibody may be monovalent in terms of its binding to either CD33 or CD3.

“Bispecific IL1RAP×CD3 antibody”, “IL1RAP/CD3 antibody”, “bispecific anti-IL1RAP×CD3 antibody” or “anti-IL1RAP/CD3 antibody” and the like refer to a molecule comprising at least one binding domain specifically binding IL1RAP and at least one binding domain specifically binding CD3. The domains specifically binding IL1RAP and CD3 are typically V_H/V_L pairs. The bispecific anti-IL1RAP×CD3 antibody may be monovalent in terms of its binding to either IL1RAP or CD3.

“Bispecific anti-TMEFF2/anti-CD3 antibody”, TMEFF2/CD3 antibody, TMEFF2×CD3 antibody and the like refer to an antibody that binds TMEFF2 and CD3.

“Valent” refers to the presence of a specified number of binding sites specific for an antigen in a molecule. As such, the terms “monovalent”, “bivalent”, “tetravalent”, and “hexavalent” refer to the presence of one, two, four and six binding sites, respectively, specific for an antigen in a molecule. “Multivalent” refers to the presence of two or more binding sites specific for an antigen in a molecule.

“An antigen specific CD4⁺ or CD8⁺ T cell” refers to a CD4⁺ or CD8⁺ T cell activated by a specific antigen, or immunostimulatory epitope thereof.

“Subject” includes any human or nonhuman animal. “Nonhuman animal” includes all vertebrates, e.g., mammals and non-mammals, such as nonhuman primates, sheep, dogs, cats,

horses, cows chickens, amphibians, reptiles, etc. Except when noted, the terms “patient” or “subject” are used interchangeably.

The numbering of amino acid residues in the antibody constant region throughout the specification is according to the EU index as described in Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD. (1991), unless otherwise explicitly stated.

Table 1. Conventional one- and three-letter amino acid codes used herein

Amino acid	Three-letter code	One-letter code
Alanine	Ala	A
Arginine	Arg	R
Asparagine	Asn	N
Aspartate	Asp	D
Cysteine	Cys	C
Glutamate	Gln	E
Glutamine	Glu	Q
Glycine	Gly	G
Histidine	His	H
Isoleucine	Ile	I
Lysine	Lys	K
Methionine	Met	M
Phenylalanine	Phe	F
Proline	Pro	P
Serine	Ser	S
Threonine	Thr	T
Tryptophan	Trp	W
Tyrosine	Tyr	Y
Valine	Val	V

Compositions of Matter

The present invention provides anti-CD3 antibodies and antigen-binding fragments thereof, antibodies and antigen-binding fragments thereof that specifically bind PSMA,

antibodies and antigen-binding fragments thereof that specifically bind CD33, antibodies and antigen-binding fragments thereof that specifically bind IL1RAP, multispecific antibodies comprising a first domain that specifically binds CD3 and a second domain that specifically binds a second antigen, and multispecific antibodies that specifically bind CD3 and one or more
5 of PSMA, CD33, IL1RAP, and TMEFF2. The present invention provides polypeptides and polynucleotides encoding the antibodies of the invention or complementary nucleic acids thereof, vectors, host cells, and methods of making and using them.

General Aspects of the Antibodies Described Herein

The anti-CD3 antibodies or antigen-binding fragments described herein include variants
10 having single or multiple amino acid substitutions, deletions, or additions that retain the biological properties (e.g., binding affinity or immune effector activity) of the described anti-CD3 antibodies or antigen-binding fragments. In the context of the present invention the following notations are, unless otherwise indicated, used to describe a mutation; i) substitution of an amino acid in a given position is written as e.g. K409R which means a substitution of a
15 Lysine in position 409 with an Arginine; and ii) for specific variants the specific three or one letter codes are used, including the codes Xaa and X to indicate any amino acid residue. Thus, the substitution of Arginine for Lysine in position 409 is designated as: K409R, or the substitution of any amino acid residue for Lysine in position 409 is designated as K409X. In case of deletion of Lysine in position 409 it is indicated by K409*. The skilled person may produce
20 variants having single or multiple amino acid substitutions, deletions, or additions.

These variants may include: (a) variants in which one or more amino acid residues are substituted with conservative or nonconservative amino acids, (b) variants in which one or more amino acids are added to or deleted from the polypeptide, (c) variants in which one or more amino acids include a substituent group, and (d) variants in which the polypeptide is fused with
25 another peptide or polypeptide such as a fusion partner, a protein tag or other chemical moiety, that may confer useful properties to the polypeptide, such as, for example, an epitope for an antibody, a polyhistidine sequence, a biotin moiety and the like. Antibodies or antigen-binding fragments described herein may include variants in which amino acid residues from one species are substituted for the corresponding residue in another species, either at the conserved or
30 nonconserved positions. In other embodiments, amino acid residues at nonconserved positions

are substituted with conservative or nonconservative residues. The techniques for obtaining these variants, including genetic (deletions, mutations, etc.), chemical, and enzymatic techniques, are known to persons having ordinary skill in the art.

The antibodies or antigen-binding fragments described herein may be an IgM, an IgD, an IgG, an IgA or an IgE isotype. In some embodiments, the antibody isotype is an IgG1, an IgG2, an IgG3, or an IgG4 isotype. In some embodiments, the antibody is an IgG1 isotype. In some embodiments, the antibody is an IgG2 isotype. In some embodiments, the antibody is an IgG3 isotype. In some embodiments, the antibody is an IgG4 isotype. The specificity of the antibody or antigen-binding fragment thereof is in part determined by the amino acid sequence and arrangement, of the CDRs. Therefore, the CDRs of one isotype may be transferred to another isotype without altering antigen specificity. Accordingly, such antibody isotypes are within the scope of the described antibodies or antigen-binding fragments.

The IgG class is divided in four isotypes: IgG1, IgG2, IgG3 and IgG4 in humans. They share more than 95% homology in the amino acid sequences in the CH1, CH2 and CH3 regions but show major differences in the amino acid composition and structure of the hinge region. The Fc region mediates effector functions, such as antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP) and complement-dependent cytotoxicity (CDC). In ADCC, the Fc region binds to Fc receptors (FcγRs) on the surface of immune effector cells such as natural killer cells and macrophages, leading to the lysis of the targeted cells. In CDC, the antibodies mediate targeted cell killing by triggering the complement cascade at the cell surface. In ADCP, the antibody mediates elimination of antibody-coated target cells by internalization by phagocytic cells, such as macrophages or dendritic cells. The antibodies described herein include antibodies with the described features of the variable domains in combination with any of the IgG isotypes, including modified versions in which the Fc region has been modified to modulate the various effector functions.

For many applications of therapeutic antibodies, Fc-mediated effector functions are not desired as they may potentially pose a safety risk due to cell depletion. Modifying effector functions can be achieved by engineering the Fc regions to reduce their binding to FcγRs or the complement factors. The binding of IgG to the activating (FcγRI, FcγRIIa, FcγRIIIa and FcγRIIIb) and inhibitory (FcγRIIb) FcγRs or the first component of complement (C1q) depends on residues located in the hinge region and the CH2 domain. Mutations may be introduced in

IgG1, IgG2 and IgG4 to reduce or silence Fc-mediated effector functions. The antibodies described herein may include these modifications.

In some embodiments, the anti-CD3, the anti-PSMA, the anti-CD33, and/or the anti-IL1RAP antibodies comprise an engineered Fc region having one or more of the following
5 properties: (a) reduced effector function when compared to the parental Fc; (b) reduced affinity to FcγRI, FcγRIIa, FcγRIIb, FcγRIIIb and/or FcγRIIIa; (c) reduced affinity to FcγRI; (d) reduced affinity to FcγRIIa; (e) reduced affinity to FcγRIIIb; or (f) reduced affinity to FcγRIIIa.

In some embodiments, the anti-CD3, the anti-PSMA, the anti-CD33, and/or the anti-IL1RAP antibodies are, e.g., IgG1, IgG2, IgG3, or IgG4 isotypes. In some embodiments
10 wherein the antibody has an IgG4 isotype, the antibody contains S228P, F234A, and L235A substitutions in its Fc region when compared to the wild-type IgG4. In some embodiments wherein the antibody has an IgG1 isotype, the antibody contains L234A, and L235A substitutions in its Fc region. The antibodies described herein may include these modifications.

In some embodiments, the anti-CD3, the anti-PSMA, the anti-CD33, and/or the anti-
15 IL1RAP antibodies are an IgG4 isotype, optionally comprising a heavy chain substitution S228P.

In some embodiments, the anti-CD3, the anti-PSMA, the anti-CD33, and/or the anti-IL1RAP antibodies are an IgG1 isotype, optionally comprising heavy chain substitutions L234A, G237A, P238S, H268A, A330S and P331S when compared to the wild type IgG1.

In some embodiments, the anti-CD3, the anti-PSMA, the anti-CD33, and/or the anti-
20 IL1RAP antibodies are an IgG2 isotype, optionally comprising heavy chain substitutions L234A, G237A, P238S, H268A, V309L, A330S and P331S when compared to the wild type IgG2.

Wild-type IgG4

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA
VLQSSGLYSLSSVVTVPSSSLGKTYTCNVDPKPSNTKVDKRVESKYGPPCPSCPAPEFL
25 GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREE
QFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPP
SQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSRLTV
DKSRWQEGNVFSCSVMHEALHNHYTQKSLSLGLK (SEQ ID NO: 602)

30 Wild-type IgG1

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS

GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGG
 PSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY
 NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR
 DELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDK
 5 SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 601)

Wild-type IgG2

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
 GLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTKVERKCCVECPPCPAPPVAGPSV
 10 FLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNST
 FRVVSVELTVVHQQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEM
 TKNQVSLTCLVKGFYPSDISVEWESNGQPENNYKTTTPMLDSGDSFFLYSKLTVDKSRW
 QQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 711)

15 In certain embodiments, labelled anti-CD3, anti-PSMA, anti-CD33, and/or anti-IL1RAP
 antibodies are provided. Exemplary labels or moieties that are detected directly (e.g.,
 fluorescent, chromophoric, electron-dense, chemiluminescent, and radioactive labels) and labels
 and moieties (e.g., enzymes or ligands) that are detected indirectly (e.g., through enzymatic
 reaction or molecular interaction). Exemplary labels include radiolabels (e.g., ³²P, ¹⁴C, ¹¹¹I, ¹²⁵I,
 20 ³H, ¹³¹I), fluorescent labels (such as DyLight® 649), epitope tags, biotin, chromophore labels,
 ECL labels, or enzymes. More specifically, the described labels include ruthenium, ¹¹¹In-DOTA,
¹¹¹In- diethylenetriaminepentaacetic acid (DTPA), horseradish peroxidase, alkaline phosphatase
 and beta-galactosidase, poly-histidine (HIS tag), acridine dyes, cyanine dyes, fluorone dyes,
 oxazin dyes, phenanthridine dyes, rhodamine dyes, Alexafluor® dyes, and the like.

25 In addition to the described anti-CD3, anti-PSMA, anti-CD33, and/or anti-IL1RAP
 antibodies and antigen-binding fragments, also provided are polynucleotide sequences capable of
 encoding the described antibodies and antigen-binding fragments. Vectors comprising the
 described polynucleotides are also provided, as are cells expressing the anti-CD3, anti-PSMA,
 anti-CD33, and/or anti-IL1RAP antibodies or antigen-binding fragments provided herein. Also
 30 described are cells capable of expressing the disclosed vectors. These cells may be mammalian
 cells (such as 293F cells, CHO cells), insect cells (such as Sf7 cells), yeast cells, plant cells, or

bacteria cells (such as *E. coli*). The described antibodies may also be produced by hybridoma cells.

Generation of Monospecific Antibodies

In some embodiments, the anti-CD3, the anti-PSMA, the anti-CD33, the anti-TMEFF2, and/or the anti-IL1RAP antibodies of the invention are human.

In some embodiments, the anti-CD3, the anti-PSMA, the anti-CD33, the anti-TMEFF2, and/or the anti-IL1RAP antibodies of the invention are humanized.

Monospecific antibodies of the invention described herein (e.g. the anti-CD3, the anti-PSMA, the anti-CD33, the anti-TMEFF2, and/or the anti-IL1RAP antibodies) may be generated using various technologies. For example, the hybridoma method of Kohler and Milstein, *Nature* 256:495, 1975 may be used to generate monoclonal antibodies. In the hybridoma method, a mouse or other host animal, such as a hamster, rat or chicken, is immunized with human, chimpanzee, or macaque PSMA, CD33, IL1RAP, TMEFF2, or CD3 or fragments of PSMA, CD33, IL1RAP, TMEFF2, or CD3, such as the extracellular domain of PSMA, CD33, IL1RAP, TMEFF2, or CD3, followed by fusion of spleen cells from immunized animals with myeloma cells using standard methods to form hybridoma cells (Goding, *Monoclonal Antibodies: Principles and Practice*, pp.59-103 (Academic Press, 1986)). Colonies arising from single immortalized hybridoma cells are screened for production of antibodies with desired properties, such as specificity of binding, cross-reactivity or lack thereof, and affinity for the antigen.

Various host animals may be used to produce the anti-CD3, the anti-PSMA, the anti-CD33, TMEFF2, and/or the anti-IL1RAP antibodies of the invention described herein. For example, Balb/c mice may be used to generate mouse anti-human PSMA antibodies. The antibodies made in Balb/c mice and other non-human animals may be humanized using various technologies to generate more human-like sequences.

Exemplary humanization techniques including selection of human acceptor frameworks are known and include CDR grafting (U.S. Patent No. 5,225,539), SDR grafting (U.S. Patent No. 6,818,749), Resurfacing (Padlan, (1991) *Mol Immunol* 28:489-499), Specificity Determining Residues Resurfacing (U.S. Patent Publ. No. 2010/0261620), human framework adaptation (U.S. Patent No. 8,748,356) or superhumanization (U.S. Patent No. 7,709, 226). In these methods, CDRs of parental antibodies are transferred onto human frameworks that may be selected based

on their overall homology to the parental frameworks, based on similarity in CDR length, or canonical structure identity, or a combination thereof.

Humanized antibodies may be further optimized to improve their selectivity or affinity to a desired antigen by incorporating altered framework support residues to preserve binding
5 affinity (backmutations) by techniques such as those described in Int. Patent Publ. Nos. WO1090/007861 and WO1992/22653, or by introducing variation at any of the CDRs for example to improve affinity of the antibody.

Transgenic animals, such as mice or rat carrying human immunoglobulin (Ig) loci in their genome may be used to generate human antibodies against a target protein, and are described in
10 for example U.S. Patent No. 6,150,584, Int. Patent Publ. No. WO99/45962, Int. Patent Publ. Nos. WO2002/066630, WO2002/43478, WO2002/043478 and WO1990/04036, Lonberg et al (1994) Nature 368:856-9; Green et al (1994) Nature Genet. 7:13-21; Green & Jakobovits (1998) Exp. Med. 188:483-95; Lonberg and Huszar (1995) Int Rev Immunol 13:65-93; Bruggemann et al., (1991) Eur J Immunol 21:1323- 1326; Fishwild et al., (1996) Nat Biotechnol 14:845-851;
15 Mendez et al., (1997) Nat Genet 15:146-156; Green (1999) J Immunol Methods 231:11-23; Yang et al., (1999) Cancer Res 59:1236-1243; Bruggemann and Taussig (1997) Curr Opin Biotechnol 8:455-458. The endogenous immunoglobulin loci in such animal may be disrupted or deleted, and at least one complete or partial human immunoglobulin locus may be inserted into the genome of the animal using homologous or non-homologous recombination, using
20 transchromosomes, or using minigenes. Companies such as Regeneron (http://_www_regeneron_com), Harbour Antibodies (http://_www_harbourantibodies_com), Open Monoclonal Technology, Inc. (OMT) (http://_www_omtinc_net), KyMab (http://_www_kymab_com), Trianni (http://_www.trianni_com) and Ablexis (http://_www_ablexis_com) may be engaged to provide human antibodies directed against a
25 selected antigen using technologies as described above.

Human antibodies may be selected from a phage display library, where the phage is engineered to express human immunoglobulins or portions thereof such as Fabs, single chain antibodies (scFv), or unpaired or paired antibody variable regions (Knappik et al., (2000) J Mol Biol 296:57-86; Krebs et al., (2001) J Immunol Meth 254:67-84; Vaughan et al., (1996) Nature
30 Biotechnology 14:309-314; Sheets et al., (1998) PITAS (USA) 95:6157-6162; Hoogenboom and Winter (1991) J Mol Biol 227:381; Marks et al., (1991) J Mol Biol 222:581). The antibodies of

the invention may be isolated for example from phage display library expressing antibody heavy and light chain variable regions as fusion proteins with bacteriophage pIX coat protein as described in Shi et al., (2010) J Mol Biol 397:385-96, and Int. Patent Publ. No. WO09/085462). The libraries may be screened for phage binding to human and/or cyno PSMA, CD33, IL1RAP, TMEFF2, or CD3 and the obtained positive clones may be further characterized, the Fabs isolated from the clone lysates, and expressed as full length IgGs. Such phage display methods for isolating human antibodies are described in for example: U.S. Patent Nos. 5,223,409, 5,403,484, 5,571,698, 5,427,908, 5,580,717, 5,969,108, 6,172,197, 5,885,793; 6,521,404; 6,544,731; 6,555,313; 6,582,915 and 6,593,081.

Preparation of immunogenic antigens and monoclonal antibody production may be performed using any suitable technique, such as recombinant protein production. The immunogenic antigens may be administered to an animal in the form of purified protein, or protein mixtures including whole cells or cell or tissue extracts, or the antigen may be formed de novo in the animal's body from nucleic acids encoding said antigen or a portion thereof.

Generation and use of bispecific and multispecific CD3 antibodies

The invention provides bispecific and multispecific antibodies comprising a first domain that specifically binds CD3 and a second domain that specifically binds a second antigen. The second antigen may be a tumor associated antigen (TAA) or an antigen on pathogenic cells.

Exemplary anti-CD3 antibodies that may be used to engineer bispecific and multispecific antibodies comprising a first domain that specifically binds CD3 and a second domain that specifically binds a second antigen include CD3 antibodies comprising the V_H/V_L sequences and heavy/light chain CDRs shown in Table 7A and 7B, respectively, and the engineered variants thereof described in Table 10 and Table 11, and accompanying text. For example, the CDRs and/or the V_H/V_L domains of the CD3 antibodies CD3B312, CD3B313, CD3B314, CD3B315, CD3B316, CD3B317, CD3B337, CD3B373, CD3B376, CD3B389, CD3B450, and CD3B467 described herein may be used to generate bispecific and multispecific antibodies comprising a first domain that specifically binds CD3 and a second domain that specifically binds a second antigen.

The herein described anti-CD3 antibody CDRs and/or the VH/VL domains may be incorporated into bispecific antibodies comprising a first domain that specifically binds CD3 and a second domain that specifically binds a second antigen.

The herein described anti-CD3 antibody CDRs and/or the VH/VL domains may be incorporated into bispecific antibodies comprising PSMA binding VH/VL domains described herein and in Table 23. The herein described anti-CD3 antibodies and/or the VH/VL domains may be incorporated into bispecific antibodies comprising IL1RAP binding VH/VL domains described herein and in Table 30. The herein described anti-CD3 antibody CDRs and/or the VH/VL domains may be incorporated into bispecific antibodies comprising CD33 binding VH/VL domains described herein and in Table 38. For example, the VH/VL domains of the PSMA antibodies PSMB119, PSMB120, PSMB121, PSMB122, PSMB123, PSMB87, PSMB126, PSMB127, PSMB128, PSMB129, PSMB130, PSMB120, PSMB121, PSMB122, PSMB123, PSMB127, PSMB128, PSMB130, PSMB344, PSMB345, PSMB346, PSMB347, PSMB349, PSMB358, PSMB359, PSMB360, PSMB361, PSMB362, PSMB363, and PSMB365 described herein may be used to generate bispecific PSMA×CD3 antibodies.

Exemplary TAAs are PSMA, CD33, TMEFF2, and IL1RAP. The exemplary multispecific PSMA×CD3, CD33×CD3, TMEFF2×CD3, and IL1RAP×CD3 antibodies provided herein have a first domain that specifically bind CD3 and a second domain that specifically binds PSMA, CD33, TMEFF2, or IL1RAP. Exemplary anti-PSMA antibodies that may be used to engineer bispecific PSMA×CD3 molecules are those described herein, which may comprise heavy and light chain sequences including but not limited to the heavy and light chain sequences listed in Table 23. Exemplary anti-IL1RAP antibodies that may be used to engineer bispecific IL1RAP×CD3 molecules are those described herein, which may comprise heavy and light chain variable region sequences including but not limited to the heavy and light chain variable region sequences provided in Table 35. Exemplary anti-CD33 antibodies that may be used to engineer bispecific CD33×CD3 molecules are those described herein, which may comprise heavy and light chain variable region sequences including but not limited to the heavy and light chain variable region sequences provided in Table 43. Exemplary anti-TMEFF2 antibodies that may be used to engineer bispecific TMEFF2×CD3 molecules are those described herein, which may comprise heavy and light chain variable region sequences including but not limited to the heavy and light chain variable region sequences provided in Tables 59, 66-68.

The generated bispecific antibodies may be tested for their binding to CD3 and/or the second antigen and/or for their desired functional characteristics, such as T-cell mediated killing of cells that express the second antigen.

The bispecific antibodies provided herein include antibodies having a full-length
5 antibody structure.

“Fab-arm” or “half molecule” refers to one heavy chain-light chain pair that specifically binds an antigen.

Full length bispecific antibodies as described herein may be generated for example using Fab arm exchange (or half molecule exchange) between two monospecific bivalent antibodies by
10 introducing substitutions at the heavy chain CH3 interface in each half molecule to favor heterodimer formation of two antibody half molecules having distinct specificity either *in vitro* in cell-free environment or using co-expression. The Fab arm exchange reaction is the result of a disulfide-bond isomerization reaction and dissociation-association of CH3 domains. The heavy chain disulfide bonds in the hinge regions of the parental monospecific antibodies are reduced.
15 The resulting free cysteines of one of the parental monospecific antibodies form an inter heavy-chain disulfide bond with cysteine residues of a second parental monospecific antibody molecule and simultaneously CH3 domains of the parental antibodies release and reform by dissociation-association. The CH3 domains of the Fab arms may be engineered to favor heterodimerization over homodimerization. The resulting product is a bispecific antibody having two Fab arms or
20 half molecules, which each bind a distinct epitope, i.e. an epitope on CD3 and an epitope on the second antigen.

“Homodimerization” refers to an interaction of two heavy chains having identical CH3 amino acid sequences. “Homodimer” refers to an antibody having two heavy chains with identical CH3 amino acid sequences.

25 “Heterodimerization” refers to an interaction of two heavy chains having non-identical CH3 amino acid sequences. “Heterodimer” refers to an antibody having two heavy chains with non-identical CH3 amino acid sequences.

In some embodiments, the bispecific antibodies include designs such as the Triomab/Quadroma (Trion Pharma/Fresenius Biotech), Knob-in-Hole (Genentech), CrossMAbs
30 (Roche) and the electrostatically-matched (Chugai, Amgen, NovoNordisk, Oncomed), the LUZ-

Y (Genentech), the Strand Exchange Engineered Domain body (SEEDbody)(EMD Serono), the Biclonic (Merus) and the DuoBody[®] Technology (Genmab A/S).

The Triomab quadroma technology may be used to generate full-length bispecific antibodies, incorporating the VH and VL of the anti-CD3 antibodies of the invention. Triomab
5 technology promotes Fab arm exchange between two parental chimeric antibodies, one parental mAb having IgG2a and the second parental mAb having rat IgG2b constant regions, yielding chimeric bispecific antibodies.

The “knob-in-hole” strategy (see, e.g., Intl. Publ. No. WO 2006/028936) may be used to generate full-length bispecific antibodies. Briefly, selected amino acids forming the interface of
10 the CH3 domains in human IgG can be mutated at positions affecting CH3 domain interactions to promote heterodimer formation. An amino acid with a small side chain (hole) is introduced into a heavy chain of an antibody specifically binding a first antigen and an amino acid with a large side chain (knob) is introduced into a heavy chain of an antibody specifically binding a second antigen. After co-expression of the two antibodies, a heterodimer is formed as a result of
15 the preferential interaction of the heavy chain with a “hole” with the heavy chain with a “knob”. Exemplary CH3 substitution pairs forming a knob and a hole are (expressed as modified position in the first CH3 domain of the first heavy chain/ modified position in the second CH3 domain of the second heavy chain): T366Y/F405A, T366W/F405W, F405W/Y407A, T394W/Y407T, T394S/Y407A, T366W/T394S, F405W/T394S and T366W/T366S_L368A_Y407V.

20 The CrossMAb technology may be used to generate full-length bispecific antibodies. CrossMAbs, in addition to utilizing the “knob-in-hole” strategy to promoter Fab arm exchange, have in one of the half arms the CH1 and the CL domains exchanged to ensure correct light chain pairing of the resulting bispecific antibody (see e.g. U.S. Patent No. 8,242,247).

Other cross-over strategies may be used to generate full length bispecific antibodies by
25 exchanging variable or constant, or both domains between the heavy chain and the light chain or within the heavy chain in the bispecific antibodies, either in one or both arms. These exchanges include for example VH-CH1 with VL-CL, VH with VL, CH3 with CL and CH3 with CH1 as described in Int. Patent Publ. Nos. WO2009/080254, WO2009/080251, WO2009/018386 and WO2009/080252.

30 Other strategies such as promoting heavy chain heterodimerization using electrostatic interactions by substituting positively charged residues at one CH3 surface and negatively

charged residues at a second CH3 surface may be used, as described in US Patent Publ. No. US2010/0015133; US Patent Publ. No. US2009/0182127; US Patent Publ. No. US2010/028637 or US Patent Publ. No. US2011/0123532. In other strategies, heterodimerization may be promoted by following substitutions (expressed as modified position in the first CH3 domain of the first heavy chain/ modified position in the second CH3 domain of the second heavy chain):

5 L351Y_F405A_Y407V/T394W, T366I_K392M_T394W/F405A_Y407V, T366L_K392M_T394W/F405A_Y407V, L351Y_Y407A/T366A_K409F, L351Y_Y407A/T366V_K409F, Y407A/T366A_K409F, or T350V_L351Y_F405A_Y407V/T350V_T366L_K392L_T394W as described in U.S. Patent

10 Publ. No. US2012/0149876 or U.S. Patent Publ. No. US2013/0195849.

LUZ-Y technology may be utilized to generate bispecific antibodies. In this technology, a leucine zipper is added into the C terminus of the CH3 domains to drive the heterodimer assembly from parental mAbs that is removed post-purification as described in Wranik et al., (2012) J Biol Chem 287(52): 42221-9.

15 SEEDbody technology may be utilized to generate bispecific antibodies. SEEDbodies have, in their constant domains, select IgG residues substituted with IgA residues to promote heterodimerization as described in U.S. Patent No. US20070287170.

The bispecific antibodies described herein may be generated *in vitro* in a cell-free environment by introducing asymmetrical mutations in the CH3 regions of two monospecific

20 homodimeric antibodies and forming the bispecific heterodimeric antibody from two parent monospecific homodimeric antibodies in reducing conditions to allow disulfide bond isomerization according to methods described in Int. Patent Publ. No. WO2011/131746). In the methods, the first monospecific bivalent antibody (i.e., the antibody that specifically binds the second antigen; e.g., anti-PSMA, anti-CD33, anti-TMEFF2 or anti-IL1RAP antibody) and the

25 second monospecific bivalent antibody (i.e., anti-CD3 antibody) are engineered to have certain substitutions at the CH3 domain that promoter heterodimer stability; the antibodies are incubated together under reducing conditions sufficient to allow the cysteines in the hinge region to undergo disulfide bond isomerization; thereby generating the bispecific antibody by Fab arm exchange. The incubation conditions are restored to non-reducing. Exemplary reducing agents

30 that may be used are 2- mercaptoethylamine (2-MEA), dithiothreitol (DTT), dithioerythritol (DTE), glutathione, tris(2-carboxyethyl)phosphine (TCEP), L-cysteine and beta-

mercaptoethanol. For example, incubation for at least 90 min at a temperature of at least 20°C in the presence of at least 25 mM 2-MEA or in the presence of at least 0.5 mM dithiothreitol at a pH of from 5-8, for example at pH of 7.0 or at pH of 7.4 may be used.

In some embodiments described herein, the bispecific antibody comprising a first domain
5 that specifically binds CD3 and a second domain that specifically binds a second antigen comprises at least one substitution in an antibody CH3 constant domain.

In some embodiments described herein, the at least one substitution in the antibody CH3 constant domain is K409R, F405L or F405L and R409K substitution, wherein residue numbering is according to the EU Index.

10 Antibody domains and numbering are well known. "Asymmetrical" refers to non-identical substitutions in the two CH3 domains in two separate heavy chains in an antibody. An IgG1 CH3 region typically consists of residues 341-446 on IgG1 (residue numbering according to the EU index).

In some embodiments described herein, the bispecific antibody is an IgG1 isotype and
15 comprises a F405L substitution in an antibody first heavy chain (HC1) and a K409R substitution in an antibody second heavy chain (HC2) when compared to the wild-type IgG1.

In some embodiments described herein, the bispecific antibody is an IgG1 isotype and comprises a K409R substitution in an antibody first heavy chain (HC1) and a F405L substitution in an antibody second heavy chain (HC2) when compared to the wild-type IgG1.

20 In some embodiments described herein, the bispecific antibody is an IgG4 isotype and comprises a S228P substitution in the HC1 and S228P, F405L and R409K substitutions in the HC2 when compared to the wild-type IgG4.

In some embodiments described herein, the bispecific antibody is an IgG4 isotype and comprises S228P, F405L and R409K substitutions in the HC1 and a S228P substitution in the
25 HC2 when compared to the wild-type IgG4.

In some embodiments described herein, the bispecific antibody is an IgG4 isotype and comprises S228P, F234A and L235A substitutions in the HC1 and S228P, F234A, L235A, F405L and R409K substitutions in the HC2 when compared to the wild-type IgG4.

In some embodiments described herein, the bispecific antibody is an IgG4 isotype and
30 comprises S228P, F234A, L235A, F405L and R409K substitutions in the HC1 and a S228P, F234A and L235A substitutions in the HC2 when compared to the wild-type IgG4.

In some embodiments described herein, the bispecific antibody of the invention comprises at least one, two, three, four, five, six, seven or eight asymmetrical substitutions in the HC1 and the HC2 at residue positions 350, 366, 368, 370, 399, 405, 407 or 409, when residue numbering is according to the EU index.

5 In some embodiments described herein, the bispecific antibody of the invention comprises at least one, two, three or four asymmetrical substitutions in the HC1 and the HC2 at residue positions 350, 370, 405 or 409, when residue numbering is according to the EU index.

In some embodiments described herein, the bispecific antibody of the invention comprises at least one asymmetrical substitution in the HC1 and the HC2 at residue positions
10 405 or 409, when residue numbering is according to the EU index.

Substitutions are typically made at the DNA level to a molecule such as the constant domain of the antibody using standard methods.

The antibodies of the invention may be engineered into various well-known antibody forms.

15 In some embodiments, the bispecific antibody of the present invention is a cross-body.

In some embodiments, the bispecific antibodies of the invention include recombinant IgG-like dual targeting molecules, wherein the two sides of the molecule each contain the Fab fragment or part of the Fab fragment of at least two different antibodies; IgG fusion molecules, wherein full length IgG antibodies are fused to an extra Fab fragment or parts of Fab fragment;
20 Fc fusion molecules, wherein single chain Fv molecules or stabilized diabodies are fused to heavy-chain constant-domains, Fc-regions or parts thereof; Fab fusion molecules, wherein different Fab-fragments are fused together; ScFv- and diabody-based and heavy chain antibodies (e.g., domain antibodies, nanobodies) wherein different single chain Fv molecules or different diabodies or different heavy-chain antibodies (e.g. domain antibodies, nanobodies) are fused to
25 each other or to another protein or carrier molecule.

In some embodiments, recombinant IgG-like dual targeting molecules include Dual Targeting (DT)-Ig (GSK/Domantis), Two-in-one Antibody (Genentech) and mAb2 (F-Star).

In some embodiments, IgG fusion molecules include Dual Variable Domain (DVD)-Ig (Abbott), Ts2Ab (MedImmune/AZ) and BsAb (Zymogenetics), HERCULES (Biogen Idec) and
30 TvAb (Roche).

In some embodiments, Fc fusion molecules include to ScFv/Fc Fusions (Academic Institution), SCORPION (Emergent BioSolutions/Trubion, Zymogenetics/BMS) and Dual Affinity Retargeting Technology (Fc-DART) (MacroGenics).

In some embodiments, Fab fusion bispecific antibodies include F(ab)₂

- 5 (Medarex/AMGEN), Dual-Action or Bis-Fab (Genentech), Dock-and-Lock (DNL) (ImmunoMedics), Bivalent Bispecific (Biotecnol) and Fab-Fv (UCB-Celltech). ScFv-, diabody-based and domain antibodies include Bispecific T Cell Engager (BITE) (Micromet), Tandem Diabody (Tandab) (Affimed), Dual Affinity Retargeting Technology (DART) (MacroGenics), Single-chain Diabody (Academic), TCR-like Antibodies (AIT, ReceptorLogics), Human Serum
- 10 Albumin ScFv Fusion (Merrimack) and COMBODY (Epigen Biotech), dual targeting nanobodies (Ablynx), dual targeting heavy chain only domain antibodies. Various formats of bispecific antibodies have been described, for example in Chames and Baty (2009) Curr Opin Drug Disc Dev 12: 276 and in Nunez-Prado et al., (2015) Drug Discovery Today 20(5):588-594.

Table 2 summarizes exemplary monoclonal antibodies described herein that can be used

15 to generate the bispecific antibodies of the invention.

Table 2. Exemplary monoclonal antibodies that can be used to generate the bispecific antibodies of the invention

First Domain	Second Domain		
anti-CD3	anti-PSMA	anti-CD33	anti-IL1RAP
CD3B312	PSMB87	C33B760	IAPB3
CD3B313	PSMB119	C33B777	IAPB9
CD3B314	PSMB120	C33B778	IAPB17
CD3B315	PSMB121	C33B782	IAPB23
CD3B316	PSMB122	C33B792	IAPB25
CD3B317	PSMB123	C33B799	IAPB29
CD3B337	PSMB124	C33B806	IAPB38
CD3B373	PSMB126	C33B830	IAPB47
CD3B376	PSMB127	C33B836	IAPB55
CD3B389	PSMB129	C33B903	IAPB57
CD3B450	PSMB130	C33B904	IAPB61
CD3B467	PSMB344		

	PSMB345	C33B905	IAPB62
	PSMB346	C33B907	IAPB63
	PSMB347	C33B908	IAPB64
	PSMB349		IAPB65
	PSMB358		
	PSMB359		
	PSMB360		
	PSMB361		
	PSMB362		
	PSMB363		
	PSMB365		

Exemplary anti-TMEFF2 antibodies that may be used to engineer bispecific TMEFF2×CD3 molecules are those described herein, which may comprise heavy and light chain variable region sequences including but not limited to the heavy and light chain variable region sequences provided in Tables 59, 66-68.

5 In some embodiments, the anti-CD3 antibody is a multispecific antibody, for example a bispecific antibody comprising a first domain that specifically binds CD3 and a second domain that specifically binds a second antigen. In some embodiments, the second, or target, antigen is a cell surface antigen that is expressed on a target cell other than an immune effector cell. In some embodiments, the second antigen is a TAA. Exemplary TAAs are PSMA, CD33, TMEFF2, and
10 IL1RAP.

The invention provides a bispecific antibody comprising a first domain that specifically binds CD3 and a second domain that specifically binds a second antigen.

In some embodiments, the first domain comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2, and the LCDR3 of SEQ ID NOs: 662, 663, 664, 671, 673, and 690,
15 respectively. In some embodiments, the first domain comprises the VH and VL of SEQ ID NOs: 652 and 661, respectively. In some embodiments, the first domain comprises the HC and LC of SEQ ID NOs: 640 and 676, respectively. In some embodiments, the first domain comprises the VH and VL of SEQ ID NOs: 657 and 678, respectively. In some embodiments, the first domain comprises the HC and LC of SEQ ID NOs: 675 and 677, respectively.

In some embodiments, the first domain comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2, and the LCDR3 of SEQ ID NOs:662, 663, 664, 773, 673, and 690, respectively. In some embodiments, the first domain comprises the VH and VL of SEQ ID NOs:657 and 678, respectively. In some embodiments, the first domain comprises the HC and
5 LC of SEQ ID NOs:675 and 677, respectively.

The invention also provides the bispecific antibody comprising a first domain that specifically binds CD3 and a second domain that specifically binds a second antigen of the invention for use in therapy.

The invention also provides the bispecific antibody comprising a first domain that
10 specifically binds CD3 and a second domain that specifically binds a second antigen of the invention for use in treating a cell proliferative disorder.

The invention also provides the bispecific antibody comprising a first domain that specifically binds CD3 and a second domain that specifically binds a second antigen of the invention for use in treating cancer.

15 The invention also provides the bispecific antibody comprising a first domain that specifically binds CD3 and a second domain that specifically binds a second antigen of the invention for use in treating an autoimmune disease.

The invention also provides the bispecific antibody comprising a first domain that specifically binds CD3 and a second domain that specifically binds a second antigen of the
20 invention for use in the manufacture of a medicament for treating cancer.

The invention also provides the bispecific antibody comprising a first domain that specifically binds CD3 and a second domain that specifically binds a second antigen of the invention for use in the manufacture of a medicament for treating an autoimmune disorder.

A further aspect of the invention is a method of treating a cell proliferative disorder or an
25 autoimmune disorder in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the anti-CD3 antibody of the invention. In some embodiments, the anti-CD3 antibody or the bispecific antibody comprising a first domain that specifically binds CD3 and a second domain that specifically binds a second antigen of the invention is administered to the subject in a dosage of about 0.01 mg/kg to about 10 mg/kg. In

some embodiments, the anti-CD3 antibody or the bispecific antibody comprising a first domain that specifically binds CD3 and a second domain that specifically binds a second antigen of the invention is administered to the subject in a dosage of about 0.1 mg/kg to about 10 mg/kg. In some embodiments, the anti-CD3 antibody or the bispecific antibody comprising a first domain that specifically binds CD3 and a second domain that specifically binds a second antigen of the invention is administered to the subject in a dosage of about 1 mg/kg. In some embodiments, the anti-CD3 antibody or the bispecific antibody comprising a first domain that specifically binds CD3 and a second domain that specifically binds a second antigen of the invention is administered subcutaneously, intravenously, intramuscularly, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally. In some embodiments, the anti-CD3 antibody or the bispecific antibody comprising a first domain that specifically binds CD3 and a second domain that specifically binds a second antigen of the invention is administered subcutaneously. In some embodiments, the anti-CD3 antibody or the bispecific antibody comprising a first domain that specifically binds CD3 and a second domain that specifically binds a second antigen of the invention is administered intravenously.

In any of the preceding uses or methods, the cell proliferative disorder is cancer. In some embodiments, the cancer is selected from the group consisting of esophageal cancer, stomach cancer, small intestine cancer, large intestine cancer, colorectal cancer, breast cancer, non-small cell lung cancer, non-Hodgkin's lymphoma (NHL), B cell lymphoma, B cell leukemia, multiple myeloma, renal cancer, prostate cancer, liver cancer, head and neck cancer, melanoma, ovarian cancer, mesothelioma, glioblastoma, germinal-center B-cell-like (GCB) DLBCL, activated B-cell-like (ABC) DLBCL, follicular lymphoma (FL), mantle cell lymphoma (MCL), acute myeloid leukemia (AML), chronic lymphoid leukemia (CLL), marginal zone lymphoma (MZL), small lymphocytic leukemia (SLL), lymphoplasmacytic lymphoma (LL), Waldenstrom macroglobulinemia (WM), central nervous system lymphoma (CNSL), Burkitt's lymphoma (BL), B-cell prolymphocytic leukemia, Splenic marginal zone lymphoma, Hairy cell leukemia, Splenic lymphoma/leukemia, unclassifiable, Splenic diffuse red pulp small B-cell lymphoma, Hairy cell leukemia variant, Waldenstrom macroglobulinemia, Heavy chain diseases, Plasma cell myeloma, Solitary plasmacytoma of bone, Extravascular plasmacytoma, Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma), Nodal marginal

zone lymphoma, Pediatric nodal marginal zone lymphoma, Pediatric follicular lymphoma, Primary cutaneous follicle centre lymphoma, T-cell/histiocyte rich large B-cell lymphoma, Primary DLBCL of the CNS, Primary cutaneous DLBCL, leg type, EBV-positive DLBCL of the elderly, DLBCL associated with chronic inflammation, Lymphomatoid granulomatosis, Primary
5 mediastinal (thymic) large B-cell lymphoma. Intravascular large B-cell lymphoma, ALK-positive large B-cell lymphoma, Plasmablastic lymphoma, Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease, Primary effusion lymphoma: B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma, and B-cell lymphoma, unclassifiable, with features intermediate between
10 diffuse large B-cell lymphoma, classical Hodgkin lymphoma and light chain amyloidosis.

In some embodiments, the cancer is esophageal cancer. In some embodiments, the cancer is an adenocarcinoma, for example, a metastatic adenocarcinoma (e.g., a colorectal adenocarcinoma, a gastric adenocarcinoma, or a pancreatic adenocarcinoma).

In any of the preceding uses or methods, the autoimmune disorder can be selected from
15 the group consisting of rheumatoid arthritis, juvenile rheumatoid arthritis, systemic lupus erythematosus (SLE), Wegener's disease, inflammatory bowel disease, idiopathic thrombocytopenic purpura (ITP), thrombotic thrombocytopenic purpura (TTP), autoimmune thrombocytopenia, multiple sclerosis, psoriasis, IgA nephropathy, IgM polyneuropathies, myasthenia gravis, vasculitis, diabetes mellitus, Reynaud's syndrome, Sjorgen's syndrome,
20 glomerulonephritis, Neuromyelitis Optica (NMO), and IgG neuropathy.

In another aspect, the invention features a kit comprising: (a) a composition comprising any one of the preceding anti-CD3 antibodies or the bispecific antibodies comprising a first domain that specifically binds CD3 and a second domain that specifically binds a second antigen of the invention and (b) a package insert comprising instructions for administering the
25 composition to a subject to treat or delay progression of a cell proliferative disorder. The term "package insert" is used to refer to instructions customarily included in commercial packages of therapeutic products, that contain information about the indications, usage, dosage, administration, combination therapy, contraindications and/or warnings concerning the use of such therapeutic products.

30 In any of the preceding uses or methods, the subject can be a human.

Polynucleotides, Vectors, and Host Cells

Also disclosed are isolated polynucleotides that encode the anti-CD3 antibodies of the invention or the bispecific antibodies comprising a first domain that specifically binds CD3 and a second domain that specifically binds a second antigen of the invention. The isolated

5 polynucleotides capable of encoding the variable domains provided herein may be included on the same, or different, vectors to produce antibodies or antigen-binding fragments of the invention.

In some embodiments, the polynucleotides of the invention include a polynucleotide encoding a leader sequence. Any leader sequence known in the art may be employed. The
10 polynucleotide encoding the leader sequence may include, a restriction endonuclease cleavage site or a translation initiation site.

Also provided are vectors comprising the polynucleotides of the invention. The vectors can be expression vectors. The expression vector may contain one or more additional sequences such as but not limited to regulatory sequences (e.g., promoter, enhancer), a selection marker,
15 and a polyadenylation signal. Vectors for transforming a wide variety of host cells are well known and include, but are not limited to, plasmids, phagemids, cosmids, baculoviruses, bacmids, bacterial artificial chromosomes (BACs), yeast artificial chromosomes (YACs), as well as other bacterial, yeast and viral vectors.

Recombinant expression vectors within the scope of the description include synthetic, or
20 cDNA-derived nucleic acid fragments that encode at least one recombinant protein which may be operably linked to suitable regulatory elements. Such regulatory elements may include a transcriptional promoter, sequences encoding suitable mRNA ribosomal binding sites, and sequences that control the termination of transcription and translation. Expression vectors, especially mammalian expression vectors, may also include one or more nontranscribed elements
25 such as an origin of replication, a suitable promoter and enhancer linked to the gene to be expressed, other 5' or 3' flanking nontranscribed sequences, 5' or 3' nontranslated sequences (such as necessary ribosome binding sites), a polyadenylation site, splice donor and acceptor sites, or transcriptional termination sequences. An origin of replication that confers the ability to replicate in a host may also be incorporated.

The transcriptional and translational control sequences in expression vectors to be used in transforming vertebrate cells may be provided by viral sources. Exemplary vectors may be constructed as described by Okayama and Berg, 3 *Mol. Cell. Biol.* 280 (1983).

In some embodiments, the antibody- or antigen-binding fragment-coding sequence is placed under control of a powerful constitutive promoter, such as the promoters for the following genes: hypoxanthine phosphoribosyl transferase (HPRT), adenosine deaminase, pyruvate kinase, beta-actin, human myosin, human hemoglobin, human muscle creatine, and others. In addition, many viral promoters function constitutively in eukaryotic cells and are suitable for use with the described embodiments. Such viral promoters include without limitation, Cytomegalovirus (CMV) immediate early promoter, the early and late promoters of SV40, the Mouse Mammary Tumor Virus (MMTV) promoter, the long terminal repeats (LTRs) of Moloney leukemia virus, Human Immunodeficiency Virus (HIV), Epstein Barr Virus (EBV), Rous Sarcoma Virus (RSV), and other retroviruses, and the thymidine kinase promoter of Herpes Simplex Virus. In one embodiment, the PSMA-specific antibody or antigen-binding fragment thereof coding sequence is placed under control of an inducible promoter such as the metallothionein promoter, tetracycline-inducible promoter, doxycycline-inducible promoter, promoters that contain one or more interferon-stimulated response elements (ISRE) such as protein kinase R 2',5'-oligoadenylate synthetases, Mx genes, ADAR1, and the like.

Vectors described herein may contain one or more Internal Ribosome Entry Site(s) (IRES). Inclusion of an IRES sequence into fusion vectors may be beneficial for enhancing expression of some proteins. In some embodiments the vector system will include one or more polyadenylation sites (e.g., SV40), which may be upstream or downstream of any of the aforementioned nucleic acid sequences. Vector components may be contiguously linked, or arranged in a manner that provides optimal spacing for expressing the gene products (i.e., by the introduction of "spacer" nucleotides between the ORFs), or positioned in another way. Regulatory elements, such as the IRES motif, may also be arranged to provide optimal spacing for expression.

The vectors may comprise selection markers, which are well known in the art. Selection markers include positive and negative selection markers, for example, antibiotic resistance genes (e.g., neomycin resistance gene, a hygromycin resistance gene, a kanamycin resistance gene, a tetracycline resistance gene, a penicillin resistance gene), glutamate synthase genes, HSV-TK,

HSV-TK derivatives for ganciclovir selection, or bacterial purine nucleoside phosphorylase gene for 6-methylpurine selection (Gadi et al., 7 *Gene Ther.* 1738-1743 (2000)). A nucleic acid sequence encoding a selection marker or the cloning site may be upstream or downstream of a nucleic acid sequence encoding a polypeptide of interest or cloning site.

5 The vectors described herein may be used to transform various cells with the genes encoding the described antibodies or antigen-binding fragments. For example, the vectors may be used to generate anti-CD3, anti-PSMA, anti-CD33, anti-TMEFF2, or anti-IL1RAP antibodies or antigen-binding fragment-producing cells. Thus, the invention also provides a host cell comprising the vectors of the invention.

10 Numerous techniques are known in the art for the introduction of foreign genes into cells and may be used to construct the recombinant cells for purposes of carrying out the described methods, in accordance with the various embodiments described and exemplified herein. The technique used should provide for the stable transfer of the heterologous gene sequence to the host cell, such that the heterologous gene sequence is heritable and expressible by the cell
15 progeny, and so that the necessary development and physiological functions of the recipient cells are not disrupted. Techniques which may be used include but are not limited to chromosome transfer (e.g., cell fusion, chromosome mediated gene transfer, micro cell mediated gene transfer), physical methods (e.g., transfection, spheroplast fusion, microinjection, electroporation, liposome carrier), viral vector transfer (e.g., recombinant DNA viruses,
20 recombinant RNA viruses) and the like (described in Cline, 29 *Pharmac. Ther.* 69-92 (1985)). Calcium phosphate precipitation and polyethylene glycol (PEG)-induced fusion of bacterial protoplasts with mammalian cells may also be used to transform cells.

Cells suitable for use in the expression of the antibodies or antigen-binding fragments described herein are preferably eukaryotic cells, more preferably cells of plant, rodent, or human
25 origin, for example but not limited to NSO, CHO, CHOK1, perC.6, Tk-ts13, BHK, HEK293 cells, COS-7, T98G, CV-1/EBNA, L cells, C127, 3T3, HeLa, NS1, Sp2/0 myeloma cells, and BHK cell lines, among others. In addition, expression of antibodies may be accomplished using hybridoma cells. Methods for producing hybridomas are well established in the art.

Cells transformed with expression vectors of the invention may be selected or screened
30 for recombinant expression of the antibodies or antigen-binding fragments of the invention. Recombinant-positive cells are expanded and screened for subclones exhibiting a desired

phenotype, such as high level expression, enhanced growth properties, or the ability to yield proteins with desired biochemical characteristics, for example, due to protein modification or altered post-translational modifications. These phenotypes may be due to inherent properties of a given subclone or to mutation. Mutations may be effected through the use of chemicals, UV-
5 wavelength light, radiation, viruses, insertional mutagens, inhibition of DNA mismatch repair, or a combination of such methods.

Pharmaceutical Compositions/Administration

The invention also provides for pharmaceutical compositions comprising the antibodies of the invention and a pharmaceutically acceptable carrier. For therapeutic use, the antibodies of
10 the invention may be prepared as pharmaceutical compositions containing an effective amount of the antibody as an active ingredient in a pharmaceutically acceptable carrier. "Carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the antibody of the invention is administered. Such vehicles may be liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil,
15 sesame oil and the like. For example, 0.4% saline and 0.3% glycine may be used. These solutions are sterile and generally free of particulate matter. They may be sterilized by conventional, well-known sterilization techniques (e.g., filtration). The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions such as pH adjusting and buffering agents, stabilizing, thickening,
20 lubricating and coloring agents, etc. The concentration of the antibodies of the invention in such pharmaceutical formulation may vary, from less than about 0.5%, usually to at least about 1% to as much as 15 or 20% by weight and may be selected primarily based on required dose, fluid volumes, viscosities, etc., according to the particular mode of administration selected. Suitable vehicles and formulations, inclusive of other human proteins, e.g., human serum albumin, are
25 described, for example, in e.g. Remington: The Science and Practice of Pharmacy, 21st Edition, Troy, D.B. ed., Lipincott Williams and Wilkins, Philadelphia, PA 2006, Part 5, Pharmaceutical Manufacturing pp 691-1092, See especially pp. 958-989.

The mode of administration for therapeutic use of the antibodies of the invention may be any suitable route that delivers the antibody to the host, such as parenteral administration, e.g.,
30 intradermal, intramuscular, intraperitoneal, intravenous or subcutaneous, pulmonary,

transmucosal (oral, intranasal, intravaginal, rectal), using a formulation in a tablet, capsule, solution, powder, gel, particle; and contained in a syringe, an implanted device, osmotic pump, cartridge, micropump; or other means appreciated by the skilled artisan, as well known in the art. Site specific administration may be achieved by for example intratumoral, intrarticular,

5 intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracerebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intracardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravascular, intravesical, intralesional, vaginal, rectal, buccal, sublingual,
10 intranasal, or transdermal delivery.

The antibodies of the invention may be administered to a subject by any suitable route, for example parentally by intravenous (i.v.) infusion or bolus injection, intramuscularly or subcutaneously or intraperitoneally. i.v. infusion may be given over for example 15, 30, 60, 90, 120, 180, or 240 minutes, or from 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 hours.

15 The dose given to a subject is sufficient to alleviate or at least partially arrest the disease being treated (“therapeutically effective amount”) and may be sometimes 0.005 mg to about 100 mg/kg, e.g. about 0.05 mg to about 30 mg/kg or about 5 mg to about 25 mg/kg, or about 4 mg/kg, about 8 mg/kg, about 16 mg/kg or about 24 mg/kg, or for example about 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 mg/kg, but may even higher, for example about 15, 16, 17, 18, 19, 20, 21, 22, 23,
20 24, 25, 30, 40, 50, 60, 70, 80, 90 or 100 mg/kg.

A fixed unit dose may also be given, for example, 50, 100, 200, 500 or 1000 mg, or the dose may be based on the patient's surface area, e.g., 500, 400, 300, 250, 200, or 100 mg/m². Usually between 1 and 8 doses, (e.g., 1, 2, 3, 4, 5, 6, 7 or 8) may be administered to treat the patient, but 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more doses may be given.

25 The administration of the antibodies of the invention may be repeated after one day, two days, three days, four days, five days, six days, one week, two weeks, three weeks, one month, five weeks, six weeks, seven weeks, two months, three months, four months, five months, six months or longer. Repeated courses of treatment are also possible, as is chronic administration. The repeated administration may be at the same dose or at a different dose. For example, the
30 antibodies of the invention described herein may be administered at 8 mg/kg or at 16 mg/kg at weekly interval for 8 weeks, followed by administration at 8 mg/kg or at 16 mg/kg every two

weeks for an additional 16 weeks, followed by administration at 8 mg/kg or at 16 mg/kg every four weeks by intravenous infusion.

For example, the antibodies in the methods described herein, may be provided as a daily dosage in an amount of about 0.1-100 mg/kg, such as 0.5, 0.9, 1.0, 1.1, 1.5, 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, 40, 45, 50, 60, 70, 80, 90 or 100 mg/kg, per day, on at least one of day 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, 36, 37, 38, 39, or 40, or alternatively, at least one of week 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 after initiation of treatment, or any combination thereof, using single or divided doses of every 24, 12, 8, 6, 4, or 2 hours, or any combination thereof.

The antibodies in the methods described herein may also be administered prophylactically in order to reduce the risk of developing cancer, delay the onset of the occurrence of an event in cancer progression, and/or reduce the risk of recurrence when a cancer is in remission.

The antibodies provided herein may be lyophilized for storage and reconstituted in a suitable carrier prior to use. This technique has been shown to be effective with conventional protein preparations and well-known lyophilization and reconstitution techniques can be employed.

Methods of Detecting CD3, PSMA, CD33, IL1RAP, TMEFF2 or target antigen and CD3

Provided herein are methods of detecting CD3, PSMA, CD33, TMEFF2, or IL1RAP in a sample, comprising obtaining the sample, contacting the sample with the anti-CD3, the anti-PSMA, the anti-CD33, anti- TMEFF2, or the anti-IL1RAP antibody of the invention and detecting the antibody bound to CD3, PSMA, CD33, TMEFF2, or IL1RAP in the sample.

Further provided are methods of detecting CD3 and the second antigen (for example PSMA, CD33, TMEFF2 or IL1RAP) in a sample, comprising obtaining the sample, contacting the sample with the bispecific antibody comprising a first domain that specifically binds CD3 and a second domain that specifically binds a second antigen, , and detecting the antibody bound to CD3 and the second antigen in the sample.

In some embodiments described herein, the sample may be derived from urine, blood, serum, plasma, saliva, ascites, circulating cells, circulating tumor cells, cells that are not tissue associated (i.e., free cells), tissues (e.g., surgically resected tumor tissue, biopsies, including fine needle aspiration), histological preparations, and the like.

5 The antibodies of the invention may be detected using known methods. Exemplary methods include direct labeling of the antibodies using fluorescent or chemiluminescent labels, or radiolabels, or attaching to the antibodies of the invention a moiety which is readily detectable, such as biotin, enzymes or epitope tags. Exemplary labels and moieties are ruthenium, ¹¹¹In-DOTA, ¹¹¹In- diethylenetriaminepentaacetic acid (DTPA), horseradish
10 peroxidase, alkaline phosphatase and beta-galactosidase, poly-histidine (HIS tag), acridine dyes, cyanine dyes, fluorone dyes, oxazin dyes, phenanthridine dyes, rhodamine dyes and Alexafluor® dyes.

 The antibodies provided herein may be used in a variety of assays to detect CD3, PSMA, CD33, IL1RAP, TMEFF2 or CD3 and the second antigen in the sample. Exemplary assays are
15 western blot analysis, radioimmunoassay, surface plasmon resonance, immunoprecipitation, equilibrium dialysis, immunodiffusion, electrochemiluminescence (ECL) immunoassay, immunohistochemistry, fluorescence-activated cell sorting (FACS) or ELISA assay.

Antibody Kits

 The invention also provides a kit comprising one or more of the anti-CD3, the anti-
20 PSMA, the anti-CD33, anti-TMEFF2 or the anti-IL1RAP antibodies or the bispecific antibodies comprising a first domain that specifically binds CD3 and a second domain that specifically binds a second antigen of the invention or antigen-binding fragments thereof. The described kits may be used to carry out the methods of using the anti-CD3, the anti-PSMA, the anti-CD33, anti-TMEFF2 or the anti-IL1RAP antibodies or the bispecific antibodies comprising a first domain
25 that specifically binds CD3 and a second domain that specifically binds a second antigen of the invention or other methods known to those skilled in the art. In some embodiments the described kits may include the antibodies or antigen-binding fragments described herein and reagents for use in detecting the presence of CD3 or the second antigen such as PSMA, CD33, IL1RAP, TMEFF2 in a biological sample. Accordingly, the described kits may include one or
30 more of the antibodies, or an antigen-binding fragment(s) thereof, described herein and a vessel

for containing the antibody or fragment when not in use, instructions for use of the antibody or fragment, the antibody or fragment affixed to a solid support, and/or detectably labeled forms of the antibody or fragment, as described herein.

The invention also provides a kit comprising the herein described antibody that
5 specifically binds PSMA. The invention also provides a kit comprising the herein described antibody specifically binding CD33. The invention also provides a kit comprising the herein described antibody specifically binding IL1RAP. The invention also provides a kit comprising the herein described antibody specifically binding TMEFF2.

The kit may be used for therapeutic uses and as diagnostic kits.

10 The kit may be used to detect the presence of CD3, PSMA, CD33, IL1RAP, TMEFF2 and/or the second antigen in a biological sample.

In some embodiments, the kit comprises the antibody of the invention described herein and reagents for detecting the antibody. The kit can include one or more other elements including: instructions for use; other reagents, e.g., a label, a therapeutic agent, or an agent useful
15 for chelating, or otherwise coupling, an antibody to a label or therapeutic agent, or a radioprotective composition; devices or other materials for preparing the antibody for administration; pharmaceutically acceptable carriers; and devices or other materials for administration to a subject.

In some embodiments, the kit comprises the antibody of the invention in a container and
20 instructions for use of the kit.

In some embodiments, the antibody in the kit is labeled.

CD3-Specific Antibodies

Described herein are isolated anti-CD3 antibodies. The anti-CD3 antibodies of the invention bind human CD3 and optionally cynomolgus CD3. In some embodiments, the anti-
25 CD3 antibodies of the invention and fragments thereof bind to human and cynomolgus CD3 with affinities within 5-fold of each other. In other words, the difference in antibody binding is less than a multiple of 5. In this case, the anti-CD3 antibody of the invention can be used for both preclinical evaluation of safety, activity and/or pharmacokinetic profile of CD3 in primates and as a drug in humans. Put in other words, the same CD3-specific molecule can be used in
30 preclinical animal studies as well as in clinical studies in humans. This human/cyno cross-

reactivity leads to highly comparable results and a much-increased predictive power of the animal studies compared to species-specific surrogate molecules. In some embodiments, the anti-CD3 antibodies and fragments thereof of the invention bind an epitope formed by the CD3e/d subunits. The CD3-specific antibodies may be human, humanized, or chimeric. Also
5 exemplified herein are human antibodies generated in OmniRat (Open Monoclonal Technologies (“OMT”), Palo Alto, California, USA, omniab.com).

In some embodiments described herein, the anti-CD3 antibody or fragment thereof has one, two, three, four or five of the following properties:

- 10 a) binds human and *Macaca fascicularis* CD3+ T lymphocytes with a calculated EC₅₀ of 20 nM or less and binds *Macaca fascicularis* CD3-expressing HEK cells with a calculated EC₅₀ of 40 nM or less, wherein the difference in calculated EC₅₀ between binding CD3+ T lymphocytes and binding *Macaca fascicularis* CD3-expressing HEK cells is less than 5-fold, and wherein the calculated EC₅₀ is measured in a whole cell binding assay at 0 °C using flow cytometry;
- 15 b) binds recombinant CD3d from human (SEQ ID NO:691), or binds recombinant CD3e from human (SEQ ID NO:636), or binds recombinant CD3e from *Macaca fascicularis* (SEQ ID NO:693) with an equilibrium dissociation constant (K_D) of 12 nM or less, wherein the K_D is measured using Proteon surface plasmon resonance assay ProteOn XPR36 system at +25°C;
- 20 c) displays no methionine or tryptophan oxidation, or displays no asparagine deamidation, or displays no asparagine isomerization as detected by peptide mapping analysis;
- d) binds residues 1-6 of CD3e as determined by X-ray crystallography; or
- e) activates T cells or induces CD69 expression to a similar degree as cOKT3 or SP34-2 as determined by fluorescence-activated cell sorting assay.

25 The anti-CD3 antibodies and fragments thereof of the invention have an in vitro binding affinity (K_d) to human T cells expressing human CD3 that is from about 5 nM to about 1000 nM, preferably from about 5 nM to about 50 nM, from about 50 nM to about 100 nM, from about 100 nM to about 200 nM, from about 200 nM to about 300 nM, from about 300 nM to about 400 nM, from about 400 nM to about 500 nM, from about 500 nM to about 600 nM, from about 600 nM
30 to about 700 nM, from about 700 nM to about 800 nM, from about 800 nM to about 900 nM, and

from about 900 nM to about 1000 nM, more preferably from about 5 nM to about 300 nM, as determined by flow cytometry.

In some aspects, the anti-CD3 antibodies and fragments thereof of the invention are bivalent antibodies having an in vitro binding affinity (K_d) to human T cells expressing human CD3 that is from about 5 nM to about 1000 nM preferably from about 5 nM to about 50 nM, from about 50 nM to about 100 nM, from about 100 nM to about 200 nM, from about 200 nM to about 300 nM, from about 300 nM to about 400 nM, from about 400 nM to about 500 nM, from about 500 nM to about 600 nM, from about 600 nM to about 700 nM, from about 700 nM to about 800 nM, from about 800 nM to about 900 nM, and from about 900 nM to about 1000 nM, more preferably from about 5 nM to about 300 nM, most preferably about 100 nM, as determined by flow cytometry.

In some aspects, the anti-CD3 antibodies and fragments thereof of the invention are monovalent constructs having an in vitro binding affinity (K_d) to human T cells expressing human CD3 that is from about 5 nM to about 1000 nM preferably from about 5 nM to about 50 nM, from about 50 nM to about 100 nM, from about 100 nM to about 200 nM, from about 200 nM to about 300 nM, from about 300 nM to about 400 nM, from about 400 nM to about 500 nM, from about 500 nM to about 600 nM, from about 600 nM to about 700 nM, from about 700 nM to about 800 nM, from about 800 nM to about 900 nM, and from about 900 nM to about 1000 nM, more preferably from about 100 nM to about 250 nM, most preferably about 250 nM, as determined by flow cytometry.

In one aspect, the anti-CD3 antibodies and fragments thereof described herein compete with commercial CD3 antibody SP34-2 (BD Biosciences 551916) for binding of CD3, as determined by a competition binding assay using an AlexaFluor 488-conjugated SP34-2 antibody on primary human T cells measured using flow cytometry.

In one aspect, the anti-CD3 antibodies and fragments thereof exhibit no post-translational modification, including no oxidation, no deamidation, and no aspartate isomerization, as determined by peptide mapping.

In one aspect, the anti-CD3 antibodies and fragments thereof are effective in activating T cells and inducing CD69 expression to a similar degree as SP34-2 in human and cynomolgus monkey T cells and cOKT3 in human T cells, as determined by a T cell based assay using flow cytometry.

In one aspect, the anti-CD3 antibodies and fragments thereof described herein have a total enthalpy of unfolding of about 400 kcal/mol or more, about 410 kcal/mol or more, about 420 kcal/mol or more, about 430 kcal/mol or more, about 440 kcal/mol or more, about 45 kcal/mol or more, about 460 kcal/mol or more, about 470 kcal/mol or more, about 480 kcal/mol or more, about 490 kcal/mol or more, about 500 kcal/mol or more, about 510 kcal/mol or more, about 520 kcal/mol or more, about 530 kcal/mol or more, about 540 kcal/mol or more, or about 550 kcal/mol or more. In certain aspects, the anti-CD3 antibodies and fragments thereof of the invention have a total enthalpy of unfolding of about 418 kcal/mol, 545 kcal/mol, about 402 kcal/mol, or about 406 kcal/mol, and the anti-CD3 antibodies are CD3B376 (IgG4 PAA),
10 CD3B450 (IgG4 PAA), CD3B389 (IgG1sigma), and CD3B467 (IgG1sigma) molecules, respectively.

Exemplary such antibodies include CD3B311, CD3B312, CD3B313, CD3B314, CD3B315, CD3B316, CD3B317, CD3B334, CD3B376 CD3B389, CD3B450 and CD3B467, and CD3B376 and CD3B450 engineered into a monovalent format

15 The anti-CD3 antibodies or antigen-binding fragments of the invention can occur in a variety of forms, but will include one or more of the antibody variable domain segments or CDRs shown in Table 7A and engineered variants thereof, for example, those shown or described in Table 9 and Table 10, and the accompanying descriptions thereof.

The invention also provides an anti-CD3 antibody, or an antigen-binding fragment
20 thereof, comprising a heavy chain comprising a HCDR1, a HCDR2, and a HCDR3 of any one of the antibodies described in Table 7B. The invention also provides an anti-CD3 antibody or an antigen-binding fragment thereof, comprising a heavy chain comprising a HCDR1, a HCDR2, and a HCDR3 of any one of the antibodies described in Table 7B and a light chain comprising a LCDR1, a LCDR2, and a LCDR3 of any one of the antibodies described in Table 7B. In some
25 embodiments, the anti-CD3 antibody or an antigen-binding fragment thereof of the invention competes for binding to CD3 with an antibody or antigen-binding fragment thereof comprising a heavy chain comprising a HCDR1, a HCDR2, and a HCDR3 of any one of the antibodies described in Table 7B and a light chain comprising a LCDR1, a LCDR2, and a LCDR3 of any one of the antibodies described in Table 7B.

30 In some embodiments, the anti-CD3 antibody or an antigen-binding fragment thereof of the invention comprises the HCDR1, the HCDR2 and the HCDR3 contained within a heavy

chain variable region (VH) of SEQ ID NOs: 651, 652, 653, 654, 655, 687, or 656, wherein the HCDR1, the HCDR2 and the HCDR3 are defined by Chothia, Kabat, or IMGT.

In some embodiments, the anti-CD3 antibody of an antigen-binding fragment thereof of the invention comprises the LCDR1, the LCDR2 and the LCDR3 contained within a light chain variable region (VL) of SEQ ID NOs: 658, 659, 694, 660, 688, or 661, wherein the LCDR1, the LCDR2 and the LCDR3 are defined by Chothia, Kabat, or IMGT.

In some embodiments, the anti-CD3 antibody of an antigen-binding fragment thereof of the invention comprises

- the HCDR1 of SEQ ID NOs: 662, 665, or 666;
- 10 the HCDR2 of SEQ ID NOs: 663, 689, or 695; and
- the HCDR3 of SEQ ID NOs: 664.

In some embodiments, the anti-CD3 antibody of an antigen-binding fragment thereof of the invention comprises

- the LCDR1 of SEQ ID NOs: 773, 710, 674 or 671;
- 15 the LCDR2 of SEQ ID NOs: 669 or 673; and
- the LCDR3 of SEQ ID NOs: 670.

In some embodiments, the anti-CD3 antibody of an antigen-binding fragment thereof of the invention comprises

- the HCDR1 of SEQ ID NOs: 662, 665, or 666;
- 20 the HCDR2 of SEQ ID NOs: 663, 689, or 695;
- the HCDR3 of SEQ ID NOs: 664;
- the LCDR1 of SEQ ID NOs: 773, 710, 674 or 671;
- the LCDR2 of SEQ ID NOs: 669 or 673; and
- the LCDR3 of SEQ ID NOs: 670.

25 In some embodiments, the anti-CD3 antibody of an antigen-binding fragment thereof of the invention comprises the HCDR1, the HCDR2 and the HCDR3 of

- SEQ ID NOs: 662, 663, and 664, respectively;
- SEQ ID NOs: 662, 695, and 664, respectively;
- SEQ ID NOs: 665, 663, and 664, respectively;
- 30 SEQ ID NOs: 665, 695, and 664, respectively;
- SEQ ID NOs: 662, 689, and 664, respectively;

SEQ ID NOs: 666, 663, and 664, respectively;

SEQ ID NOs: 666, 695, and 664, respectively

SEQ ID NOs: 665, 689, and 664, respectively; or

SEQ ID NOs: 666, 689, 664, respectively.

- 5 In some embodiments, the anti-CD3 antibody of an antigen-binding fragment thereof of the invention comprises the LCDR1, the LCDR2 and the LCDR3 of

SEQ ID NOs: 773, 669, and 670, respectively;

SEQ ID NOs: 773, 673, and 670, respectively;

SEQ ID NOs: 710, 673, and 670, respectively;

- 10 SEQ ID NOs: 674, 673, and 670, respectively;

SEQ ID NOs: 671, 673, and 690, respectively;

SEQ ID NOs: 773, 673, and 690, respectively;

SEQ ID NOs: 671, 669, and 670, respectively; or

SEQ ID NOs: 776, 673, and 670, respectively.

- 15 In some embodiments, the anti-CD3 antibody of an antigen-binding fragment thereof of the invention comprises the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 of SEQ ID NOs: 662, 663, 664, 773, 669, and 670, respectively.

In some embodiments, the anti-CD3 antibody of an antigen-binding fragment thereof of the invention comprises the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 of SEQ

- 20 ID NOs: 662, 663, 664, 773, 673, and 670, respectively.

In some embodiments, the anti-CD3 antibody of an antigen-binding fragment thereof of the invention comprises the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 of SEQ ID NOs: 662, 663, 664, 671, 669, and 670, respectively.

- 25 In some embodiments, the anti-CD3 antibody of an antigen-binding fragment thereof of the invention comprises the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 of SEQ ID NOs: 662, 663, 664, 671, 673, and 690, respectively.

In some embodiments, the anti-CD3 antibody of an antigen-binding fragment thereof of the invention comprises the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 of SEQ ID NOs: 662, 695, 664, 773, 669, and 670, respectively.

In some embodiments, the anti-CD3 antibody of an antigen-binding fragment thereof of the invention comprises the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 of SEQ ID NOs: 662, 695, 664, 773, 673, and 670, respectively.

In some embodiments, the anti-CD3 antibody of an antigen-binding fragment thereof of the invention comprises the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 of SEQ ID NOs: 662, 695, 664, 671, 669, and 670, respectively.

In some embodiments, the anti-CD3 antibody of an antigen-binding fragment thereof of the invention comprises the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 of SEQ ID NOs: 662, 695, 664, 671, 673, and 670, respectively.

10 In some embodiments, the anti-CD3 antibody of an antigen-binding fragment thereof of the invention comprises the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 of SEQ ID NOs: 665, 663, 664, 773, 669, and 670, respectively.

In some embodiments, the anti-CD3 antibody of an antigen-binding fragment thereof of the invention comprises the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 of SEQ ID NOs: 665, 663, 664, 773, 673, and 670, respectively.

In some embodiments, the anti-CD3 antibody of an antigen-binding fragment thereof of the invention comprises the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 of SEQ ID NOs: 665, 663, 664, 671, 669, and 670, respectively.

20 In some embodiments, the anti-CD3 antibody of an antigen-binding fragment thereof of the invention comprises the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 of SEQ ID NOs: 665, 663, 664, 671, 673, and 670, respectively.

In some embodiments, the anti-CD3 antibody of an antigen-binding fragment thereof of the invention comprises the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 of SEQ ID NOs: 665, 695, 664, 773, 669, and 670, respectively.

25 In some embodiments, the anti-CD3 antibody of an antigen-binding fragment thereof of the invention comprises the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 of SEQ ID NOs: 665, 695, 664, 773, 673, and 670, respectively.

In some embodiments, the anti-CD3 antibody of an antigen-binding fragment thereof of the invention comprises the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 of SEQ ID NOs: 665, 695, 664, 776, 669, and 670, respectively.

In some embodiments, the anti-CD3 antibody of an antigen-binding fragment thereof of the invention comprises the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 of SEQ ID NOs: 665, 695, 664, 776, 673, and 670, respectively.

In some embodiments, the anti-CD3 antibody of an antigen-binding fragment thereof of the invention comprises the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 of SEQ ID NOs: 666, 663, 664, 773, 669, and 670, respectively.

In some embodiments, the anti-CD3 antibody of an antigen-binding fragment thereof of the invention comprises the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 of SEQ ID NOs: 666, 663, 664, 773, 673, and 670, respectively.

10 In some embodiments, the anti-CD3 antibody of an antigen-binding fragment thereof of the invention comprises the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 of SEQ ID NOs: 666, 663, 664, 776, 669, and 670, respectively.

In some embodiments, the anti-CD3 antibody of an antigen-binding fragment thereof of the invention comprises the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 of SEQ ID NOs: 666, 663, 664, 671, 673, and 670, respectively.

In some embodiments, the anti-CD3 antibody of an antigen-binding fragment thereof of the invention comprises the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 of SEQ ID NOs: 666, 695, 664, 773, 669, and 670, respectively.

20 In some embodiments, the anti-CD3 antibody of an antigen-binding fragment thereof of the invention comprises the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 of SEQ ID NOs: 666, 695, 664, 773, 673, and 670, respectively.

In some embodiments, the anti-CD3 antibody of an antigen-binding fragment thereof of the invention comprises the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 of SEQ ID NOs: 666, 695, 664, 671, 669, and 670, respectively.

25 In some embodiments, the anti-CD3 antibody of an antigen-binding fragment thereof of the invention comprises the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 of SEQ ID NOs: 666, 695, 664, 671, 673, and 670, respectively.

In some embodiments, the anti-CD3 antibody of an antigen-binding fragment thereof of the invention comprises the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 of SEQ ID NOs: 662, 689, 664, 671, 673, and 670, respectively.

In some embodiments, the anti-CD3 antibody of an antigen-binding fragment thereof of the invention comprises the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 of SEQ ID NOs: 662, 663, 664, 710, 673, and 670, respectively.

In some embodiments, the anti-CD3 antibody of an antigen-binding fragment thereof of the invention comprises the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 of SEQ ID NOs: 662, 663, 664, 671, 673, and 690, respectively.

In some embodiments, the anti-CD3 antibody of an antigen-binding fragment thereof of the invention comprises the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 of SEQ ID NOs: 662, 663, 664, 773, 673, and 690, respectively.

10 In some embodiments, the anti-CD3 antibody of an antigen-binding fragment thereof of the invention comprises a heavy chain (HC) sequence of SEQ ID NO: 709, 640, 641, 642, 643, 675, or 644 and/or a light chain (LC) sequence of SEQ ID NO: 645, 716, 649, 676, 677, or 650. In some embodiments, the anti-CD3 antibody of an antigen-binding fragment thereof of the invention comprises a HC having a polypeptide sequence at least 85%, preferably 90%, more preferably 95% or more, such as 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 709, 640, 641, 642, 643, 675, or 644, and a LC having a polypeptide sequence at least 85%, preferably 90%, more preferably 95% or more, such as 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 645, 716, 649, 676, 677, or 650. In some embodiments, the anti-CD3 antibody of an antigen-binding fragment thereof of the invention comprises a HC having a polypeptide
15 sequence at least 85%, preferably 90%, more preferably 95% or more, such as 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 709, 640, 641, 642, 643, 675, or 644, and a LC having a polypeptide sequence at least 85%, preferably 90%, more preferably 95% or more, such as 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 645, 716, 649, 676, 677 or 650, wherein the variation in sequence does not occur in a CDR region.

25 In some embodiments, the anti-CD3 antibody of an antigen-binding fragment thereof of the invention comprises a heavy chain variable region (VH) sequence of SEQ ID NO: 651, 652, 657, 653, 654, 655, 687, or 656 and/or a light chain variable region (VL) sequence of SEQ ID NO: 658, 659, 694, 660, 688, 678, or 661. In some embodiments, the anti-CD3 antibody of an antigen-binding fragment thereof of the invention comprises a VH having a polypeptide
30 sequence at least 85%, preferably 90%, more preferably 95% or more, such as 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 651, 652, 657, 653, 654, 655, 687, or 656, and a VL

having a polypeptide sequence at least 85%, preferably 90%, more preferably 95% or more, such as 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NOS 658, 659, 694, 660, 688, 678, or 661.

In some embodiments, the anti-CD3 antibody of an antigen-binding fragment thereof of the invention comprises a VH having a polypeptide sequence at least 85%, preferably 90%, more preferably 95% or more, such as 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 651, 652, 657, 653, 654, 655, 687, or 656, and a VL having a polypeptide sequence at least 85%, preferably 90%, more preferably 95% or more, such as 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 658, 659, 694, 660, 688, 678, or 661, wherein the variation in sequence does not occur in a CDR region.

10 **PSMA-Specific Antibodies**

The antibodies and fragments thereof that bind to PSMA bind to the chimpanzee target antigen. In one embodiment, the antibodies and fragments thereof bind to the human and macaque PSMA target antigens with affinities within 5-fold of each other. In other words, the difference in antibody binding is less than a multiple of 5. In this case, the identical antibody molecule can be used both for preclinical evaluation of safety, activity and/or pharmacokinetic profile of PSMA in primates and as a drug in humans. Put in other words, the same PSMA-specific molecule can be used in preclinical animal studies as well as in clinical studies in humans. This leads to highly comparable results and a much-increased predictive power of the animal studies compared to species-specific surrogate molecules. Since the PSMA domain is cross-species specific, i.e. reactive with the human and macaque antigens, the antibody or fragments thereof of the invention can be used both for preclinical evaluation of safety, activity and/or pharmacokinetic profile of these binding domains in primates and—in the identical form—as drug in humans.

The present invention also provides for multispecific antibodies that specifically bind to PSMA. According to the invention, a bispecific, i.e. bifunctional, antibody can be used to engage two different therapeutic targets or perform two distinct functions. Such antibodies can be used for example to recruit an immune effector cell, e.g. T- or NK-cell, towards a particular target cell. Various antibody-fragment based molecules are known and under investigation, for example for cancer therapy.

The present invention also provides for a PSMA×“effector antigen” bispecific antibody. In one embodiment, the effector antigen of the PSMA×“effector antigen” bispecific antibody is CD3. It has been found in the present invention that it is possible to generate a PSMA×CD3 bispecific antibody wherein the identical molecule can be used in preclinical animal testing, as well as clinical studies and even in therapy in human. This is due to the identification of the PSMA×CD3 bispecific antibody, which, in addition to binding to human PSMA and human CD3, respectively, also binds to the homologs of antigens of chimpanzee and macaques. The PSMA×CD3 bispecific antibody of the invention can be used as a therapeutic agent against various diseases, including, but not limited, to cancer. In view of the above, the need to construct a surrogate target PSMA×CD3 bispecific antibody for testing in a phylogenetically distant (from humans) species disappears. As a result, the identical molecule can be used in animal preclinical testing as is intended to be administered to humans in clinical testing as well as following market approval and therapeutic drug administration.

In some embodiments described herein, the isolated antibody or antibody fragment thereof specifically binding PSMA has one, two, three, four or five of the following properties:

- a. binds *Pan troglodytes* PSMA extracellular domain (ECD) with an equilibrium dissociation constant (K_D) of 25 nM or less, wherein the K_D is measured using ProteOn XPR36 system at +25°C,
- b. binds LNCaP cells with a calculated EC50 of 20 nM or less and binds *Macaca fascicularis* PSMA-expressing HEK cells with a calculated EC50 of 40 nM or less, wherein the difference in calculated EC50 between binding LNCaP cells and binding *Macaca fascicularis* PSMA-expressing HEK cells is less than 5-fold, and wherein the calculated EC50 is measured in a whole cell binding assay at 0 °C using flow cytometry,
- c. binds recombinant PSMA ECD from human (SEQ ID NO:55), *Pan troglodytes* (SEQ ID NO:52) and *Macaca fascicularis* (SEQ ID NO:53) with an equilibrium dissociation constant (K_D) of 12 nM or less, wherein the K_D is measured using Proteon surface plasmon resonance assay ProteOn XPR36 system at +25°C;
- d. displays T-cell mediated killing of LNCaP cells, C42 cells, human PSMA-expressing HEK cells or *Macaca fascicularis* PSMA-expressing HEK cells when

- paired in a bispecific antibody with anti-CD3 antibody, wherein the T-cell mediated killing is measured by Chromium-51 or by caspase 3/7 activation assay, or
- e. recognizes a conformational epitope wherein the epitope is comprised of residues I138, F235, P237, G238, D244, Y299, Y300, Q303, K304, E307, and K324-P326 of human PSMA (SEQ ID NO:51)

Exemplary such antibodies or fragments thereof are PSMA antibodies PSMB119, PSMB120, PSMB121, PSMB122, PSMB123, PSMB87, PSMB126, PSMB127, PSMB128, PSMB129, PSMB130, PSMB120, PSMB121, PSMB122, PSMB123, PSMB127, PSMB128, PSMB130, PSMB344, PSMB345, PSMB346, PSMB347, PSMB349, PSMB358, PSMB359, PSMB360, PSMB361, PSMB362, PSMB363, and PSMB365 described herein.

In some embodiments of the invention described herein, the antibody specifically binding PSMA of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs:56, 57, 58, 59, 60, and 61, respectively.

In some embodiments of the invention described herein, the antibody specifically binding PSMA of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs:62, 63, 64, 65, 66, and 66, respectively.

In some embodiments of the invention described herein, the antibody specifically binding PSMA of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs:67, 68, 69, 70, 71, and 72, respectively.

In some embodiments of the invention described herein, the antibody specifically binding PSMA of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs:73, 74, 75, 76, 60, and 61, respectively.

In some embodiments of the invention described herein, the antibody specifically binding PSMA of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs:78, 79, 80, 81, 82, and 83, respectively.

In some embodiments of the invention described herein, the antibody specifically binding PSMA of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs:84, 85, 86, 87, 60, and 88, respectively.

In some embodiments of the invention described herein, the antibody specifically binding PSMA of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs:89, 90, 91, 92, 93, and 94, respectively.

In some embodiments of the invention described herein, the antibody specifically binding PSMA of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs:95, 96, 97, 65, 60, and 66, respectively.

In some embodiments of the invention described herein, the antibody specifically binding
5 PSMA of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs:84, 98, 99, 100, 82, and 101, respectively.

In some embodiments of the invention described herein, the antibody specifically binding PSMA of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs:89, 90, 102, 103, 104, and 105, respectively.

10 In some embodiments of the invention described herein, the antibody specifically binding PSMA of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs:89, 90, 106, 103, 104, and 105, respectively.

In some embodiments of the invention described herein, the antibody specifically binding PSMA of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the
15 LCDR2 and the LCDR3 of SEQ ID NOs: 107, 108, 109, 76, 60, and 88, respectively.

In some embodiments of the invention described herein, the antibody specifically binding PSMA of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 78, 1, 80, 81, 82, and 83, respectively.

In some embodiments of the invention described herein, the antibody specifically binding
20 PSMA of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 78, 1, 80, 81, 82, and 83, respectively.

In some embodiments of the invention described herein, the antibody specifically binding PSMA of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 78, 1, 80, 4, 82, and 686, respectively.

25 In some embodiments of the invention described herein, the antibody specifically binding PSMA of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 78, 1, 80, 81, 792, and 686, respectively.

In some embodiments of the invention described herein, the antibody specifically binding PSMA of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the
30 LCDR2 and the LCDR3 of SEQ ID NOs: 78, 2, 80, 81, 82, and 83, respectively.

In some embodiments of the invention described herein, the antibody specifically binding PSMA of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 78, 3, 80, 81, 82, and 5, respectively.

In some embodiments of the invention described herein, the antibody specifically binding
5 PSMA of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 78, 3, 80, 81, 82, and 83, respectively.

In some embodiments of the invention described herein, the antibody specifically binding PSMA of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 78, 3, 80, 4, 82, and 686, respectively.

10 In some embodiments of the invention described herein, the antibody specifically binding PSMA of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 78, 3, 80, 81, 792, and 686, respectively.

In some embodiments of the invention described herein, the antibody specifically binding PSMA of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the
15 LCDR2 and the LCDR3 of SEQ ID NOs: 78, 2, 81, 81, 82, and 5, respectively.

In some embodiments of the invention described herein, the antibody specifically binding PSMA of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 78, 2, 80, 4, 792, and 686, respectively.

In some embodiments of the invention described herein, the antibody specifically binding
20 PSMA of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 78, 2, 80, 4, 792, and 686, respectively.

In some embodiments of the invention described herein, the antibody specifically binding PSMA of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 78, 683, 80, 81, 792, and 686, respectively.

25

In some embodiments of the invention described herein, the antibody specifically binding PSMA of the invention comprises a heavy chain variable region (VH) of SEQ ID NOs: 6, 7, 8, 110, 112, 114, 116, 118, 120, 121, 123, 125, 126, 128, 130, or 681. In some embodiments of the invention described herein, the antibody specifically binding PSMA of the invention comprises a
30 light chain variable region (VL) of SEQ ID NOs: 9, 111, 113, 115, 117, 119, 122, 124, 127, 129, 131, or 682.

In some embodiments of the invention described herein, the antibody specifically binding PSMA of the invention comprises a heavy chain sequence of SEQ ID NOs: 12, 13, 132, 134, 136, 138, 140, 141, 143, 145, 146, 148, 150, 151, or 679.

In some embodiments of the invention described herein, the antibody specifically binding PSMA of the invention comprises a light chain sequence of SEQ ID NOs: 14, 15, 75, 133, 135, 137, 139, 142, 144, 147, 149 or 680.

CD33-Specific Antibodies

The CD33-specific antibodies of the invention possess one or more desirable functional properties, including but not limited to high-affinity binding to CD33 and/or CD3, high specificity to CD33 and/or CD3, and the ability to treat or prevent cancer when administered alone or in combination with other anti-cancer therapies.

In certain embodiments, the isolated monoclonal antibodies or antigen-binding fragments thereof bind the C2 domain of CD33. In certain embodiments, the isolated monoclonal antibodies or antigen-binding fragments thereof bind the V domain of CD33. The full length human CD33 is provided by Uniprot P20138 (SEQ ID NO:244).

As used herein, an antibody that “specifically binds to CD33” refers to an antibody that binds to a CD33, preferably a human CD33, preferably the C2 domain of CD33, with a KD of 1×10^{-7} M or less, preferably 1×10^{-8} M or less, more preferably 5×10^{-9} M or less, 1×10^{-9} M or less, 5×10^{-10} M or less, or 1×10^{-10} M or less.

The antibodies or antigen-binding fragments described herein can occur in a variety of forms, but will include one or more of the antibody CDRs shown in Table 39 and 40.

Described herein are recombinant antibodies and antigen-binding fragments that specifically bind to CD33. In some embodiments, the CD33-specific antibodies or antigen-binding fragments are human IgG, or derivatives thereof. While the CD33-specific antibodies or antigen-binding fragments exemplified herein are human, the antibodies or antigen-binding fragments exemplified may be chimerized.

In some embodiments are provided an CD33-specific antibody, or an antigen-binding fragment thereof, comprising a heavy chain comprising a CDR1, a CDR2, and a CDR3 of any one of the antibodies described in Table 39. In some embodiments are provided an CD33-specific antibody, or an antigen-binding fragment thereof, comprising a heavy chain comprising

a CDR1, a CDR2, and a CDR3 of any one of the antibodies described in Table 39 and a light chain comprising a CDR1, a CDR2, and a CDR3 of any one of the antibodies described in Table 40.

In some embodiments are provided a CD33-specific antibody, or antigen-binding
5 fragment thereof, comprising a heavy chain variable region shown in Table 38. In some
embodiments are provided a CD33-specific antibody, or antigen-binding fragment thereof,
comprising a light chain variable region shown in Table 38.

The heavy chain variable domain and light chain variable domain of antibodies discussed
in this section and shown in Table 38 are suitable for inclusion in bispecific constructs. For
10 example, in some embodiments of the CD33 bispecific antibodies, the effector arm is a CD3
arm. In some embodiments of the CD33xCD3 bispecific antibody, the CD3 arm comprises the
HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2, and the LCDR3 of SEQ ID
NOs:662, 663, 664, 671, 673, and 670, respectively. In some embodiments of the CD33xCD3
bispecific antibody, the CD3 arm comprises the VH and VL of SEQ ID NOs: 652 and 661,
15 respectively. In some embodiments of the CD33xCD3 bispecific antibody, the CD3 arm
comprises the HC and LC of SEQ ID NOs: 640 and 676, respectively.

In some embodiments of the CD33xCD3 bispecific antibody, the CD3 arm comprises the
HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2, and the LCDR3 of SEQ ID
NOs:662, 663, 664, 773, 673, and 670, respectively. In some embodiments of the CD33xCD3
20 bispecific antibody, the CD3 arm comprises the VH and VL of SEQ ID NOs:657 and 678,
respectively. In some embodiments of the CD33xCD3 bispecific antibody, the CD3 arm
comprises the HC and LC of SEQ ID NOs:675 and 677, respectively.

In certain embodiments, the anti-CD33 antibody or antigen-binding fragment thereof
comprises a heavy chain variable region having a polypeptide sequence at least 95% identical to
25 SEQ ID NO:267, 260, 275, 270, 262, 258, 257, 281, 292, 291, 261, 269, 280, 259, 263, 264, 265,
266, 272, 277, 279, 284, or 285, or a light chain variable region having a polypeptide sequence at
least 95% identical to SEQ ID NO:287, 314, 309, 301, 298, 297, 290, 332, 331, 302, 310, 320,
300, 304, 305, 306, 307, 317, 319, 324, or 325; and the anti-CD3 antibody or antigen-binding
fragment thereof comprises a heavy chain variable region having a polypeptide sequence at least
30 95% identical to SEQ ID NO:257 or 258, or a light chain variable region having a polypeptide
sequence at least 95% identical to SEQ ID NO:298 or 299.

IL1RAP-Specific Antibodies

As used herein, the terms “interleukin-1 receptor accessory protein”, “IL1RAP” and “IL1-RAP” specifically include the human IL1RAP protein (SEQ ID NO:576), for example as described in GenBank Accession No. AAB84059, NCBI Reference Sequence: NP_002173.1 and
5 UniProtKB/Swiss-Prot Accession No. Q9NPH3-1 (see also Huang et al., 1997, Proc. Natl. Acad. Sci. USA. 94 (24), 12829-12832). IL1RAP is also known in the scientific literature as IL1 R3, C3orf13, FLJ37788, IL-1 RAcP and EG3556.

The antibodies or antigen-binding fragments described herein can occur in a variety of forms, but will include one or more of the antibody CDRs shown in Table 29.

10 Described herein are recombinant antibodies and antigen-binding fragments that specifically bind to IL1RAP. In some embodiments, the IL1RAP-specific antibodies or antigen-binding fragments are human IgG, or derivatives thereof. While the IL1RAP-specific antibodies or antigen-binding fragments exemplified herein are human, the antibodies or antigen-binding fragments exemplified may be chimerized.

15 In some embodiments are provided an IL1RAP-specific antibody, or an antigen-binding fragment thereof, comprising a heavy chain comprising a CDR1, a CDR2, and a CDR3 of any one of the antibodies described in Table 29. In some embodiments are provided an IL1RAP-specific antibody, or an antigen-binding fragment thereof, comprising a heavy chain comprising a CDR1, a CDR2, and a CDR3 of any one of the antibodies described in Table 29 and a light
20 chain comprising a CDR1, a CDR2, and a CDR3 of any one of the antibodies described in Table 29.

In some embodiments are provided a IL1RAP-specific antibody, or antigen-binding fragment thereof, comprising a heavy chain variable region of any one of the antibodies shown in Table 30. In some embodiments are provided a IL1RAP-specific antibody, or antigen-binding
25 fragment thereof, comprising a light chain variable region of any one of the antibodies shown in Table 30. In some embodiments are provided a IL1RAP-specific antibody, or antigen-binding fragment thereof, comprising a heavy chain variable region and a light chain variable region of any one of the antibodies shown in Table 30.

The heavy chain variable domain and light chain variable domain of antibodies discussed
30 in this section and shown in Table 30 are suitable for inclusion in bispecific constructs in which the targeting arm is an anti-IL1RAP arm. For example, in some embodiments of the IL1RAP

bispecific antibodies, the effector arm is a CD3 arm. In some embodiments of the IL1RAPxCD3 bispecific antibody, the CD3 arm comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2, and the LCDR3 of SEQ ID NOs:662, 663, 664, 671, 673, and 670, respectively. In some embodiments of the IL1RAPxCD3 bispecific antibody, the CD3 arm comprises the VH and VL of SEQ ID NOs: 652 and 661, respectively. In some embodiments of the IL1RAPxCD3 bispecific antibody, the CD3 arm comprises the HC and LC of SEQ ID NOs: 640 and 676, respectively.

In some embodiments of the IL1RAPxCD3 bispecific antibody, the CD3 arm comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2, and the LCDR3 of SEQ ID NOs:662, 663, 664, 773, 673, and 670, respectively. In some embodiments of the IL1RAPxCD3 bispecific antibody, the CD3 arm comprises the VH and VL of SEQ ID NOs:657 and 678, respectively. In some embodiments of the IL1RAPxCD3 bispecific antibody, the CD3 arm comprises the HC and LC of SEQ ID NOs:675 and 677, respectively.

TMEFF2-Specific Antibodies

The invention provides an isolated anti-TMEFF2 antibody or an antigen binding fragment thereof that binds to a membrane proximal region of SEQ ID NO: 629 of TMEFF2. The anti-TMEFF2 antibodies of the invention binding the membrane proximal region of TMEFF2 are not internalized by cells. While wishing not to be bound by any particular theory, it can be expected that non-internalizing anti-TMEFF2 antibodies have improved oncogenic effect mediated by antibody effector functions resulting from lack of internalization and degradation of TMEFF2 when compared to internalizing anti-TMEFF2 antibodies.

“Binds to a membrane proximal region” means that 90% of antibody epitope residues identified using hydrogen/deuterium exchange (H/D exchange) reside within the membrane proximal region of TMEFF2. The epitope residues are those which are protected by the test antibody by at least 5% difference in deuteration levels through H/D exchange. Exemplary such antibodies are TMEB675, TMEB570, TMEB674, TMEB565, TMEB762 and TMEB757 as described herein.

In some embodiments, the isolated anti-TMEFF2 antibody or the antigen binding fragment thereof binds within residues HGKCEHSINMQEPSC (SEQ ID NO: 592) or DAGYTGQHCEKKDYSVL (SEQ ID NO: 600) to the membrane proximal region of TMEFF2.

An exemplary anti-TMEFF2 antibody binding within residues HGKCEHSINMQEPSC (SEQ ID NO: 592) is TMEB570. An exemplary anti-TMEFF2 antibody binding within residues DAGYTGQHCEKKDYSVL (SEQ ID NO: 600) is TMEB675. TMEB675 variants TMEB762 and TMEB757 are also expected to bind the membrane proximal region of TMEFF2 within
5 residues DAGYTGQHCEKKDYSVL (SEQ ID NO: 600).

In an H/D exchange assay, recombinantly expressed TMEFF2 ECD is incubated in the presence or absence of the antibody in deuterated water for predetermined times resulting in deuterium incorporation at exchangeable hydrogen atoms which are unprotected by the antibody, followed by protease digestion of the protein and analyses of the peptide fragments using LC-
10 MS. H/D exchange assay can be performed using known protocols. An exemplary protocol is described in Example 5.

The invention also provides an isolated anti-TMEFF2 antibody or an antigen binding fragment thereof, wherein the antibody or the antigen binding fragment thereof competes for binding to the membrane proximal region of TMEFF2 with a reference antibody comprising a
15 heavy chain variable region (VH) of SEQ ID NO: 25 and a light chain variable region (VL) of SEQ ID NO: 28, the VH of SEQ ID NO: 589 and the VL of SEQ ID NO: 29, the VH of SEQ ID NO: 27 and the VL of SEQ ID NO: 30, the VH of SEQ ID NO: 589 and the VL of SEQ ID NO: 31, the VH of SEQ ID NO: 604 and the VL of SEQ ID NO: 607, or the VH of SEQ ID NO: 612 and the VL of SEQ ID NO: 613.

20 Competition for binding of a test antibody to the membrane proximal region of TMEFF2 with the reference antibody may be assayed *in vitro* using well known methods. For example, binding of MSD Sulfo-TagTM NHS-ester-labeled test antibody to the membrane proximal region of TMEFF2 in the presence of an unlabeled reference antibody may be assessed by ELISA, or Bioacore analyses or flow cytometry may be used to demonstrate competition. The test antibody
25 competes for binding to TMEFF2 with the reference antibody when the test antibody inhibits binding of the reference antibody to the membrane proximal region of TMEFF2 by 85% or more, for example 90% or more, or 95% or more.

The invention also provides an isolated anti-TMEFF2 antibody or an antigen binding fragment thereof comprising a heavy chain complementarity determining region 1 (HCDR1), a
30 HCDR2, a HCDR3, a light chain complementarity determining region 1 (LCDR1), a LCDR2 and a LCDR3 of

SEQ ID NOs: 582, 584, 587, 18, 588 and 22, respectively;

SEQ ID NOs: 583, 585, 16, 19, 21, and 23, respectively;

SEQ ID NOs: 582, 586, 17, 18, 588 and 24, respectively;

SEQ ID NOs: 583, 585, 16, 18, 588 and 22, respectively; or

5 SEQ ID NOs: 582, 584, 587, 18, 588 and 603, respectively.

In some embodiments, the isolated anti-TMEFF2 antibody or the antigen binding fragment thereof of the invention binds to the membrane proximal region of TMEFF2 with an equilibrium dissociation constant (K_D) of about 0.4×10^{-9} M or less, wherein the K_D is measured using surface plasmon resonance in acetate buffer at pH 4.5-5.0 at room temperature.

10 In some embodiments, the isolated anti-TMEFF2 antibody or the antigen binding fragment thereof binds to the membrane proximal region of TMEFF2 with the K_D of between about 0.1×10^{-10} M and about 0.4×10^{-9} M.

The affinity of an antibody to the membrane proximal region of TMEFF2 may be determined experimentally using any suitable method. An exemplary method utilizes ProteOn
15 XPR36, Biacore 3000 or KinExA instrumentation, ELISA or competitive binding assays known to those skilled in the art. The measured affinity of an antibody to TMEFF2 may vary if measured under different conditions (e.g., osmolarity, pH). Thus, measurements of affinity and other binding parameters (e.g., K_D , K_{on} , and K_{off}) are typically made with standardized conditions and a standardized buffer, such as the buffer described herein. Skilled in the art will
20 appreciate that the internal error for affinity measurements for example using Biacore 3000 or ProteOn (measured as standard deviation, SD) can typically be within 5-33% for measurements within the typical limits of detection. Therefore, the term “about” when referring to a K_D value reflects the typical standard deviation in the assay. For example, the typical SD for a K_D of 1×10^{-9} M is up to $\pm 0.33 \times 10^{-9}$ M.

25 The invention also provides an isolated anti-TMEFF2 antibody or an antigen binding fragment thereof that binds to the membrane proximal region of TMEFF2, comprising a heavy chain variable region (VH) framework derived from VH3_3-23 (SEQ ID NO: 53) or VH1_1-69 (SEQ ID NO: 54).

The invention also provides an isolated anti-TMEFF2 antibody or an antigen binding
30 fragment thereof that binds to the membrane proximal region of TMEFF2, comprising a light

chain variable region (VL) framework derived from VKI_L11 (SEQ ID NO: 55) or VKIII_A27 (SEQ ID NO: 591).

The invention also provides an isolated anti-TMEFF2 antibody or an antigen binding fragment thereof that binds to the membrane proximal region of TMEFF2, comprising a VH framework and a VL framework derived from VH3_3-23 of SEQ ID NO: 53 and VKI_L11 of SEQ ID NO: 55, respectively.

The invention also provides an isolated anti-TMEFF2 antibody or an antigen binding fragment thereof that binds to the membrane proximal region of TMEFF2, comprising a VH framework and a VL framework derived from VH1_1-69 of SEQ ID NO: 54 and VKIII_A27 of SEQ ID NO: 591, respectively.

The invention also provides an isolated anti-TMEFF2 antibody or an antigen binding fragment thereof that binds to the membrane proximal region of TMEFF2, comprising a VH framework and a VL framework derived from VH1_1-69 of SEQ ID NO: 54 and VKI_L11 of SEQ ID NO: 55, respectively.

Antibodies comprising heavy or light chain variable regions “derived from” a particular framework or germline sequence refer to antibodies obtained from a system that uses human germline immunoglobulin genes, such as from transgenic mice, rats or chicken or from phage display libraries as discussed herein. An antibody containing particular framework derived from germline sequence may contain amino acid differences as compared to the sequence it was derived from, due to, for example, naturally-occurring somatic mutations or intentional substitutions.

The invention also provides an isolated anti-TMEFF2 antibody or an antigen binding fragment thereof, comprising a HCDR1, a HCDR2, a HCDR3, a LCDR1, a LCDR2 and a LCDR3 of SEQ ID NOs: 582, 584, 587, 18, 588 and 22, respectively.

In some embodiments, the isolated anti-TMEFF2 antibody or the antigen-binding fragment thereof comprises a VH of SEQ ID NO: 25 and a VL of SEQ ID NO: 28.

In some embodiments, the VH is encoded by a polynucleotide of SEQ ID NO: 39 and the VL is encoded by a polynucleotide of SEQ ID NO: 42.

In some embodiments, the isolated anti-TMEFF2 antibody or the antigen binding fragment thereof comprises a HC of SEQ ID NO: 32 and a LC of SEQ ID NO: 35.

In some embodiments, the HC is encoded by a polynucleotide of SEQ ID NO: 46 and the VL is encoded by a polynucleotide of SEQ ID NO: 49.

The invention also provides an isolated anti-TMEFF2 antibody or an antigen binding fragment thereof comprising a HCDR1, a HCDR2, a HCDR3, a LCDR1, a LCDR2 and a
5 LCDR3 of SEQ ID NOs: 583, 585, 16, 19, 21 and 23, respectively.

In some embodiments, the isolated anti-TMEFF2 antibody or the antigen-binding fragment thereof comprises a VH of SEQ ID NO: 589 and a VL of SEQ ID NO: 29.

In some embodiments, the VH is encoded by a polynucleotide of SEQ ID NO: 40 and the VL is encoded by a polynucleotide of SEQ ID NO: 43.

10 In some embodiments, the isolated anti-TMEFF2 antibody or the antigen binding fragment thereof comprises a HC of SEQ ID NO: 33 and a LC of SEQ ID NO: 36.

In some embodiments, the HC is encoded by a polynucleotide of SEQ ID NO: 47 and the LC is encoded by a polynucleotide of SEQ ID NO: 50.

The invention also provides an isolated anti-TMEFF2 antibody or an antigen binding
15 fragment thereof comprising a HCDR1, a HCDR2, a HCDR3, a LCDR1, a LCDR2 and a LCDR3 of SEQ ID NOs: 582, 586, 17, 18, 588 and 24, respectively.

In some embodiments, the isolated anti-TMEFF2 antibody or the antigen binding fragment thereof comprises a VH of SEQ ID NO: 27 and a VL of SEQ ID NO: 30.

In some embodiments, the VH is encoded by a polynucleotide of SEQ ID NO: 41 and the
20 VL is encoded by a polynucleotide of SEQ ID NO: 44.

In some embodiments, the isolated anti-TMEFF2 antibody or the antigen binding fragment thereof comprises a HC of SEQ ID NO: 34 and a LC of SEQ ID NO: 37.

In some embodiments, the HC is encoded by a polynucleotide of SEQ ID NO: 48 and the LC is encoded by a polynucleotide of SEQ ID NO: 51.

25 The invention also provides an isolated anti-TMEFF2 antibody or an antigen binding fragment thereof comprising a HCDR1, a HCDR2, a HCDR3, a LCDR1, a LCDR2 and a LCDR3 of SEQ ID NOs: 583, 585, 16, 18, 588 and 22, respectively.

In some embodiments, the isolated anti-TMEFF2 antibody or the antigen binding fragment thereof comprises a VH of SEQ ID NO: 589 and a VL of SEQ ID NO: 31.

30 In some embodiments, the VH is encoded by a polynucleotide of SEQ ID NO: 40 and the VL is encoded by a polynucleotide of SEQ ID NO: 45.

In some embodiments, the isolated anti-TMEFF2 antibody or the antigen binding fragment thereof comprises a HC of SEQ ID NO: 33 and a LC of SEQ ID NO: 38.

In some embodiments, the HC is encoded by a polynucleotide of SEQ ID NO: 47 and the LC is encoded by a polynucleotide of SEQ ID NO: 590.

5 The invention also provides an isolated anti-TMEFF2 antibody or an antigen binding fragment thereof comprising a HCDR1, a HCDR2, a HCDR3, a LCDR1, a LCDR2 and a LCDR3 of SEQ ID NOs: 582, 584, 587, 18, 588 and 603, respectively.

In some embodiments, the isolated anti-TMEFF2 antibody or the antigen-binding fragment thereof comprises a VH of SEQ ID NO: 604 and a VL of SEQ ID NO: 607.

10 In some embodiments, the VH is encoded by a polynucleotide of SEQ ID NO: 618 and the VL is encoded by a polynucleotide of SEQ ID NO: 619.

In some embodiments, the isolated anti-TMEFF2 antibody or the antigen binding fragment thereof comprises a HC of SEQ ID NO: 614 and a LC of SEQ ID NO: 615.

15 In some embodiments, the HC is encoded by a polynucleotide of SEQ ID NO: 620 and the LC is encoded by a polynucleotide of SEQ ID NO: 621.

The invention also provides an isolated anti-TMEFF2 antibody or an antigen binding fragment thereof comprising a HCDR1, a HCDR2, a HCDR3, a LCDR1, a LCDR2 and a LCDR3 of SEQ ID NOs: 582, 584, 587, 18, 588 and 603, respectively.

20 In some embodiments, the isolated anti-TMEFF2 antibody or the antigen binding fragment thereof comprises a VH of SEQ ID NO: 612 and a VL of SEQ ID NO: 613.

In some embodiments, the VH is encoded by a polynucleotide of SEQ ID NO: 622 and the VL is encoded by a polynucleotide of SEQ ID NO: 623.

In some embodiments, the isolated anti-TMEFF2 antibody or the antigen binding fragment thereof comprises a HC of SEQ ID NO: 616 and a LC of SEQ ID NO: 617.

25 In some embodiments, the HC is encoded by a polynucleotide of SEQ ID NO: 624 and the LC is encoded by a polynucleotide of SEQ ID NO: 625.

In some embodiments, the isolated anti-TMEFF2 antibody or the antigen binding fragment thereof is a multispecific antibody.

30 In some embodiments, the isolated anti-TMEFF2 antibody or the antigen binding fragment thereof is a bispecific antibody.

In some embodiments, the isolated anti-TMEFF2 bispecific antibody or the antigen binding fragment thereof binds a T cell antigen.

In some embodiments, the isolated anti-TMEFF2 bispecific antibody or the antigen binding fragment thereof binds CD3.

5 In some embodiments, the isolated anti-TMEFF2 bispecific antibody or the antigen-binding fragment thereof binds CD3 epsilon.

The VH, the VL, the HCDR, the LCDR, the HC and the LC sequences of exemplary anti-TMEFF2 antibodies of the invention are shown in **Tables 60-67**.

Although the embodiments illustrated in the Examples comprise pairs of variable
10 domains, one from a heavy chain and one from a light chain, a skilled artisan will recognize that alternative embodiments may comprise single heavy or light chain variable domains. The single variable domain may be used to screen for variable domains capable of forming a two-domain specific antigen-binding fragment capable of binding to TMEFF2. The screening may be accomplished by phage display screening methods using for example hierarchical dual
15 combinatorial approach disclosed in Int. Patent Publ. No. WO1992/01047. In this approach, an individual colony containing either a VH or a VL chain clone is used to infect a complete library of clones encoding the other chain (VL or VH), and the resulting two-chain specific antigen-binding domain is selected in accordance with phage display techniques using known methods and those described herein. Therefore, the individual VH and VL polypeptide chains are useful
20 in identifying additional anti-TMEFF2 antibodies using the methods disclosed in Int. Patent Publ. No. WO1992/01047.

Bispecific anti-TMEFF2/anti-CD3 antibodies

The invention also provides an isolated bispecific anti-TMEFF2/anti-CD3 antibody or an antigen binding fragment thereof comprising a first domain that binds TMEFF2 and a second
25 domain that binds CD3, wherein the antibody binds to the membrane proximal region of TMEFF2. While not wishing to be bound by any particular theory, bispecific antibodies binding to the membrane proximal region of TMEFF2 may be more efficient in mediating T-cell mediated killing of tumor cells.

The invention also provides an isolated bispecific anti-TMEFF2/anti-CD3 antibody or an
30 antigen binding fragment thereof comprising a first domain that binds TMEFF2 and a second domain that binds CD3, wherein the antibody competes for binding to the membrane proximal

region of TMEFF2 with a reference antibody comprising a heavy chain variable region (VH) of SEQ ID NO: 25 and a light chain variable region (VL) of SEQ ID NO: 28, the VH of SEQ ID NO: 589 and the VL of SEQ ID NO: 29, the VH of SEQ ID NO: 27 and the VL of SEQ ID NO: 30, the VH of SEQ ID NO: 589 and the VL of SEQ ID NO: 31, the VH of SEQ ID NO: 604 and
5 the VL of SEQ ID NO: 607, or the VH of SEQ ID NO: 612 and the VL of SEQ ID NO: 613.

In some embodiments, the isolated bispecific anti-TMEFF2/anti-CD3 antibody or an antigen binding fragment thereof binds the membrane proximal region of TMEFF2 with a dissociation constant (K_D) of about 0.4×10^{-9} M or less, wherein the K_D is measured using surface plasmon resonance in acetate buffer at pH 4.5-5.0 at room temperature.

10 In some embodiments, the isolated bispecific anti-TMEFF2/anti-CD3 antibody or the antigen binding fragment thereof binds the membrane proximal region TMEFF2 with the K_D of between about 0.1×10^{-10} M and about 0.4×10^{-9} M.

The invention also provides an isolated bispecific anti-TMEFF2/anti-CD3 antibody or an antigen binding fragment thereof, wherein the first domain comprises a HCDR1, a HCDR2, a
15 HCDR3, a LCDR1, a LCDR2 and a LCDR3 of

SEQ ID NOs: 582, 584, 587, 18, 588 and 22, respectively;

SEQ ID NOs: 583, 585, 16, 19, 21 and 23, respectively;

SEQ ID NOs: 582, 586, 17, 18, 588 and 24, respectively; or

SEQ ID NOs: 583, 585, 16, 18, 588 and 22, respectively; or

20 SEQ ID NOs: 582, 584, 587, 18, 588 and 603, respectively.

The invention also provides an isolated bispecific anti-TMEFF2/anti-CD3 antibody or an antigen binding fragment thereof, wherein the second domain comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 662, 663, 664, 671, 673, and 690, respectively.

25 The invention also provides an isolated bispecific anti-TMEFF2/anti-CD3 antibody or an antigen binding fragment thereof, wherein the first domain comprises

the VH of SEQ ID NO: 25 and the VL of SEQ ID NO: 28;

the VH of SEQ ID NO: 589 and the VL of SEQ ID NO: 29;

the VH of SEQ ID NO: 27 and the VL of SEQ ID NO: 30;

30 the VH of SEQ ID NO: 589 and the VL of SEQ ID NO: 31;

the VH of SEQ ID NO: 604 and the VL of SEQ ID NO: 607; or

the VH of SEQ ID NO: 612 and the VL of SEQ ID NO: 613.

The invention also provides an isolated bispecific anti-TMEFF2/anti-CD3 antibody or an antigen binding fragment thereof, wherein the second domain comprises

the VH of SEQ ID NO: 652 and the VL of SEQ ID NO: 661.

5 In some embodiments, the second domain comprises the VH of SEQ ID NO: 657 and the VL of SEQ ID NO: 658.

The invention also provides an isolated bispecific anti-TMEFF2/anti-CD3 antibody or an antigen binding fragment thereof comprising a first domain that binds TMEFF2 and a second

10 domain that binds CD3, wherein

the first domain comprises a HCDR1, a HCDR2, a HCDR3, a LCDR1, a LCDR2 and a LCDR3 of SEQ ID NOs: 582, 584, 587, 18, 588 and 22, respectively, and the second domain comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 662, 663, 664, 671, 673, and 690, respectively;

15 the first domain comprises a VH of SEQ ID NO: 25 and a VL of SEQ ID NO: 28, and the second domain comprises the VH of SEQ ID NO: 652 and the VL of SEQ ID NO: 661;

the first domain comprises a VH of SEQ ID NO: 25 and a VL of SEQ ID NO: 28, and the second domain comprises the VH of SEQ ID NO: 657 and the VL of SEQ ID NO: 678;

20 the bispecific anti-TMEFF2/anti-CD3 antibody or the antigen binding fragment thereof comprises a HC1 of SEQ ID NO: 32, a LC1 of SEQ ID NO: 35, a HC2 of SEQ ID NO: 640 and a LC2 of SEQ ID NO: 676; and/or

the bispecific anti-TMEFF2/anti-CD3 antibody or the antigen binding fragment thereof comprises a HC1 of SEQ ID NO: 32, a LC1 of SEQ ID NO: 35, a HC2 of SEQ ID NO: 675 and
25 a LC2 of SEQ ID NO: 677.

The invention also provides an isolated bispecific anti-TMEFF2/anti-CD3 antibody or an antigen binding fragment thereof comprising a first domain that binds TMEFF2 and a second domain that binds CD3, wherein

the first domain comprises a HCDR1, a HCDR2, a HCDR3, a LCDR1, a LCDR2 and a
30 LCDR3 of SEQ ID NOs: 583, 585, 16, 19, 21, and 23, respectively, and the second domain

comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 662, 663, 664, 671, 673, and 690, respectively;

the first domain comprises a VH of SEQ ID NO: 589 and a VL of SEQ ID NO: 29, and the second domain comprises the VH of SEQ ID NO: 652 and the VL of SEQ ID NO: 661;

5 the first domain comprises a VH of SEQ ID NO: 589 and a VL of SEQ ID NO: 29, and the second domain comprises the VH of SEQ ID NO: 657 and the VL of SEQ ID NO: 678 and/or

the bispecific anti-TMEFF2/anti-CD3 antibody or the antigen binding fragment thereof comprises a HC1 of SEQ ID NO: 33, a LC1 of SEQ ID NO: 36, a HC2 of SEQ ID NO: 640 and
10 a LC2 of SEQ ID NO: 676;

the bispecific anti-TMEFF2/anti-CD3 antibody or the antigen binding fragment thereof comprises a HC1 of SEQ ID NO: 33, a LC1 of SEQ ID NO: 36, a HC2 of SEQ ID NO: 675 and a LC2 of SEQ ID NO: 677.

The invention also provides an isolated bispecific anti-TMEFF2/anti-CD3 antibody or an
15 antigen binding fragment thereof comprising a first domain that binds TMEFF2 and a second domain that binds CD3, wherein

the first domain comprises a HCDR1, a HCDR2, a HCDR3, a LCDR1, a LCDR2 and a LCDR3 of SEQ ID NOs: 582, 586, 17, 18, 588 and 24, respectively, and the second domain comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of
20 SEQ ID NOs: 662, 663, 664, 671, 673, and 690, respectively;

the first domain comprises a VH of SEQ ID NO: 27 and a VL of SEQ ID NO: 30, and the second domain comprises the VH of SEQ ID NO: 652 and the VL of SEQ ID NO: 661;

the first domain comprises a VH of SEQ ID NO: 27 and a VL of SEQ ID NO: 30, and the second domain comprises the VH of SEQ ID NO: 657 and the VL of SEQ ID NO: 678, and/or

25 the bispecific anti-TMEFF2/anti-CD3 antibody or the antigen binding fragment thereof comprises a HC1 of SEQ ID NO: 34, a LC1 of SEQ ID NO: 37, a HC2 of SEQ ID NO: 640 and a LC2 of SEQ ID NO: 676;

the bispecific anti-TMEFF2/anti-CD3 antibody or the antigen binding fragment thereof comprises a HC1 of SEQ ID NO: 34, a LC1 of SEQ ID NO: 37, a HC2 of SEQ ID NO: 675 and
30 a LC2 of SEQ ID NO: 677.

The invention also provides an isolated bispecific anti-TMEFF2/anti-CD3 antibody or an antigen binding fragment thereof comprising a first domain that binds TMEFF2 and a second domain that binds CD3, wherein

the first domain comprises a HCDR1, a HCDR2, a HCDR3, a LCDR1, a LCDR2 and a
5 LCDR3 of SEQ ID NOs: 583, 585, 16, 18, 588 and 22, respectively, and the second domain
comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of
SEQ ID NOs: 662, 663, 664, 671, 673, and 690, respectively;

the first domain comprises a VH of SEQ ID NO: 589 and a VL of SEQ ID NO: 31, and
the second domain comprises the VH of SEQ ID NO: 652 and the VL of SEQ ID NO: 661;

10 the first domain comprises a VH of SEQ ID NO: 589 and a VL of SEQ ID NO: 31, and
the second domain comprises the VH of SEQ ID NO: 657 and the VL of SEQ ID NO: 678;
and/or

the bispecific anti-TMEFF2/anti-CD3 antibody or the antigen binding fragment thereof
comprises a HC1 of SEQ ID NO: 33, a LC1 of SEQ ID NO: 38, a HC2 of SEQ ID NO: 640 and a
15 LC2 of SEQ ID NO: 676;

the bispecific anti-TMEFF2/anti-CD3 antibody or the antigen binding fragment thereof
comprises a HC1 of SEQ ID NO: 33, a LC1 of SEQ ID NO: 38, a HC2 of SEQ ID NO: 675 and a
LC2 of SEQ ID NO: 677.

20 The invention also provides an isolated bispecific anti-TMEFF2/anti-CD3 antibody or an
antigen binding fragment thereof comprising a first domain that binds TMEFF2 and a second
domain that binds CD3, wherein

the first domain comprises a HCDR1, a HCDR2, a HCDR3, a LCDR1, a LCDR2 and a
LCDR3 of SEQ ID NOs: 582, 584, 587, 18, 588 and 603, respectively, and the second domain
25 comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of
SEQ ID NOs: 662, 663, 664, 671, 673, and 690, respectively;

the first domain comprises a VH of SEQ ID NO: 604 and a VL of SEQ ID NO: 607, and
the second domain comprises the VH of SEQ ID NO: 652 and the VL of SEQ ID NO: 661;

the first domain comprises a VH of SEQ ID NO: 604 and a VL of SEQ ID NO: 607, and
30 the second domain comprises the VH of SEQ ID NO: 657 and the VL of SEQ ID NO: 678;
and/or

the bispecific anti-TMEFF2/anti-CD3 antibody or the antigen binding fragment thereof comprises a HC1 of SEQ ID NO: 614, a LC1 of SEQ ID NO: 615, a HC2 of SEQ ID NO: 640 and a LC2 of SEQ ID NO: 676;

the bispecific anti-TMEFF2/anti-CD3 antibody or the antigen binding fragment thereof
5 comprises a HC1 of SEQ ID NO: 614, a LC1 of SEQ ID NO: 615, a HC2 of SEQ ID NO: 675 and a LC2 of SEQ ID NO: 677.

The invention also provides an isolated bispecific anti-TMEFF2/anti-CD3 antibody or an antigen binding fragment thereof comprising a first domain that binds TMEFF2 and a second domain that binds CD3, wherein

10 the first domain comprises a HCDR1, a HCDR2, a HCDR3, a LCDR1, a LCDR2 and a LCDR3 of SEQ ID NOs: 582, 584, 587, 18, 588 and 603, respectively, and the second domain comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 662, 663, 664, 671, 673, and 690, respectively;

the first domain comprises a VH of SEQ ID NO: 612 and a VL of SEQ ID NO: 613, and
15 the second domain comprises the VH of SEQ ID NO: 652 and the VL of SEQ ID NO: 661;

the first domain comprises a VH of SEQ ID NO: 612 and a VL of SEQ ID NO: 613, and the second domain comprises the VH of SEQ ID NO: 657 and the VL of SEQ ID NO: 678; and/or

the bispecific anti-TMEFF2/anti-CD3 antibody or an antigen binding fragment thereof
20 comprises a HC1 of SEQ ID NO: 616, a LC1 of SEQ ID NO: 617, a HC2 of SEQ ID NO: 640 and a LC2 of SEQ ID NO: 676;

the bispecific anti-TMEFF2/anti-CD3 antibody or an antigen binding fragment thereof comprises a HC1 of SEQ ID NO: 616, a LC1 of SEQ ID NO: 617, a HC2 of SEQ ID NO: 675 and a LC2 of SEQ ID NO: 677.

25 .

EMBODIMENTS:

This invention provides the following non-limiting embodiments.

1. An isolated recombinant anti-CD3 antibody, or antigen-binding fragment thereof,
30 comprising:

- 5 a) a heavy chain comprising a heavy chain complementarity determining region (HCDR) 1 comprising SEQ ID NO: 662; a HCDR2 comprising SEQ ID NO: 663; and a HCDR3 comprising SEQ ID NO: 664 and a light chain comprising a light chain complementarity determining region (LCDR) 1 comprising SEQ ID NO: 671, a LCDR2 comprising SEQ ID NO: 673, and a LCDR3 comprising SEQ ID NO: 690;
- b) a heavy chain variable region comprising SEQ ID NO: 652 and a light chain variable region comprising SEQ ID NO: 661;
- c) a heavy chain comprising SEQ ID NO: 640 and a light chain comprising SEQ ID NO: 676;
- 10 d) a heavy chain comprising a HCDR1 comprising SEQ ID NO: 662; a HCDR2 comprising SEQ ID NO: 663; and a HCDR3 comprising SEQ ID NO: 664 and a light chain comprising a LCDR1 comprising SEQ ID NO: 773, a LCDR2 comprising SEQ ID NO: 673, and a LCDR3 comprising SEQ ID NO: 690;
- e) a heavy chain variable region comprising SEQ ID NO: 657 and a light chain variable region comprising SEQ ID NO: 678; or
- 15 f) a heavy chain comprising SEQ ID NO: 675 and a light chain comprising SEQ ID NO: 678.
2. An isolated recombinant anti-CD3 antibody or antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment specifically binds *Macaca fascicularis* or human
- 20 CD3d, or CD3e, or CD3e and CD3d with a binding affinity of about 300 nM or less.
3. The isolated recombinant anti-CD3 antibody or antigen-binding fragment thereof of embodiment 2, wherein the binding affinity is about 100 nM or less.
4. The isolated recombinant anti-CD3 antibody or antigen-binding fragment thereof of embodiment 2 or 3, wherein the binding affinity is measured by flow cytometry or by
- 25 Proteon surface plasmon resonance assay ProteOn XPR36 system at +25°C.
5. The isolated recombinant anti-CD3 antibody or antigen-binding fragment thereof of any one of the previous embodiments, wherein the antibody or antigen-binding fragment has one, two, three, or four of the following properties:
- a) binds human and *Macaca fascicularis* CD3+ T lymphocytes with a calculated EC50 of
- 30 300 nM or less and binds *Macaca fascicularis* CD3-expressing HEK cells with a calculated EC50 of 300 nM or less, wherein the difference in calculated EC50 between

binding CD3⁺ T lymphocytes and binding *Macaca fascicularis* CD3-expressing HEK cells is less than 5-fold, and wherein the calculated EC₅₀ is measured in a whole cell binding assay at 0 °C using flow cytometry;

- 5 b) binds recombinant CD3d from human (SEQ ID NO:691), or binds recombinant CD3e from human (SEQ ID NO:636), or binds recombinant CD3d from *Macaca fascicularis* (SEQ ID NO:692), or binds recombinant CD3e from *Macaca fascicularis* (SEQ ID NO:693) with an equilibrium dissociation constant (K_D) of 300 nM or less, wherein the K_D is measured using Proteon surface plasmon resonance assay ProteOn XPR36 system at +25°C;
- 10 c) binds residues 1-6 of CD3e as determined by X-ray crystallography; or
- d) activates T cells or induces CD69 expression to a similar degree as cOKT3 or SP34-2 as determined by fluorescence-activated cell sorting assay.
6. The antibody or antigen-binding fragment thereof of any one of the previous embodiments comprising at least one substitution in an antibody constant domain, the at least one
- 15 substitution comprising:
- a) heavy chain substitutions K409R, F405L, or F405L and R409K;
- b) heavy chain substitutions S228P, F234A, and L235A;
- c) heavy chain substitutions L234A, G237A, P238S, H268A, A330S and P331S, wherein the antibody is an IgG1 isotype; or
- 20 d) heavy chain substitution S228P, wherein the antibody is an IgG4 isotype;
- wherein residue numbering is according to the EU Index.
7. The antibody or antigen-binding fragment thereof of any one of the previous embodiments, comprising the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2, and the LCDR3 of SEQ ID NOs:662, 663, 664, 671, 673, and 690, respectively.
- 25 8. The antibody or antigen-binding fragment thereof of any one of the previous embodiments, comprising a heavy chain variable region (VH) and a light chain variable region (VL) of SEQ ID NOs:652 and 661, respectively.

9. The antibody or antigen-binding fragment thereof of any one of the previous embodiments, comprising a heavy chain sequence (HC) and a light chain sequence (LC) of SEQ ID NOs:640 and 676, respectively.
10. The antibody or antigen-binding fragment thereof of any one of embodiments 1-5,
5 comprising the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2, and the LCDR3 of SEQ ID NOs:662, 663, 664, 773, 673, and 690, respectively.
11. The antibody or antigen-binding fragment thereof of any one of embodiments 1-5, comprising a VH and a VL of SEQ ID NOs:657 and 678, respectively.
12. The antibody or antigen-binding fragment thereof of any one of embodiments 1-5,
10 comprising a HC and a LC of SEQ ID NOs:675 and 677, respectively.
13. An antibody or antigen-binding fragment thereof, comprising the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2, and the LCDR3 of SEQ ID NOs: 662, 663, 664, 671, 673, and 690, respectively.
14. An antibody or antigen-binding fragment thereof, comprising a VH and a VL of SEQ ID
15 NOs:652 and 661, respectively.
15. An antibody or antigen-binding fragment thereof, comprising a HC and a LC of SEQ ID NOs:640 and 676, respectively.
16. An antibody or antigen-binding fragment thereof, comprising the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2, and the LCDR3 of SEQ ID NOs:662, 663, 664, 773, 673,
20 and 690, respectively.
17. An antibody or antigen-binding fragment thereof, comprising a VH and a VL of SEQ ID NOs:657 and 678, respectively.
18. An antibody or antigen-binding fragment thereof, comprising a HC and a LC of SEQ ID NOs:675 and 677, respectively.
- 25 19. The antibody or antigen-binding fragment thereof of any one of the previous embodiments, wherein the antibody is human or humanized.
20. The antibody of embodiment 19, wherein the antibody is an IgG4 or IgG1 isotype.

21. The antibody of embodiment 20, comprising one, two, three, four, five, six, seven, eight, nine or ten substitutions in the antibody Fc.
22. The antibody of embodiment 18, comprising:
- a) D43G, L49M, L50I, S62N, Q85E light chain substitutions;
 - 5 b) D43G, V48L, L49M, L50I, S62N, Q85E, H89Y light chain substitutions;
 - c) R10G, R13K, V73I, R70K, T83S, L96V heavy chain substitutions;
 - d) any one of light chain substitutions D43G, V48L, L49M, L50I, S62N, Q85E, or H89Y; or
 - e) any one of heavy chain substitutions R10G, R13K, V73I, R79K, T83S, or L96V,
- 10 wherein residue numbering for light chain substitutions is according to SEQ ID No: 661, and for heavy chain substitutions is according to SEQ ID No: 652.
23. The antibody of any one of the previous embodiments, wherein the antibody is bispecific or multispecific.
24. A bispecific antibody comprising a first domain that specifically binds CD3 and a second domain that specifically binds a second antigen, wherein the first domain comprises the
- 15 HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2, and the LCDR3 of SEQ ID NOs:662, 663, 664, 671, 673, and 690, respectively.
25. The bispecific antibody of embodiment 24 wherein the first domain and second domain are an IgG4 isotype, and wherein the first or the second domain comprises S228P, F234A, L235A, F405L and R409K heavy chain substitutions and the other domain of the first or the
- 20 second domain comprises S228P, F234A and L235A heavy chain substitution, wherein residue numbering is according to the EU Index.
26. The bispecific antibody of embodiment 24, wherein the first and/or the second domain comprises at least one substitution in a CH3 constant domain comprising a F405L, or F405L and R409K substitution, wherein residue numbering is according to the EU Index.
- 25 27. The bispecific antibody of embodiment 24, wherein one of the first or the second domains comprises a F405L heavy chain substitution and the other of the first or second domains comprises a K409R heavy chain substitution, wherein residue numbering is according to the EU Index.

28. The bispecific antibody of embodiment 24, wherein the first domain and the second domain are an IgG4 isotype, wherein one of the first or the second domains comprises a S228P heavy chain substitution and the other of the first or the second domains comprises S228P, F405L and R409K heavy chain substitutions, wherein residue numbering is according to the EU Index.
29. The bispecific antibody of claim 24, wherein the first domain comprises the VH and the VL of SEQ ID NOs: 652 and 661, respectively.
30. The bispecific antibody of claim 24, wherein the first domain comprises the HC and the LC of SEQ ID NOs: 640 and 676, respectively.
31. The bispecific antibody of claim 24, wherein the first domain comprises the VH and the VL of SEQ ID NOs: 657 and 678, respectively.
32. The bispecific antibody of claim 24, wherein the first domain comprises the HC and the LC of SEQ ID NOs: 675 and 677, respectively.
33. The bispecific antibody of claim 24, wherein the second antigen is a cell surface antigen that is expressed on a target cell other than an immune effector cell.
34. The bispecific antibody of claim 33, wherein the cell surface antigen is a tumor associated antigen.
35. The bispecific antibody of any one of claims 24-34, wherein the second antigen is CD33, IL1RAP, PSMA or TMEFF2.
36. The bispecific antibody of embodiment 35, wherein the first domain comprises the HCDR1, HCDR2, the HCDR3, the LCDR1, the LCDR2, and the LCDR3 of SEQ ID NOs: 662, 663, 664, 671, 673, and 690, respectively; and wherein the second domain comprises the HCDR1, HCDR2, the HCDR3, the LCDR1, the LCDR2, and the LCDR3 of SEQ ID NOs: 78, 683, 80, 81, 792, and 686, respectively.
37. The bispecific antibody of embodiment 33, wherein the first domain comprises the VH and VL of SEQ ID NOs: 652 and 661, respectively; and wherein the second domain comprises the VH and VL of SEQ ID NOs: 681 and 682, respectively.

38. The bispecific antibody of embodiment 33, wherein the first domain comprises the HC and LC of SEQ ID NOs:640 and 676, respectively; and wherein the second domain comprises the HC and LC of SEQ ID NOs:679 and 680, respectively.
39. The bispecific antibody of embodiment 33, wherein the first domain comprises the HCDR1, HCDR2, the HCDR3, the LCDR1, the LCDR2, and the LCDR3 of SEQ ID NOs:662, 663, 664, 671, 673, and 690, respectively; and wherein the second domain comprises the the HCDR1, HCDR2, the HCDR3, the LCDR1, the LCDR2, and the LCDR3 of SEQ ID NOs:78, 3, 80, 81, 792 and 686, respectively .
40. The bispecific antibody of embodiment 33, wherein the first domain comprises the VH and VL of SEQ ID NOs:652 and 661, respectively; and wherein the second domain comprises the VH and VL of SEQ ID NOs 8 and 682, respectively. .
41. The bispecific antibody of embodiment 33, wherein the first domain comprises the HC and LC of SEQ ID NOs:640 and 676, respectively; and wherein the second domain comprises the HC and LC of SEQ ID NOs 13 and 680, respectively.
42. The bispecific antibody of embodiment 33, wherein the first domain comprises the HCDR1, HCDR2, the HCDR3, the LCDR1, the LCDR2, and the LCDR3 of SEQ ID NOs:662, 663, 664, 671, 673, and 690, respectively; and wherein the second domain comprises the the HCDR1, HCDR2, the HCDR3, the LCDR1, the LCDR2, and the LCDR3 of SEQ ID NOs:78, 79, 80, 81, 82 and 83, respectively.
43. The bispecific antibody of embodiment 33, wherein the first domain comprises the VH and VL of SEQ ID NOs:652 and 661, respectively; and wherein the second domain comprises the VH and VL of SEQ ID NOs:116 and 117, respectively.
44. The bispecific antibody of embodiment 33, wherein the first domain comprises the HC and LC of SEQ ID NOs:640 and 676, respectively; and wherein the second domain comprises the HC and LC of SEQ ID NOs:138 and 139, respectively.
45. The bispecific antibody of embodiment 31, wherein the first domain comprises the HCDR1, HCDR2, the HCDR3, the LCDR1, the LCDR2, and the LCDR3 of SEQ ID NOs: 662, 663, 664, 671, 673, and 670, respectively; and wherein the second domain comprises the the

HCDR1, HCDR2, the HCDR3, the LCDR1, the LCDR2, and the LCDR3 of SEQ ID NOs:164, 165, 166, 167, 168, and 169, respectively.

46. The bispecific antibody of embodiment 31, wherein the first domain comprises the VH and VL of SEQ ID NOs:652 and 661, respectively; and wherein the second domain comprises the VH and VL of SEQ ID NOs:215 and 216, respectively.
47. The bispecific antibody of embodiment 31, wherein the first domain comprises the HCDR1, HCDR2, the HCDR3, the LCDR1, the LCDR2, and the LCDR3 of SEQ ID NOs: 662, 663, 664, 671, 673, and 670, respectively; and wherein the second domain comprises the the HCDR1, HCDR2, the HCDR3, the LCDR1, the LCDR2, and the LCDR3 of SEQ ID NOs:349, 390, 341, 471, 513, and 555, respectively.
48. The bispecific antibody of embodiment 31, wherein the first domain comprises the VH and VL of SEQ ID NOs:652 and 661, respectively; and wherein the second domain comprises the VH and VL of SEQ ID NOs:267 and 306, respectively.
49. The bispecific antibody of embodiment 31, wherein the first domain comprises the HCDR1, HCDR2, the HCDR3, the LCDR1, the LCDR2, and the LCDR3 of SEQ ID NOs: 662, 663, 664, 671, 673, and 670, respectively; and wherein the second domain comprises the HCDR1, HCDR2, the HCDR3, the LCDR1, the LCDR2, and the LCDR3 of SEQ ID NOs:363, 404, 445, 485, 527, and 569, respectively.
50. The bispecific antibody of embodiment 31, wherein the first domain comprises the VH and VL of SEQ ID NOs:652 and 661, respectively; and wherein the second domain comprises the VH and VL of SEQ ID NOs:281 and 320, respectively.
51. A pharmaceutical composition comprising the antibody of any one of the previous embodiments and a pharmaceutically acceptable carrier.
52. A polynucleotide encoding the antibody of any one of the embodiments 1-50.
53. A vector comprising the polynucleotide of embodiment 52.
54. A host cell comprising the vector of embodiment 53.

55. A method of producing the antibody of any one of embodiments 1-50, comprising culturing the host cell of embodiment 52 in conditions that the antibody is expressed, and recovering the antibody produced by the host cell.
56. A method of treating a cancer in a subject, comprising administering a therapeutically effective amount of the isolated antibody of any one of embodiments 1-50 to the subject in need thereof for a time sufficient to treat the cancer.
57. The method of embodiment 56, wherein the cancer is a solid tumor or a hematological malignancy.
58. The method of embodiment 57, wherein the solid tumor is a prostate cancer, a colorectal cancer, a gastric cancer, a clear cell renal carcinoma, a bladder cancer, a lung cancer, a squamous cell carcinoma, a glioma, a breast cancer, a kidney cancer, a neovascular disorder, a clear cell renal carcinoma (CCRCC), a pancreatic cancer, a renal cancer, a urothelial cancer or an adenocarcinoma to the liver.
59. The method of embodiment 58, wherein the prostate cancer is a refractory prostate cancer, a prostatic intraepithelial neoplasia, an androgen independent prostate cancer, or a malignant prostate cancer.
60. The method of embodiment 57, wherein the hematological malignancy is acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), acute lymphocytic leukemia (ALL), diffuse large B-cell lymphoma (DLBCL), chronic myeloid leukemia (CML) or blastic plasmacytoid dendritic cell neoplasm (DPDCN).
61. The method of any one of embodiments 56-60, wherein the antibody is administered in combination with a second therapeutic agent.
62. The antibody of any one of embodiments 1-50 for use in therapy.
63. An anti-idiotypic antibody binding to the antibody of any one of embodiments 1-50.

EXAMPLES

1 De novo generation and functional characterization of anti-CD3 mAbs

1-1 Immunization of OmniRats® with CD3 antigens to generate CD3 monoclonal antibodies

OmniRats® were immunized with proprietary vectors (Aldevron, Fargo, North Dakota, USA) encoding for: human CD3e and human CD3d; cynomolgus CD3e and cynomolgus CD3d. Animals received alternating boosts with human and cynomolgus DNA. From the 6th application on, the animals received optimized vectors with the same insert. Cells from lymph nodes were fused with the Ag8 myeloma cell line. 40 million cells from fusion BLW were put on three 96-well plates following IgM depletion. 133 million cells from fusion BLX were put on nine 96-well plates without IgM depletion.

Hybridoma supernatants from fusions BLW (with magnetic bead depletion of lymphocytes) and BLX (without magnetic bead depletion of lymphocytes) were analyzed a) by a cell-based ELISA (CELISA) on cells transiently transfected with human and cynomolgus cDNA cloned into screening vectors: pOPT-CD3e-hum-epsilon-TCE.OMT + pOPT-CD3d-hum-delta.OMT, 1:1 (pOPT-CD3e/d-hum-mix) and pcDNA3.1-CD3e-cyn-delta + pcDNA3.1-CD3d-cyn-delta, 1:1 (pcDNA3.1-CD3e/d-cyn-mix). Human and cynomolgus cDNA sequences (and corresponding amino acid sequences) are provided in Table 4. For CELISA negative control, non-transfected mammalian cells were incubated with hybridoma supernatants and detected with the secondary Bethyl antibody. For a CELISA transfection control, mammalian cells, transfected with the constructs described above, were detected with anti-tag antibody.

Hybridoma supernatants were further analyzed by flow cytometry (FACS) on CD3 positive and CD3 negative Jurkat cells: Jurkat CD3+ (E6-1) and Jurkat CD3- (J.RT3-T3.5). For FACS negative control, CD3 negative Jurkat cells (J.RT3-T3.5), were incubated with dilution buffer and detected with Southern anti-rat Ig HRP and Bethyl anti-rat IgG1, 2a, 2b, 2c- HRP secondary antibodies.

The specificity of the antibodies in the hybridoma supernatants of the hybridomas from fusion BLW and fusion BLX for human and cynomolgus CD3e/d complex presented on transiently transfected cells or, in the case of the human CD3e/d complex on Jurkat CD3+ (E6-1)

cells, was demonstrated by CELISA on transiently transfected cells, as well as when tested in FACS on Jurkat cell lines (Table 3). No significant signal was detected for any samples in the experimental samples serving as negative controls.

- 5 Table 3. Test of the specificity of individual hybridoma supernatants by cell-based ELISA (top) and by flow-cytometry (bottom). CELISA values represent the relative fluorescence units (rfu) of each sample. FACS values represent the geometric means (geomean) of the relative fluorescence intensities of each sample.

		Cell based ELISA (relative fluorescence units)					
		Hybridoma supernatants incubated on cells transfected with :					
		pOPT-CD3e/d-hum-mix		pcDNA3.1-CD3e/d-cyn-mix		Non-transfected CHO negative control	
		BLW: fusion with lymphocytes from immunization group MR14—379 rat 1&2 (magnetic-bead depletion of IgM+ applied)					
No	Clone	Rfu	% positive	Rfu	% positive	Rfu	% positive
1	BLW-2B4	689	101	230	47	30	
2	BLW-2E6	231	34	121	25	20	
3	BLW-3B4	867	127	320	66	24	
		BLX: fusion with lymphocytes from immunization group MR14—379 rat 1&2 (without magnetic-bead depletion of IgM+)					
No	Clone	Rfu	% positive	Rfu	% positive	Rfu	% positive
4	BLX-1F8	689	101	230	47	30	
5	BLX-2E9	867	127	320	66	24	
6	BLX-3F4	896	131	371	76	17	
7	BLX-3G8	759	111	340	70	22	
8	BLX-4D9	1042	153	483	99	24	
9	BLX-6A2	110	16	38	8	19	
	Positive control	682	100	488	100	-	
	Negative control	25	4	42	9	-	
		Flow Cytometry (FACS)					
		Hybridoma supernatants incubated on Jurkat cell line					
		Jurkat CD3+ (E6-1)		Jurkat CD3- (J.RT3.T3.5) negative control			
		BLW: fusion with lymphocytes from immunization group MR14—379 rat 1&2 (magnetic-bead depletion of IgM+ applied)					
No	Clone	geomean	% positive	geomean	% positive		
1	BLW-2B4	148034	53	4012			
2	BLW-2E6	7503	3	687			
3	BLW-3B4	198849	72	2884			
		BLX: fusion with lymphocytes from immunization group MR14—379 rat 1&2 (without magnetic-bead depletion of IgM+)					
No	Clone	geomean	% positive	geomean	% positive		
4	BLX-1F8	148034	53	4012			
5	BLX-2E9	198849	72	2884			
6	BLX-3F4	181963	66	4613			

7	BLX-3G8	214697	77	3096	
8	BLX-4D9	25839	9	1471	
9	BLX-6A2	3385	1	1219	
	Positive control	277338	100	2051	
	Negative control	869	0	599	

Table 4. CD3 sequences used for immunization

Human CD3d	NP_000723.1 (www.uniprot.org/uniprot/P04234) (SEQ ID NO:691)
Human CD3e	(NP_000724.1 (www.uniprot.org/uniprot/P07766) (SEQ ID NO:636)
Cyno CD3d	XP_001097302 (www.uniprot.org/uniprot/Q95LI8) (SEQ ID NO:692)
Cyno CD3e	CD3e + TCE (www.uniprot.org/uniprot/Q95LI5) (SEQ ID NO:693)

1-2 Cloning anti-CD3 antibodies

Anti-human CD3 antibodies were generated in OmniRats (OMT, Palo Alto, California, USA). Variable region (“V region”) sequences of these clones were extracted from the genomic
5 sequences and analyzed. All sequences obtained were either human IgG heavy chain or lambda light chain and the sequences, especially LC, showed high homology. Aligning the sequences to germline showed some mutations in the framework (**Fig. 1**). The V-region DNA sequences were synthesized and cloned into mammalian expression vectors, heavy chain sequences into human IgG1 vector and light chain sequences into human lambda vector. Sequences are shown in
10 Tables 6 and 7. Seven mAbs were assigned protein identifiers (Table 5A).

CD3B312 was chosen as the most representative clone and the heavy chain sequences were cloned into human IgG1sigma and IgG4 PAA with S228P, F234A, L235A mutations and assigned protein identifiers as shown in Table 5B. These were used to generate bispecific antibodies and to demonstrate T cell redirection functionality through cytotoxicity.

15 Table 5A. Peptide ID and protein ID of clones

clone ID	HC peptide ID	LC peptide ID	protein ID
BLW-2B4	CD3H218	CD3L123	CD3B311
BLW-2E6	CD3H219	CD3L124	CD3B312
BLW-3B4	CD3H218	CD3L125	CD3B313
BLX-1F8	CD3H220	CD3L126	CD3B314
BLX-2E9	CD3H221	CD3L124	CD3B315

BLX-3F4	CD3H222	CD3L124	CD3B316
BLX-3G8	CD3H223	CD3L124	CD3B317

Table 5B. CD3B312 was chosen as the most representative clone and the heavy chain sequences were cloned into human IgG1sigma and IgG4 PAA with mutations and assigned protein identifiers.

IgG1	IgG1sigma	IgG4PAA
CD3B312	CD3B337	CD3B373

Table 6. Heavy chain and light chain sequences of 7 monoclonal CD3 antibodies

Protein AA ID	Heavy Chain Amino Acid Sequence	SEQ ID NO.	Light Chain Amino Acid Sequence	SEQ ID NO.
CD3B311 (BLW-2B4)	HC Peptide ID: CD3H218 QVQLQQSGPGLVKPSQTLSTCAIS GDSVFNNNAAWTWIRQSPSRGLEW LGRYYRSKWLYDYAVSVKSRITV NPDTSRNQFTLQLKSVTPEDTALYY CSRGYSSFDYWGGQTLVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTF PAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHKPSNTKVDKKVEPKSCD KTHTCPPCPAPELLGGPSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTPP PVLDSDDGSFFLYSKLTVDKSRWQQG NVFSCSVMHREALHNHYTQKSLSLSP GK	(637)	LC Peptide ID: CD3L123 QSALTQPASVSGSPGQSITIS CTGTSSNIGTYKFVSWYQQH PDKAPKVLLYEVS KRPSGVS SRFSGSKSGNTASLTISGLQA EDQADYHCCSYAGSGTLLF GGGTKLTVLGQPKAAPSVTL FPPSSEELQANKATLVCLISD FYPGAVTVAWKADSSPVKA GVETTTPSKQSNNKYAASSY LSLTPEQWKSHRSYSCQVTH EGSTVEKTVAPTECS	(645)
CD3B312	HC Peptide ID: CD3H219		LC Peptide ID: CD3L124	

(BLW-2E6)	QVRLQQSGPGLVKPSQTLSTCAISG DSVFNNNAAWSWIRQSPSRGLEWL GRYYRSKWLYDYAVTVKSRITVN PDTSRNQFTLQLTSVTPEDTALYYC ARGYSSSFYWGQGT LVTVSSASTK GPSVFPLAPSSKSTSGGTAALGCLV KD YFPEPVT VSWNSGALTSGVHTFP AVLQSSGLYSLSSVVTVPSSSLGTQT YICNVNHKPSNTKVDKKVEPKSCD KTHTCPPCPAPELLGGPSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTTP PVLDS DGSFFLYSKLTVDKSRWQQG NVFSCSV MHEALHNHYTQKSLSLSP GK	(640)	QSALTQPASVSGSPGQSITIS CTGTSSNIGTYKFVSWYQQH PDKAPKVLLYEVS KRPSGVS SRFSGSKSGNTASLTISGLQA EDQADYHCCSYAGSGTLLF GGGTKLTVLGQPKAAPSVTL FPPSSEELQANKATLVCLISD FYPGAVTVAWKADSSPVKA GVETTTPSKQSNNKYAASSY LSLTPEQWKSHRSYSCQVTH EGSTVEKTVAPTECS	(646)
CD3B313 (BLW-3B4)	HC Peptide ID: CD3H218 QVQLQQSGPGLVKPSQTLSTCAIS GDSVFNNNGAWSWIRQSPSRGLEW LGRTYYRSKWLYDYAVSVKSRITV NPDTSRNQFTLQLNSVTPEDTALYY CARGYSSSFYWGQGT LVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVT VSWNSGALTSGVHTF PAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHKPSNTKVDKKVEPKSCD KTHTCPPCPAPELLGGPSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTTP PVLDS DGSFFLYSKLTVDKSRWQQG NVFSCSV MHEALHNHYTQKSLSLSP GK	(638)	LC Peptide ID: CD3L125 QSALTQPASVSGSPGQSITIS CTGTSSNIGTYKFVSWYQQH PDKAPKVLLYEVS KRPSGVS SRFSGSKSGNTASLTISGLQA EDQADYHCCSYAGSGTLLF GGGTKLTVLGQPKAAPSVTL FPPSSEELQANKATLVCLISD FYPGAVTVAWKADSSPVKA GVETTTPSKQSNNKYAASSY LSLTPEQWKSHRSYSCQVTH EGSTVEKTVAPTECS	(649)
CD3B314	HC Peptide ID: CD3H220		LC Peptide ID: CD3L126	

(BLX-1F8)	QVQLQQSGPGLVKPSQTLSTCAIS GDSVFNNNAAWSWIRQSPSRGLEW LGRYYRSKWLYDYAVSVKSRITV NPDTSRNQFTLQLKSVTPEDTALYY CSRGYSSSFDYWGGQTLVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTF PAVLQSSGLYSLSSVTVPSSSLGTQ TYICNVNHKPSNTKVDKKVEPKSCD KTHTCPPCPAPELLGGPSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTPP PVLDSGDGSFFLYSKLTVDKSRWQQG NVFSCSVMHREALHNHYTQKSLSLSP GK	(641)	QSALTQPASVSGSPGQSITIS CTGTSSDIGTYKFVSWYQQH PDKAPKVLLYEVS KRPSGVS SRFSGSKSDNTASLTISGLQA EDQADYHCCSYAGSGTLLF GGGTKLTVLGQPKAAPSVTL FPPSSEELQANKATLVCLISD FYPGAVTVAWKADSSPVKA GVETTTPSKQSNNKYAASSY LSLTPEQWKSHRSYSCQVTH EGSTVEKTVAPTECS	(650)
CD3B315 (BLX-2E9)	HC Peptide ID: CD3H221 QVQLQQSGPGLVKPSQTLSTCAIS GDSVFNNNAAWSWIRQSPSRGLEW LGRYYRSKWLYDYAVSVKSRITV NPDTSRNQFTLQLNSVTPEDTALYY CVRGYSSSFDYWGGQTLVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTF PAVLQSSGLYSLSSVTVPSSSLGTQ TYICNVNHKPSNTKVDKKVEPKSCD KTHTCPPCPAPELLGGPSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTPP PVLDSGDGSFFLYSKLTVDKSRWQQG NVFSCSVMHREALHNHYTQKSLSLSP GK	(642)	LC Peptide ID: CD3L124 QSALTQPASVSGSPGQSITIS CTGTSRDIGTYKFVSWYQQH PDKAPKVLLYEVS KRPSGVS SRFSGSKSGNTASLTISGLQA EDQADYHCCSYAGSGTLLF GGGTKLTVLGQPKAAPSVTL FPPSSEELQANKATLVCLISD FYPGAVTVAWKADSSPVKA GVETTTPSKQSNNKYAASSY LSLTPEQWKSHRSYSCQVTH EGSTVEKTVAPTECS	(647)
CD3B316	HC Peptide ID: CD3H222		LC Peptide ID: CD3L124	

(BLX-3F4)	QVQLQQSGPRLVRPSQTLSTLCAISG DSVFNNNAAWSWIRQSPSRGLEWL GRITYYRSKWLYDYAVSVKSRITVN PDTSRNQFTLQLNSVTPEDTALYYC ARGYSSSFDYWGGTLVTVSSASTK GPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFP AVLQSSGLYSLSSVVTVPSSSLGTQT YICNVNHKPSNTKVDKKVEPKSCD KTHTCPPCPAPELLGGPSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTPP PVLDSGDGSFFLYSKLTVDKSRWQQG NVFSCSVMEALHNHYTQKSLSLSP GK	(643)	QSALTQPASVSGSPGQSITIS CTGTSSNIGTYKFVSWYQQH PDKAPKVLLYEVS KRPSGV SRFSGSKSGNTASLTISGLQA EDQADYHCCSYAGSGTLLF GGGTKLTVLGQPKAAPSVTL FPPSSEELQANKATLVCLISD FYPGAVTVAWKADSSPVKA GVETTTTPSKQSNNKYAASSY LSLTPEQWKSHRSYSCQVTH EGSTVEKTVAPTECS	(646)
CD3B317 (BLX-3G8)	HC Peptide ID: CD3H223 QVQLQQSGPGLVKPSQTLSTLCAIS GDSVFNNNAAWSWIRQSPSRGLEW LGRITYYRSKWLYDYAVSVKSRITV NPDTSRNQFTLQLNSVTPEDTALYY CVRGYSSSFDYWGGTLVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTF PAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHKPSNTKVDKKVEPKSCD KTHTCPPCPAPELLGGPSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTPP PVLDSGDGSFFLYSKLTVDKSRWQQG NVFSCSVMEALHNHYTQKSLSLSP GK	(644)	LC Peptide ID: CD3L124 QSALTQPASVSGSPGQSITIS CTGTSRDIGTYKFVSWYQQH PDKAPKVLLYEVS KRPSGV SRFSGSKSGNTASLTISGLQA EDQADYHCCSYAGSGTLLF GGGTKLTVLGQPKAAPSVTL FPPSSEELQANKATLVCLISD FYPGAVTVAWKADSSPVKA GVETTTTPSKQSNNKYAASSY LSLTPEQWKSHRSYSCQVTH EGSTVEKTVAPTECS	(648)

Table 7A. VH and VL sequences with HC and LC isotype of 7 monoclonal CD3 antibodies from the first panel of 9 described above (see Table 3). All HC isotypes were huIgG1_G1m(17). All LC isotypes were huLambda 2.

Fab ID	Peptide ID	VH (SEQ ID NO:)	Peptide ID	VL (SEQ ID NO:)
CD3B311	CD3H218	qvqlqqsgpglvkpsqtlsltc caisgdsvfnnnaawsirqs psrglewlgrityyrskwlydy avsvksritvnpdtsrnqftl	CD3L123	qsaltqpasvsgspgqsitisc tgsrdigtykfvsyqqhpdka p kvlllyevnkrpsgvssrfsgsks

		qlnsvtpedtalyyccvrgyss sfdywgqgtlvtvss (651)		gntasltisglqaedqadyhccs yagsgtllfgggtklvtl (658)
CD3B312	CD3H219	qvqlqqsgprrlvrsqtlslt caisgdsvfnnnaawswirqs psrglewlgrtyyrskwlydy avsvksritvnpdtsrnqftl qlnsvtpedtalyyccvrgyss sfdywgqgtlvtvss (652)	CD3L124	qsaltqpasvsgspgqsitist gtssnigtykfvswyqqhpdka kvlllyevskrpsgvssrfsgsks gntasltisglqaedqadyhccs yagsgtllfgggtklvtl (659)
CD3B313	CD3H218	qvqlqqsgpglvkpsqtlslt caisgdsvfnnnaawswirqs psrglewlgrtyyrskwlydy avsvksritvnpdtsrnqftl qlnsvtpedtalyyccvrgyss sfdywgqgtlvtvss (687)	CD3L124	qsaltqpasvsgspgqsitist gtsrdigtykfvswyqqhpdka kvlllyevskrpsgvssrfsgsks gntasltisglqaedqadyhccs yagsgtllfgggtklvtl (688)
CD3B314	CD3H220	qvqlqqsgpglvkpsqtlslt caisgdsvfnnnaawswirqs psrglewlgrtyyrskwlydy avsvksritvnpdtsrnqftl qlksvtpedtalyyccvrgyss sfdywgqgtlvtvss (653)	CD3L126	qsaltqpasvsgspgqsitist gtssdigtykfvswyqqhpdka kvlllyevskrpsgvssrfsgsks dntasltisglqaedqadyhccs yagsgtllfgggtklvtl (660)
CD3B315	CD3H221	qvqlqqsgpglvkpsqtlslt caisgdsvfnnngawswirqs psrglewlgrtyyrskwlydy avsvksritvnpdtsrnqftl qlnsvtpedtalyyccvrgyss sfdywgqgtlvtvss (654)	CD3L124	qsaltqpasvsgspgqsitist gtssnigtykfvswyqqhpdka kvlllyevskrpsgvssrfsgsks gntasltisglqaedqadyhccs yagsgtllfgggtklvtl (659)
CD3B316	CD3H222	qvrlqqsgpglvkpsqtlslt caisgdsvfnnnaawswirqs psrglewlgrtyyrskwlydy avtvksritvnpdtsrnqftl qltsvtpedtalyyccvrgyss sfdywgqgtlvtvss (655)	CD3L124	qsaltqpasvsgspgqsitist gtssnigtykfvswyqqhpdka kvlllyevskrpsgvssrfsgsks gntasltisglqaedqadyhccs yagsgtllfgggtklvtl (659)
CD3B317	CD3H223	qvqlqqsgpglvkpsqtlslt caisgdsvfnnnaawtwirqs psrglewlgrtyyrskwlydy avsvksritvnpdtsrnqftl qlksvtpedtalyyccvrgyss sfdywgqgtlvtvss (656)	CD3L124	qsaltqpasvsgspgqsitist gtssnigtykfvswyqqhpdka kvlllyevskrpsgvssrfsgsks gntasltisglqaedqadyhccs yagsgtllfgggtklvtl (659)

Table 7B. CDR sequences with HC and LC isotype of 7 monoclonal CD3 antibodies from the first panel of 9 described above (see Table 3). Sequences are defined according to Kabat. All HC isotypes were huIgG1_G1m(17). All LC isotypes were huLambda 2.

FAB ID	Peptide ID	CDRs (SEQ ID NO:)		
		CDR1	CDR2	CDR3
CD3B311	HC CD3H218	NNNAAWS (662)	RTYYRSKWLYDYAVSVKS (663)	GYSSSFDY (664)
	LC CD3L123	TGTSRDIGTYKFVS (667)	EVNKRPS (669)	CSYAGSGTLL (670)
CD3B312	HC CD3H219	NNNAAWS (662)	RTYYRSKWLYDYAVSVKS (663)	GYSSSFDY (664)
	LC CD3L124	TGTSSNIGTYKFVS (671)	EVSKRPS (673)	CSYAGSGTLL (670)
CD3B313	HC CD3H218	NNNAAWS (662)	RTYYRSKWLYDYAVSVKS (663)	GYSSSFDY (664)
	LC CD3L124	TGTSRDIGTYKFVS (672)	EVSKRPS (673)	CSYAGSGTLL (670)
CD3B314	HC CD3H220	NNNAAWS (662)	RTYYRSKWLYDYAVSVKS (663)	GYSSSFDY (664)
	LC CD3L126	TGTSSDIGTYKFVS (674)	EVSKRPS (673)	CSYAGSGTLL (670)
CD3B315	HC CD3H221	NNNGAWS (665)	RTYYRSKWLYDYAVSVKS (663)	GYSSSFDY (664)
	LC CD3L124	TGTSSNIGTYKFVS (671)	EVSKRPS (673)	CSYAGSGTLL (670)
CD3B316	HC CD3H222	NNNAAWS (662)	RTYYRSKWLYDYAVTVKS (689)	GYSSSFDY (664)
	LC CD3L124	TGTSSNIGTYKFVS (671)	EVSKRPS (673)	CSYAGSGTLL (670)
CD3B317	HC CD3H223	NNNAAWT (666)	RTYYRSKWLYDYAVSVKS (663)	GYSSSFDY (664)
	LC CD3L124	TGTSSNIGTYKFVS (671)	EVSKRPS (673)	CSYAGSGTLL (670)

5 1-3 Screening of hybridomas for binding to human and cynomolgus purified T cells

A cell-based binding assay was designed to assess the binding capacity of individual rat hybridoma supernatants to human (**Fig. 2**) and cynomolgus (**Fig. 3**) purified CD3+ T lymphocytes. The T cells were counted, diluted to 1×10^6 cells/mL and incubated with 0.5
 10 ul/mL of Live/Dead Fixable Green Dead Cell Stain (Life Technologies, L-2301). Next the cells were aliquoted into a U-bottom (Falcon 353077) plate at 100ul/well (1×10^5 cells/well). The plates were centrifuged at 300g for 5 minutes to pellet the cells and the supernatant removed. The plate was vortexed briefly to resuspend the cells. The hybridoma supernatants were diluted

in FACS staining buffer (BSA, BD Biosciences 554657) to 4.5 µg/mL and then serially diluted 6 times at 1:3 dilutions to the lowest concentration of 0.006 µg/mL. A positive control of mouse anti-human CD3 (SP34-2, BD Biosciences 551916) and negative isotype control (mouse IgG1 BD Biosciences 556648) were also diluted to 4.5 µg/mL. 50µl of each sample was added to the
5 T cells and incubated at 4°C for 1 hour. The cells were washed once with staining buffer and secondary AF647 Goat anti-mouse IgG (Life Technologies, A21235) or AF647 goat anti-rat IgG (Life Technologies, A21247) was added at 10 µg/mL in 50 µl was added according to the appropriate species (anti-rat for hybridoma samples and anti-mouse for the control antibodies). The plates were incubated at 4°C for 45 minutes and washed with staining buffer twice. The cells
10 were resuspended in 25 µl of running buffer (staining buffer + 1 mM EDTA (Life technologies, AM9260G) + 0.1% pluronic F-68 (Life Technologies 24040-032)) and read on the Intellicyt system (Intellicyt Corp.). The results are shown in **Figs. 2 and 3**.

In other experiments, purified human T cells were plated at 1.1×10^5 cells/well in U-bottom plates. The plates were centrifuged at 300g for 5 minutes to pellet the cells and the
15 supernatant removed. The plate was vortexed briefly to resuspend the cells. The hybridoma supernatants were diluted in FACS staining buffer (BSA, BD Biosciences 554657) to 30ug/mL and then serially diluted 11 times at 1:3 dilutions to the lowest concentration of 0.00017ug/mL. 50ul of each sample was added to the T cells and incubated at 4C for 1 hour. The cells were washed once with staining buffer and secondary Dylight 650 goat anti-rat IgG (Bethyl, A110-
20 239D5) was added at 10ug/mL in 50ul was added. The plates were incubated at 4C for 1 hour and washed with staining buffer twice. The cells were resuspended in 30ul of FACS buffer and read on the Hypercyte flow cytometer (Intellicyt Corp.). Representative dose-response curves for the anti-CD3 clones binding to primary human T cells are shown in **Fig. 5**.

Representative competition binding curves with SP34-2 (a commercial anti-human CD3
25 antibody which has a known epitope and is cross-reactive with cynomolgus CD3) are shown in **Fig. 6**. The initial screening results are summarized in Table 8. Six of the clones showed positive binding and also compete with SP34-2 for binding to primary human T cells.

1-4 Competition assay with SP34-2 commercial CD3 antibody

The hybridoma supernatants were also assessed for their ability to compete with commercial anti-human CD3 antibody SP34-2 which has a known epitope and is cross-reactive with cynomolgus CD3. First a concentration titration curve of AF488 fluorescently labelled SP34-2 (BD, 557705) was performed to determine a fixed concentration of SP34-2 for the following competition assays. Briefly, human purified T cells were diluted to 1×10^6 cell/mL in PBS. Fc block (Human TruStain Fc Block, Biolegend, 422302) was added at 5 μ L/100 μ L cells and plated at 100 μ L/well in U-bottom plates. AF488 SP34-2 and the AF488 labelled isotype control (AF488 mouse IgG1, BD, 400129) were serially diluted from 50 μ g/mL to 0.049 μ g/mL in a 1:2 dilution scheme. The plates were centrifuged at 300xg for 5 minutes to pellet the cells and the supernatant removed. The plate was gently vortexed briefly to resuspend the cells. 50 μ L of each AF488 SP34-2 dilution was added to the cells and incubated at 4°C for 1 hour. The plates were washed with staining buffer twice and once with running buffer (staining buffer + 1 mM EDTA (Life technologies, AM9260G) + 0.1% pluronic F-68 (Life Technologies 24040-032)). The cells were resuspended in 25 μ L of running buffer and read on the HTFC Screening System (IntelliCyt Corporation). Based on the dose response curve, a fixed concentration of 2 μ g/mL SP34-2 was chosen for the competition assay.

Seven hybridomas that demonstrated binding to purified T cells were assayed for competition with SP34-2 binding to human T cells (**Fig. 4**). Control antibodies were included in the competition assay. Unlabeled Mouse Anti-Human CD3, SP34-2 antibody and Mouse Anti-Human CD3, UCHT1 antibody were used as positive controls and rat IgG and Mouse isotype were used as negative controls for AF488 labeled SP34-2. Purified human T cells were diluted to a concentration of 1×10^6 cells/mL in PBS. Fc block at 5 μ L per 100 μ L cells (Human TruStain Fc Block, Biolegend, 422302) and Live/Dead Fixable Far Red Dead Cell Stain at 0.5 μ L per mL cells (Life Technologies L10120) were added to the cells and incubated for 15 minutes at 4°C. Next, 10^5 cells per well (1×10^5 cells/well) were aliquoted into a 96-well U-bottom plate (Falcon 353077). The plates were centrifuged at 300xg for 5 minutes to pellet the cells and the supernatant removed. The plate was gently vortexed briefly to resuspend the cells. The hybridoma supernatants and the control antibodies were diluted in FACS staining buffer (BSA, BD Biosciences 554657) at 2X the desired final concentration. 35 μ L of the 2X hybridoma

supernatants and the control antibodies were mixed with 35 μ L of 2X AF488 SP34-2 (4 μ g/mL) to give the desired 1X concentration of hybridoma supernatants, 1X concentration of control antibodies and 2 μ g/mL AF488 SP34-2. The hybridoma supernatants and control antibodies were assayed using a 7-point titration with a concentration range. Hybridoma supernatants were
 5 assayed from 200 μ g/mL to 0.08 μ g/mL and control antibodies were assayed from 100 μ g/mL to 0.04 μ g/mL. 50 μ L of the 1X hybridoma supernatants or 1X control antibodies with 2 μ g/mL AF488 SP34-2 were added to the T cells and incubated at 4°C for 2 hours. The plates were washed with staining buffer twice and once with running buffer (staining buffer + 1 mM EDTA (Life technologies, AM9260G) + 0.1% pluronic F-68 (Life Technologies 24040-032)). The cells
 10 were resuspended in 25 μ L of running buffer and read on the HTFC Screening System (IntelliCyt Corporation). Representative competition binding curves with SP34-2 (a commercial anti-human CD3 antibody which has a known epitope and is cross-reactive with cynomolgus CD3) are shown in **Fig. 4** and **Fig. 6**. The initial screening results are summarized in Table 8. Six of the clones showed positive binding and also competed with SP34-2 for binding to primary human T
 15 cells.

As shown in **Fig. 4** the seven antibodies competed with SP34-2 with similar curves. The right shift of the curves relative to the control SP34-2 indicates a weaker binding affinity. The isotype control rat IgG did not compete with SP34-2, as expected.

Table 8. Summary of anti-CD3 antibody binding on primary human T cells. Anti-CD3 clones
 20 **BLX-4E5, BLX-5H7, BLX-8B4, BLX-8B6, BLX-8G8 and BLW-1E3** were positive for binding to human T cells and competed with SP34-2 binding

Ab clone	Binds with human T cells	Competes with SP34-2
BLW-2B4	+	+
BLW-2E6	+	+
BLW-3B4	+	+
BLX-1F8	+	+
BLX-2E9	+	+
BLX-3F4	+	+
BLX-3G8	+	+
BLX-1G10	-	-
BLX-3H6	-	-
BLX-4E5	+	+
BLX-5H7	+	+
BLX-8B4	+	+
BLX-8B6	+	+

BLX-8G8	+	+
BLW-1E3	+	+
BLW-1F1	+	-
BLW-2C4	-	-
BLW-2C11	-	-
BLW-2F9	-	-
BLW-3B5	-	-
BLW-3H5	-	-

1-5 Screening of hybridoma hits for T cell activation as measured by CD69 upregulation

A primary human and cynomolgus monkey T cell based assay was used to determine the capacity of the hybridoma hits to activate T cells. This was accomplished by coating antibodies to a plate to mimic the cross-linking effect of TCR activation. Upon activation, T cells are known to upregulate the surface expression of the protein, CD69. The experiment was conducted by coating 50µl of a 10µg/ml antibody preparation with unknown samples or controls (positive control: in house, Okt-3 BISB264.002, BD Bioscience SP-34-2 #551916; negative control: anti-CD20 in house BISB266.004) to a 96 well plate (Costar #3361). The plates were incubated overnight at 4°C. The next day the plates were washed twice with PBS. Frozen primary T cells (human sourced from Biological Specialities or Hemacare; cynomolgus sourced from WorldWide Primates) were thawed, counted for viability and resuspended at 2×10^6 cell/ml in RPMI 1640 medium (Gibco #11875 with 10% HI FBS (Gibco #10062)). 100µl of the cells was added to the plate and incubated overnight (approximately 16 hours) at 37°C, 5% CO₂. The following day the plates were spun at 1300rpm for 3 minutes to pellet the cells and the supernatants were discarded. The cells were washed once in PBS and spun as before. 10µl of a 2.5% solution of Live/Dead Green Fixable Dye (Life Technologies #L23101) in PBS was added to each well and incubated at room temperature and in the dark for 10 minutes. Next 50µl of a 1% solution of anti-CD69 AF488 (Biolegend #310916 lot #B125271) in FACS buffer (BD Biosciences #554657) was added and the plates were incubated for 45 minutes at 4°C. The plates were washed twice by pelleting the cells as before and discarding the supernatant and resuspending in 150µl of FACS buffer. After the final wash the cells were resuspended in 150µl of FACS buffer and read on the FACS Canto. As seen in **Fig. 20**, the positive controls cOkt3 and

SP34-2 induced the upregulation of CD69 on human T cells as indicated by the measured mean fluorescence intensity of the anti-CD69 staining. Only SP34-2 induced CD69 expression in the cynomolgus T cells, as it binds to a region of CD3 sequence that is conserved from monkey to man. The OKT3 anti-CD3 clone did not bind cynomolgus CD3 and did not induce CD69

5 upregulation. The negative control in both human and cynomolgus T cells was an anti-CD20 which is not expressed on T cells. Of the hybridoma clones that were tested for T cell activation, several induced CD69 expression to a similar degree as the positive control, namely 2B4, 2E6, 3B4, 1F8, 2E9, 3F4, 3G8, 4E5, 5H7, 8B4, 8G8 and 1F1. Most also bound and activated cynomolgus T cells except for 5H7, 8B4, and 8G8.

10 1-6 Framework engineering of BLW-2E6

Clones showed high homology and carried framework mutations comparing to human immunoglobulin germline sequences (**Figs. 1A and 1B**). Clone 2E6 was selected to adapt the standard framework sequence. All 6 mutations on HC and 7 mutations on LC were mutated back to human germline sequence, either individually or combined (Table 9). The mutated V-region

15 DNA sequences were synthesized and cloned into the same mammalian expression vectors as their parental constructs. The HC and LC constructs were paired via matrix format to generate proteins carrying individual or combinatorial mutations and protein activity was tested. V48 on LC could not be changed back to germline. All other back mutations were not critical but reduced activity to some degree.

20 Table 9. BLW-2E6 framework variants.

Heavy chain back mutation to human germline	peptide ID
WT	CD3H219
R10G	CD3H225
R13K	CD3H226
V73I	CD3H227
R79K	CD3H228
T83S	CD3H229
L96V	CD3H230
R10G/R13K/V73I/R79K/T83S/L96V	CD3H231
Light chain back mutation to human germline	peptide ID
WT	CD3L124

D43G	CD3L128
V48L	CD3L129
L49M	CD3L130
L50I	CD3L131
S62N	CD3L132
Q85E	CD3L133
H89Y	CD3L134
D43G/L49M/L50I/S62N/Q85E	CD3L135
D43G/L49M/L50I/S62N/Q85E/H89Y	CD3L137
D43G/V48L/L49M/L50I/S62N/Q85E/H89Y	CD3L136
D43G/L49M/L50I/S62N/Q85E/H89Y/C91V	CD3L197

Framework mutations were engineered to one hybridoma clone, BLW-2E6, resulting in 80 mutant clones, some of which are indicated in Table 10. The 80 mutant clones were assayed for binding to primary human T cells (**Figs. 7 and 8**). The T cells were counted, diluted to 1×10^6 cells/mL and incubated with 5 μ L Fc block (Human TruStain Fc Block, Biolegend, 422302) per 100 μ L cells and 0.5 μ L per mL of Live/Dead Fixable Green Dead Cell Stain (Life Technologies, L-2301) per 100 μ L cells. Next, the cells were aliquoted into a 96-well U-bottom plate (Falcon 353077) at 100 μ L/well (1×10^5 cells/well). The plates were centrifuged at 300xg for 5 minutes to pellet the cells and the supernatant removed. The plate was gently vortexed briefly to resuspend the cells. The hybridoma supernatants were diluted in FACS staining buffer (BSA, BD Biosciences 554657) to 7.5 μ g/mL, 1.5 μ g/mL, 0.3 μ g/mL, and 0.06 μ g/mL. 50 μ L of each sample was added to the T cells and incubated at 4°C for 1 hour. The cells were washed once with staining buffer, and 50 μ L of 5 μ g/mL secondary AF647 goat anti-Human IgG F(ab')₂ (Jackson ImmunoResearch catalog 109-605-097) was added to the cells. The plates were incubated at 4°C for 45 minutes and washed with staining buffer twice and once with running buffer (staining buffer + 1mM EDTA (Life technologies, AM9260G) + 0.1% pluronic F-68 (Life Technologies 24040-032)). The cells were resuspended in 25 μ L of running buffer and read on the HTFC Screening System (IntelliCyt Corporation). The results demonstrate that a change in the LC at position 48 abolished binding so that mutation was not carried forward. A slight reduction in binding was seen in the HC with all positions returned to germline (CD3H231).

1-7 C91 scanning of BLW-2E6 LC

Clone 2E6 and its derivatives expressed poorly and protein aggregation was observed. One residue, C91 of light chain, was predicted to have post-translational modification (PTM) risk and was mutated to all other possible amino acids to improve protein stability (Table 10).

- 5 The mutated V-region DNA sequences were synthesized and cloned into the same human lambda expression vector as their parental construct. The SPR results demonstrated a change to valine or leucine at position 91 did not dramatically alter binding affinity. This change was also incorporated into wild type sequence and the framework adaptation above resulting in antibodies CD3B376 (CD3H219/CD3L150) and CD3B450 (CD3H231/CD3L197). CD3B376 and
- 10 CD3B450 were cloned as IgG4PAA (IgG4 with S228P, F234A, L235A mutations).

Sequence information for CD3B376 is provided below:

CD3H219 HC amino acid sequence (SEQ ID NO:640):

15 QVQLQQSGPRLVLRPSQTLSTCAISGDSVFNNNAAWSWIRQSPSRGLEWLGRITYYRSKW
LYDYAVSVKSRITVNPDTSRNQFTLQLNSVTPEDTALYYCARGYSSSFYDWGQGLTVT
SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
QSSGLYSLSSVVTVPSSSLGTKYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEAAG
GPSVFLFPPKPKDTLMISRTPEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQ
20 FNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPS
QEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFLLYSKLTVD
KSRWQEGNVFSCSVMHREALHNHYTQKSLSLSLGK

CD3H219 HC nucleic acid sequence (SEQ ID NO: 712)

25 caggtgcagotgcagcagtcctggccctagactcgtgcggccttccagaccctg
tctctgacctgtgccatctccggcgactccgtgttcaacaacaacgcgcgcctggctcctg
gatccggcagagacccttctagaggccttggaatggctgggcccggacctaactacgggtcca
agtggctgtacgactacgcctgttccgtgaagtcccggatcaaccgtgaaccctgacacc
tcccggaaaccagttcaccctgcagctgaactccgtgacccctgaggacaccgcctgtga
30 ctactgcgccagaggctactcctcctccttcgactattggggccagggcaccctcgtga
ccgtgtcctct

CD3L150 LC amino acid sequence (SEQ ID NO:676):

QSALTQPASVSGSPGQSITISCTGTSSNIGTYKFVSWYQQHPDKAPKVLLYEVS KRPSG
VSSRFSGSKSGNTASLTISGLQAEDQADYHCVSYAGSGTLLFGGGTKLTVLGQPKAAPS
5 VTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNNKYA
ASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

CD3L150 LC nucleic acid sequence (SEQ ID NO: 713)

cagtctgctctgacccagcctgcctccgtgtctggctctcccgccagtcaccatc
10 accatcagctgtacoggcacctcctccaacatcggcacctacaagttcgtgtcctggta
tcagcagcaccocgacaaggcccccacaaagtgtgtgtgtacgaggtgtccaagcggccct
ctggcgtgtcctccagattctccggctccaagtcctggcaacacgcctcctgaccatc
agcggactgcaggctgaggaccaggccgactaccactgtgtgtcctacgctggctctgg
caccctgctgtttggcggaggcaccaagctgaccgtgtgtg

VH amino acid sequence of CD3H219 (SEQ ID NO:652):

qvqlqqsgprlvprsqtlsltcaisgdsfvnnnaawswirqspsrglewlgrtyyrskw
lydyavsvksritvnpdtsrnqftlqlnsvtpedtalyyccargysssfdywgqgtlvtv
ss

VL amino acid sequence of CD3L150 (SEQ ID NO:661):

qsaltqpasvsgspgqsitistgtssnigtykfvswwyqqhpdkapkvlllyevskrp sg
vssrfsgsksgntasltisglqaedqadyhcVsyagsgtllfgggtkltvl

HCDR1 of CD3H219 (SEQ ID NO:662): NNNAAWSHCDR2 of CD3H219 (SEQ ID NO:663): RTYYRSKWLYDYAVSVKSHCDR3 of CD3H219 (SEQ ID NO:664): GYSSSFYDLCDR1 of CD3L150 (SEQ ID NO:671): TGTSSNIGTYKFVS

LCDR2 of CD3L150 (SEQ ID NO:673): EVSKRPS

LCDR3 of CD3L150 (SEQ ID NO:690): VSYAGSGTLL

5 Sequence information for CD3B450 is provided below:

CD3H231 HC amino acid sequence (SEQ ID NO:675):

QVQLQQSGPGLVKPSQTLSTCAISGDSVFNNNAAWSWIRQSPSRGLEWLGRTYYRSKW
 LYDYAVSVKSRITINPDTSKNQFSLQLNSVTPEDTAVYYCARGYSSSFYWGQGTTLTV
 10 SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
 QSSGLYSLSSVTVFPSSSLGTKYTCNVDHKPSNTKVDKRVESKYGPCCPPCPAPEAAG
 GPSVFLFPPKPKDTLMISRTPEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQ
 FNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPS
 QEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFLLYSKLTVD
 15 KSRWQEGNVFSCSVMEALHNHYTQKSLSLGLK

CD3H231 HC nucleic acid sequence (SEQ ID NO: 714):

caggtgcagctgcagcagagcggccccggcctgggtcaagcccagccagaccctgagcct
 gacctgcgccatcagcggcgacagcgtgttcaacaacaacgcgcgcctgggtcctggatcc
 20 gccagagccccagccgcggcctggagtggtggggccgcacctaactaccgcagcaagtgg
 ctgtacgactacgcggtgtccgtgaagtccccgcataccatcaacccccgacaccagcaa
 gaaccagttctccctgcagotgaacagcgtgacccccgaggacaccgcgcgtgtactact
 ggcggcggggtacagcagcagcttcgactactgggggcagggcacccctgggtcaccgtg
 tccagc

25

CD3L197 LC amino acid sequence (SEQ ID NO:677):

QSALTQPASVSGSPGQSITISCTGTSSNIGTYKFVSWYQQHPGKAPKVMIEVSKRPSG
 VSNRFGSKSGNTASLTISGLQAEDEADYYCVSYAGSGTLLFGGGTKLTVLGQPKAAPS
 VTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNKYA
 30 ASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

CD3L197 LC nucleic acid sequence (SEQ ID NO: 715):

Cagtctgctctgacccagcctgcctccgtgtctggctctcccgccagtcctaccat
 cagctgtacccggcaccctcctccaacatcggcacctacaagttcgtgtcctgggtatcagcagcac
 cccggcaaggcccccaggatgatctacgaggtgtccaagcgccctccggcgtgtccaaca
 gattctccggctccaagtcgggcaacaccgcctccctgacaatcagcggactgcaggccgagga
 5 cgaggccgactactactgtgtgtcctacgcggctctggcaccctgctgtttggcggcggaaca
 aagctgaccgtgctg

VH amino acid sequence of CD3H231 (SEQ ID NO:657):

qvqlqqsgpglvkpsqtlsltcaisgdsfvnnnaawswirqspsrglewlgertyyrskw
 10 lydyavsvksritinpdtsknqfslqlnsvtpedtavvyycargysssfdywgqgtlvtv
 ss

VL amino acid sequence of CD3L197 (SEQ ID NO:678):

15 QSALTQPASVSGSPGQSITISCTGTSSNIGTYKFVSWYQQHPGKAPKVMIIYEVSKRPSGVSNRFSGSKSGNTAS
 LTISGLQAEDEADYYCVSYAGSGTLLFGGGTKLTVL

HCDR1 of CD3H231 (SEQ ID NO:662): NNNAAWS

HCDR2 of CD3H231 (SEQ ID NO:663): RTYYRSKWLYDYAVSVKS

HCDR3 of CD3H231 (SEQ ID NO:664): GYSSSFYD

LCDR1 of CD3L197 (SEQ ID NO:671): TGTSSNIGTYKFVS

LCDR2 of CD3L197 (SEQ ID NO:673): EVSKRPS

LCDR3 of CD3L197 (SEQ ID NO:690): VSYAGSGTLL

Table 10. Engineered variants of BLW-2E6 LC by C91 scanning

C91 scanning	peptide ID
CD3 2E6 LC	CD3L124
CD3 2E6 LC, C91S	CD3L146
CD3 2E6 LC, C91G	CD3L147
CD3 2E6 LC, C91E	CD3L148

CD3 2E6 LC, C91D	CD3L149
CD3 2E6 LC, C91V	CD3L150
CD3 2E6 LC, C91A	CD3L151
CD3 2E6 LC, C91R	CD3L152
CD3 2E6 LC, C91K	CD3L153
CD3 2E6 LC, C91N	CD3L154
CD3 2E6 LC, C91M	CD3L155
CD3 2E6 LC, C91I	CD3L156
CD3 2E6 LC, C91T	CD3L157
CD3 2E6 LC, C91W	CD3L158
CD3 2E6 LC, C91Y	CD3L159
CD3 2E6 LC, C91L	CD3L160
CD3 2E6 LC, C91F	CD3L161
CD3 2E6 LC, C91Q	CD3L162
CD3 2E6 LC, C91H	CD3L163
CD3 2E6 LC, C91P	CD3L164

1-8 Binding of BLW-2E6 CD3 mAbs to hCD3ε construct by ProteOn SPR

The binding of BLW-2E6 anti-CD3 mAbs with point mutations on the light and/or heavy chain(s) to a recombinant human CD3ε(1-27) peptide with a C-terminal Tencon25 fusion

- 5 (Janssen production, referred as hCD3ε(1-27)-Tn25) was measured by ProteOn SPR (Bio-Rad). Goat anti-human Fc IgG (Jackson ImmunoResearch, Cat# 109-005-098) was directly immobilized via amine coupling at 30 µg/mL in acetate buffer, pH 5.0 on all 6 ligand channels in vertical orientation on GLC Sensor Chip (Bio-Rad, catalog no. 176-5011) with a flow rate of 30 µL/min in PBS containing 0.005% Tween-20. The immobilization densities averaged about
- 10 6000 Response Units (RU) with less than 5% variation among different channels. Five different mAbs were captured on the anti-human Fc IgG surface at 1.5 µg/ml (1000~1250 RU) in vertical ligand orientation, with the 6th ligand channel as no ligand surface control. The hCD3ε(1-27)-Tn25 at 1 µM concentration in 3-fold dilution series of 5 concentrations flew in as analyte to bind to captured mAbs in the horizontal orientation. A 6th buffer sample was also injected to
- 15 monitor the dissociation of captured mAb and baseline stability. The dissociation phase for all concentrations of hCD3ε(1-27)-Tn25 was monitored at a flow rate of 100 µL/min for 30 minutes. The binding surface was regenerated for the next interaction cycle using a 18 second pulse of 0.8% phosphoric acid to remove the antigen and the bound mAb. The raw data were

processed by subtracting two sets of reference data from the response data: 1) the inter-spot signals to correct for the non-specific interactions between the Ag and the empty chip surface; 2) the buffer channel signals to correct for baseline drifting due to the dissociation of captured mAb surface over time. The processed data at all concentrations for each mAb were globally fit to a 1:1 simple Langmuir binding model to extract estimates of the kinetic (k_{on} , k_{off}) and affinity (K_D) constants. Results are provided in **Fig. 11**.

Table 11. Summary of the kinetics/affinities of BLW-2E6 variants binding to hCD3 ϵ (1-27)-Tn25 (N=1)

Protein AA ID	Heavy Chain	Light Chain	k_a (1/Ms)	k_d (1/s)	K_D (nM)	HC Mutation(s)	LC mutation(s)
C3B312	CD3H219	CD3L124	9.08E+04	1.87E-03	20.6	Wild type	Wild type
CD3B376	CD3H219	CD3L150	1.02E+05	2.37E-03	23.3	Wild type	C91V
N/A	CD3H219	CD3L160	9.84E+04	4.05E-03	41.1	Wild type	C91L
N/A	CD3H219	CD3L137	6.13E+04	2.02E-03	32.9	Wild type	D43G/L49M/L50I/S62N/Q85E/H89Y
CD3B334	CD3H231	CD3L137	6.96E+04	5.54E-03	79.6	R10G/R13K/V73I/R79K/T83S/L96V	D43G/L49M/L50I/S62N/Q85E/H89Y

N/A = not assigned

10

1-9 Binding of anti-CD3 monoclonal antibodies to human T cells

In vitro binding affinity of CD3B376 and CD3B450 to human T cells was determined by flow cytometry after crossing with antigen specific target arm. A preliminary study was carried out on human T cells to determine the saturation binding constant of an anti-CD3 tracer molecule (K_dT). A fixed concentration of the tracer ($[T]$) was then used in a competition binding assay with titrated concentrations of the test mAbs. The IC_{50} (concentration at which 50% inhibition is achieved) value of the test molecule was used to determine the binding affinity (K_d) using the following formula: $K_d = IC_{50}/(1 + ([T]/K_dT))$. Five human donors were used to determine the saturation binding constant (K_dT) of the tracer, a commercially available AlexaFluor488 SP34-2 anti-CD3 (BioScience #557705) (data not shown).

20

Determining Saturation Binding Constant of Tracer (K_d)

Methods: Human pan T cells were cryogenically-stored in nitrogen tanks until used. T cells were thawed, washed with PBS, re-suspended in FACS Staining buffer, counted (with viability noted), and re-suspended at 0.5×10^6 cells/mL. Far Red Live/Dead stain (Life Technologies, AKA Invitrogen # L34974) (50 μ L of DMSO into a vial) was added at 1 μ L per 1×10^6 cells; and FcR blocker (Miltenyi Biotec #130-059-901) (1 mL of a 1:20 dilution per 0.5×10^6 cells) were added to the cells for 10 minutes each. Cells were plated at 50,000 cells/well and washed. Increasing concentrations of the AlexaFluor488 SP-34 anti-CD3 were added to the T cells for 2 hours at 4 °C. Cells were washed to remove un-bound antibody, fixed for 15 minutes, washed, and re-suspended in FACS Staining buffer containing 1mM EDTA.

The iQue Intellicyte Flow Cytometer was used to measure binding. Cells were gated for T cell population, followed by cell singlets, followed by Live Cells (FL4). Geometric mean of staining (FL1) was determined for each well.

The acquired mean fluorescence intensity values were plotted as a function of the antibody molecule concentration and analyzed using Prism software in a one-site binding analysis (Total Binding) (**Fig. 9**). The software calculates the corresponding K_d value that describes the binding of the antibody molecule to a receptor (the CD3 on Human Pan T cells) that follows the law of mass action. The formula is as follows: $Y = (B_{\max} \times X) / (K_d + X)$; where: $B_{\max}$ is maximal binding; K_d is the concentration of ligand required to reach half-maximal binding.

Results: K_d values were derived for each donor, and the mean value obtained. The Saturation Binding Constant (K_d) for human T-Cells was derived to be 5.6 ± 1.0 nM (n=4) and was used in the previously mentioned formula to determine K_d binding affinities.

Determining Binding Affinity of anti-CD3 mAbs by Competition Assay

Methods: Competition binding studies were performed using bivalent antibodies against CD3:

- Anti CD3 bivalents: CD3B376 and CD3B450 (**Fig. 10**)

Human pan T cells were used to determine the binding affinity of the test mAbs. The tracer used was the commercially available AlexaFluor488 SP-34 anti-CD3 (BioScience #557705) and the saturation binding constant for this tracer is described above.

T cells were cryogenically-stored in nitrogen tanks until used. T cells were thawed, washed with PBS, re-suspended in FACS Staining buffer, counted with viability noted, and re-suspended at 0.5×10^6 cells/mL. Far Red Live/Dead stain (Life Technologies, AKA Invitrogen # L34974) (50 μ L of DMSO into a vial) was added at 1 μ L per 1×10^6 cells; and FcR blocker
5 (Miltenyi Biotec #130-059-901) (1 mL of a 1:20 dilution per 0.5×10^6 cells) was added to the cells for 10 minutes each. Cells were plated at 50,000 cells/well and washed.

The mAbs (and isotype control), were serially diluted 1:2 from a starting concentration of 1000 or 200 μ g/mL (2X), and a fixed concentration of the tracer (5 μ g/mL; 2X) was mixed together to give 1X concentrations. Therefore, the final (1X) concentration of the tracer was 2.5
10 μ g/mL = 16.6 nM. The mixture was added to the T cells for 2 hours at 4 °C. Cells were then washed to remove un-bound antibody, fixed for 15 minutes, washed, and re-suspended in FACS Staining buffer containing 1mM EDTA.

The iQue Intellicyte Flow Cytometer was used to measure binding. Cells were gated for T-cell population, followed by cell singlets, followed by Live Cells (FL4). Geometric mean of
15 staining (FL1) was determined for each well. The acquired mean fluorescence intensity values were plotted as a function of the log antibody molecule concentration (converted to nM) and analyzed using Prism software in a sigmoidal dose-response (variable slope) from which the EC50/IC50 values (in nM) are derived. The binding affinity (K_d) was derived using the following formula: $K_d = IC50 / (1 + ([T]/K_dT))$. Where: K_d is the affinity of the competitor
20 (unlabeled molecule); IC50 in nM of the test compound; [T] is concentration of the tracer (16.6 nM); K_dT is the K_d of the tracer determined by saturation binding (5.6 nM for human).

Production of monoclonal and bispecific antibodies

The bispecific CD3 antibodies of the present invention may be generated through controlled Fab-arm exchanged (FAE) as described in Labrijn et al., 2013, PNAS, vol. 110(13):
25 5145-5150; PCT Publ. WO 2011/131746; or in Labrijn et al., 2014, Nat Protoc, 9(10):2450-63. Briefly, in this in vitro method, two full-length parental bivalent antibodies are provided, each comprising a mutation in the antibody CH3 region that favors heterodimer formation resulting in bispecific antibodies containing a half-arm from each parental antibody. Mutations that may be used to favor heterodimer formation are F405L in one parental antibody and R409K in the other

parental antibody for IgG1 antibodies, or F405L and K409R one parental antibody while retaining wild-type CH3 for IgG4 antibodies.

The monospecific antibodies were expressed in HEK cell lines under CMV promoters.

The parental antibodies were purified using a protein A column with an elution buffer of 100mM NaAc pH3.5 and a neutralization puffer of 2M Tris pH 7.5 and 150 mM NaCl. The mabs were desalted using PD10 (Sephadex G25M) column and dialyzed into D-PBS, pH 7.2 buffer.

Post purification the parental antibodies were mixed under reducing conditions in 75mM cysteamine-HCl and incubated at 31°C for 4h. The recombination reactions were based on molar ratios, where a set amount of target parent (eg, 10mg, or ~71.8 nanomoles) was combined with CD3 antibody (eg, ~67.8 nanomoles), where the target parent antibody was added in a 6% excess of the CD3 antibody. The recombinations were subsequently dialyzed against PBS to remove the reductant. The bispecific antibody reactions were performed with an excess of the target parent antibody (ratio) to minimize the amount of unreacted CD3 parental antibody remaining after recombination. Following the partial reduction of the parental mAbs, the reductant was removed via overnight dialysis into PBS.

Results: **Fig. 10** shows the inhibition curves for the bivalent and monovalent anti CD3 constructs, CD3B376 and CD3B450, competing for binding against the AlexaFluor488 SP-34 anti CD3 tracer antibody. Increasing concentrations of the test anti CD3 antibodies decreased the binding of the AlexaFluor488 tracer antibody, thus decreasing the mean fluorescence intensity (MFI). IC₅₀ values were generated, and using the aforementioned formula, K_d affinities were calculated and summarized in Table 13.

The CD3B376 binding site was tighter than the CD3B450 in both bivalent and monovalent form.

Table 13. IC₅₀ and K_d affinity values of the anti CD3 bivalent and monovalent CD3B376 and CD3B450 constructs

Construct	anti CD3	IC ₅₀ (nM)	K _d (nM)
Bivalent	CD3B376	29	7.3
	CD3B450	60	15
Monovalent Construct	CD3B376	409	103
	CD3B450	1011	254

1-10 Conformational stability of anti-CD3 monoclonal antibodies

Conformational stability of the anti-CD3 antibodies CD3B376, CD3B389 (IgG1 sigma version of CD3B376; heavy chain is SEQ ID NO: 729; light chain is SEQ ID NO: 676), CD3B450, and CD3B467 (IgG1 sigma version of CD3B450; heavy chain is SEQ ID NO: 728; light chain is SEQ ID NO: 677) was determined by differential scanning calorimetry (DSC). The mid-point of thermal transition, T_m , was determined from the thermal denaturation profiles of each of the Ab candidates. **Fig. 12A – Fig. 12E** show the thermal denaturation profiles of the anti-CD3 antibodies in PBS. Table 14 includes a summary of the T_m and the enthalpy values (ΔH) for the thermal unfolding of the anti-CD3 antibodies as determined by DSC.

The DSC results indicate that all anti-CD3 antibodies CD3B376, CD3B389, CD3B450, and CD3B467 have folded domains. Based on the onset of unfolding, the relative stability of each antibody was as follows: CD3B389 < CD3B467 < CD3B376 < CD3B450. The anti-CD3 molecules tested by DSC displayed some differences in their thermal stability. The CD3B376 (IgG4 PAA) molecule displayed three partially unresolved transitions at 59.7, 62.4 and 69.2°C with a total enthalpy of unfolding of 417.6 kcal/mol, while the CD3B450 (IgG4 PAA) molecule displayed two unresolved transitions at 62.5 and 66.3°C with a total enthalpy of unfolding of 545.1 kcal/mol. The CD3B389 (IgG1sigma) molecule displayed four transitions at 54.6, 58.2, 73.1 and 77.1°C with a total enthalpy of unfolding of 401.7 kcal/mol, while the CD3B467 (IgG1sigma) molecule displayed four transitions at 56.3, 59.6, 66.5 and 75.6°C with a total enthalpy of unfolding of 406.2 kcal/mol.

Table 14. Summary of the thermal transition data for the anti-CD3 antibodies in PBS. Values represent averages of duplicate runs. Sequence information is provided for HC and LC peptides (SEQ ID NOs in parentheses).

	CD3B376 HC: SEQ ID NO: 640 LC: SEQ ID NO: 676		CD3B450 HC: SEQ ID NO: 675 LC: SEQ ID NO: 677		CD3B389 HC: SEQ ID NO: 729 LC: SEQ ID NO: 676		CD3B467 HC: SEQ ID NO: 728 LC: SEQ ID NO: 677	
	Average	Error	Average	Error	Average	Error	Average	Error
T_{m1} (°C)	59.7	0.1	62.5	0.9	54.6	0.1	56.3	0.1
ΔH_1 (cal/mol)	151900.0	4200.0	158175.0	64025.0	166150.0	2450.0	98160.0	17840.0
T_{m2} (°C)	62.4	0.1	66.3	0.2	58.2	0.1	59.6	0.0

$\Delta H2$ (cal/mol)	202200.0	4300.0	386900.0	71000.0	62050.0	1290.0	72900.0	370.0
Tm3 (°C)	69.2	0.0	NA	NA	73.5	0.1	66.5	0.0
$\Delta H3$ (cal/mol)	63450.0	2080.0	NA	NA	101900.0	1600.0	92785.0	6785.0
Tm4 (°C)	NA	NA	NA	NA	77.1	0.0	75.6	0.1
$\Delta H3$ (cal/mol)	NA	NA	NA	NA	71560.0	2500.0	142400.0	4800.0
Total ΔH	601000.0	NA	545075.0	NA	401660.0	NA	406245.0	NA

The two IgG1 antibodies display lower stability compared to the corresponding IgG4 PAA antibodies (comparing the molecules with the same variable domains) with Tm of the first transition being 5-6°C lower (**Fig. 13A** and **Fig. 13B** and Table 14).

5 1-11 Crystal structure of CD3B334 Fab in complex with CD3e N-terminal peptide

Anti-CD3 mAb CD3B334 (CD3H231/CD3L137) was modified to increase the “humanness” index by replacing a number of framework residues in the antibody by the human germline residues. This procedure yielded antibody CD3B334 with the following mutations:

10 D43G/L49M/L50I/S62N/Q85E/H89Y in VL when compared to the parental VL CD3L124 and R10G/R13K/V73I/R79K/T83S/L96V in VH when compared to the parental VH CD3H219. The His-tagged Fab fragment of CD3B334 was expressed in HEK 293Expi cells and purified using affinity and size-exclusion chromatography. The N-terminal 9-mer peptide of human CD3e was synthesized at New England Peptide (Lot V1108-19/21) and mixed with Fab at molar ratio 10:1
15 (excess of peptide). The complex was crystallized by the vapor-diffusion method from solution containing 4 M Na formate in 0.1 M Tris, pH 8.5. The crystals belong to the orthorhombic space group P212121 with unit cell dimensions of 66.5×69.4×100.4 Å and one complex molecule in the asymmetric unit. The structure of the complex was determined at 1.8 Å resolution by the molecular replacement method using the crystal structure of the Fab as a search model.

20 CD3B334 bound residues 1-6 of CD3e. The N-terminal Gln of the peptide was in the pyroglutamate form and in a hydrophobic environment, between F107 of HCDR3 and L99 of LCDR3 (**Fig. 18**). Two arginine residues, R52 and R56, from HCDR2 were engaged in

electrostatic interactions with the acidic residues of CD3. In total, 16 residues formed the CD3B334 paratope. Residues from all CDRs except LC2DR2 were in direct contact (within 4 Å distance) with the CD3 peptide (see **Fig. 19**).

5 2 **PSMA Antibodies**

2-1 **Generation of PSMA cell lines**

Expression vectors presenting full-length chimpanzee PSMA (H2Q3K5_PANTR, SEQ ID NO: 49) or full length Cynomolgous monkey PSMA (EHH56646.1, SEQ ID NO: 50) were generated for use as screening tools to assess the anti-PSMA leads using an in-house expression
10 vector with the CMV promoter using standard molecular biology techniques. Vectors were transiently transfected into HEK293F cells in suspension using standard methods. Transfected 293F suspension cells were plated in growth medium plus serum to become adherent and selected for stable plasmid integration. Single cell populations were selected by serial dilution and the PSMA surface receptor expression was quantified by FACS using the (PSMAL antibody
15 (Center) affinity Purified Rabbit Polyclonal Antibody (Catalog # OAAB02483, Aviva Systems Biology) as the primary antibody with a R-PE anti-rabbit secondary antibody (Catalog # 111-116-144, Jackson ImmunoResearch Laboratories, Inc.) and a rabbit polyclonal IgG (Catalog # SC-532, Santa Cruz Biotechnology) as the isotype control).

Human PSMA expressing cell lines were generated using lentivirus (Genecopoeia, cat #
20 EX-G0050-Lv105-10) containing full length human PSMA (FOLH1_HUMAN, SEQ ID NO:51) and puromycin for selection of PSMA positive cells. HEK293F cells (ATCC), negative for PSMA, were transduced with Lentiviral particles to overexpress human PSMA. Following transduction, cells positively expressing PSMA and the resistance marker were selected by treating pooled cells, grown in DMEM + 10% HI FBS (Life Technologies) and supplemented
25 with varying concentrations of Puromycin (Life Technologies).

In addition to the HEK generated cell lines, several commercial cell lines were used for phage panning and binding and cellular toxicity assays. LNCaP clone FGC cells (ATCC cat#CRL-1740) are a commercially available human prostate cancer cell lines. C4-2B cells were

originally developed at MD Anderson and are derived from LNCaP FGC grown *in vivo* and metastasize to bone marrow (Thalmann, et al 1994, Cancer Research 54, 2577-81).

2-2 Generation of Soluble PSMA ECD Proteins

Recombinant chimpanzee PSMA Extra Cellular Domain (ECD) protein (Chimp PSMA ECD, SEQ ID NO:52) was generated for panning and to assess the anti-PSMA leads using an in-house expression vector with the CMV promoter using standard molecular biology techniques. The chimp PSMA ECD gene fragment (amino acid 44 – 750 of SEQ ID NO:49) with N-terminal signal sequence (SEQ ID NO:594), N-terminal Avitag (SEQ ID NO:595) and 6-His tags (SEQ ID NO:596) was cloned using an in-house expression vector with the CMV promoter using standard molecular biology techniques and transiently expressed in 293Expi cells (Invitrogen). cDNA was prepared using gene synthesis techniques (U.S. Pat. No. 6,670,127; U.S. Pat. No. 6,521,427). Supernatants were harvested and clarified by centrifugation. The proteins were purified using a two-step purification process: 1) IMAC purification with a HisTrap HP column (GE Healthcare) and 2) size exclusion purification (Superdex 200, Ge Healthcare) where the elution buffer is Dulbecco's phosphate-buffered saline, calcium, magnesium (Thermofisher, #14040) containing 0.5mM ZnCl₂ to stabilize PSMA dimerization. Fractions containing the protein of interest were pooled and protein concentration was determined by A280. This material was used for binding and affinity measurements and is referred to as PSMG8.

Chimp PSMA ECD was also biotinylated for panning. The BirA plasmid that was co-transfected into mammalian cells to biotinylate proteins containing the Avi tag was created in-house. The BirA coding region (SEQ ID NO:597) was fused to the signal peptide from mouse IgG heavy chain (SEQ ID NO:598), and an ER retention signal (KDEL (SEQ ID NO: 716)) was added to the C-terminus to generate the BirA plasmid (SEQ ID NO:599). The constructed gene was cloned into an expression vector under the control of the CMV promoter. To produce biotinylated PSMA antigen, the PSMA plasmid DNA was added in a 4-fold excess (w/w) to the BirA plasmid into the transfection mix.

Biotinylation of the Chimp PSMA ECD protein was performed via the Avi tag by cotransfection of a BirA expression construct and the resulting secreted protein was purified using a two-step purification process: 1) IMAC purification with a HisTrap HP column (GE Healthcare) and 2) size exclusion purification (Superdex 200, Ge Healthcare) where the elution

buffer is Dulbecco's phosphate-buffered saline, calcium, magnesium (Thermofisher, #14040) containing 0.5mM ZnCl₂ to stabilize PSMA dimerization. The protein was tested for endotoxin prior to use in phage panning studies.

Recombinant cynomolgous monkey PSMA extracellular domain (ECD) protein (cyno PSMA ECD, SEQ ID NO:53), corresponding to amino acids 44-750 of SEQ ID NO:50 with N-terminal signal (SEQ ID NO:594), N-terminal Avi- (SEQ ID NO:595) and 6His- (SEQ ID NO:596) tags was cloned and expressed as described previously for the chimp PSMA ECD. Biotinylation of the cyno PSMA ECD protein was performed via the Avi tag by cotransfection of a BirA expression construct and the resulting secreted protein was purified by a two-step purification using IMAC HisTrap HP column (GE Healthcare) and MonoAvidin columns. The protein was tested for endotoxin prior to use in phage panning studies. This material was also used for binding and affinity measurements and is referred to as PSMG1.

A second recombinant cyno PSMA ECD protein (Cyno PSMA Fc, SEQ ID NO:54) with an IgG1 Fc (SEQ ID NO:593) was cloned and expressed using an in-house expression vector with the CMV promoter using standard molecular biology techniques. CynoPSMA Fc protein was transiently expressed in 293HEK-expi cells. Transient transfection of PSMG3 in HEK293 Expi cells were harvested 5 days after transfection, clarified by centrifugation (30 min, 6000 rpm) and filtered (0.2µ PES membrane, Corning). The relative amount of IgG was determined with the Octet instrument (ForteBio) using a purified known IgG (same isotype) spiked into spent medium to generate the standard curve.

Clarified Cyno PSMA Fc supernatant was loaded onto an equilibrated (dPBS, pH 7.2) HiTrap MabSelect Sure Protein A column (GE Healthcare) at a relative concentration of ~30 mg protein per ml of resin. After loading, the column was washed with dPBS, pH7.2 and protein eluted with 10 column volumes of 0.1 M Na-Acetate, pH 3.5. Peak fractions were pooled, neutralized with 2M Tris, pH 7, and filtered (0.2µ). The neutralized protein sample was dialyzed against 3 changes of dPBS containing Ca²⁺, Mg²⁺, and 0.5 mM ZnCl₂, pH 7.2 overnight at 4°C. The next day, sample was removed from dialysis, filtered (0.2µ) and the protein concentration determined by absorbance at 280nm on a BioTek SynergyHTTM spectrophotometer. The quality of the purified proteins was assessed by SDS-PAGE and analytical size exclusion HPLC (Dionex HPLC system). Endotoxin levels were measured using a LAL assay (Pyrotell-T, Associates of Cape Cod). Purified proteins were stored at 4°C.

Recombinant human PSMA extracellular domain (ECD) protein (human PSMA ECD, SEQ ID NO:55), corresponding to amino acids 44-750 of SEQ ID NO:51 with N-terminal Avi- and 6His tags (SEQ ID NO: 596) was cloned, expressed and purified as described previously for the chimp and cyno PSMA ECD proteins.

5 2-3 **Identification of Anti-chimp and anti-human PSMA Fabs**

Panning with recombinant protein

A first solution panning of the de novo Human Fab-pIX libraries [Shi, L., et al J Mol Biol, 2010. 397(2): p. 385-396. WO 2009/085462], consisting of VH1-69, 3-23 and 5-51 heavy chain libraries paired with four human VL germline genes (A27, B3, L6, O12) libraries, was
10 performed using an alternating panning approach with one round of phage capture on Streptavidin beads (Invitrogen Cat# 112.05D, Lot# 62992920) coated with biotinylated Chimp PSMA ECD according to the manufacturer's protocol, followed by phage capture on ProtG beads (Invitrogen, Cat#10003D) coated with Cyno-PSMA-Fc according to the manufacturer's protocol followed by phage capture on Sera-mag Double Speed magnetic Neutravidin beads
15 (Thermo, Cat #7815-2104-011150) coated with biotinylated Chimp PSMA ECD according to the manufacturer's protocol. This panning yielded two hits: PSMM18 and PSMM25.

Whole cell panning for anti-PSMA Fabs

Additional panning experiments were performed on whole cells using the Round #1 output from the chimpanzee ECD panning experiments described above or fresh *de novo* phage
20 libraries, as input. Briefly, phage was produced by helper phage infection and concentrated by PEG/NaCl precipitation according to standard protocols known in the art. The phage libraries were pre-cleared on untransfected parental HEK293F cells overnight at 4°C with gentle rocking. Following PEG/NaCl precipitation, the pre-cleared libraries were incubated with chimp PSMA expressing HEK293 cells or LNCAP cells with gentle rocking for 2 hr at 4°C. The removal of
25 unbound phage and the recovery of phage-bound cells was performed by Ficoll gradient, and following several wash steps with, cells carrying bound phage were incubated with 1mL of TG-1 *E. coli* culture at 37°C for 30 minutes without agitation. The resulting mixture was plated on

LB-Carbenicillin-1% Glucose plates and grown over night at 37°C. The process was then repeated for subsequent panning rounds.

Conversion of phage Fab-pIX to Fab-His for generating E. coli supernatants

5 The resulting phage Fab-pIX hits were converted to Fab-His using a standard procedure. Plasmid DNA was isolated from phage panned E. coli (Plasmid Plus Maxi Kit, Qiagen cat#12963) and subjected to NheI/SpeI restriction digest. The resulting 5400 and 100bp fragments were separated on a 0.8% agarose gel and the 5400bp fragment was gel purified (MinElute PCR purification kit, Qiagen cat#28006). The purified 5400bp band was self-ligated
10 using T4 ligase and the resulting product (encoding the Fab-his fusion) was transformed back into the TG-1 E. coli strain and clonally isolated. Fab-His supernatants were generated from clones by overnight induction of cultures with 1mM IPTG. Following centrifugation of the overnight culture, clarified supernatants were ready for use in downstream assays. To determine the relative expression levels of different Fab-his supernatants, an anti-kappa (Southern Biotech
15 cat#2061-05) ELISA on serially diluted supernatants was performed. All of the clones tested exhibited similar Fab-his expression (data not shown).

Cell binding of Fab-his fusions from E. coli

A cell-based binding assay was designed to assess the binding capabilities of individual Fab-his fusions from E.coli supernatants to PSMA-expressing cells. Individual Fab clones were
20 isolated from the round 3 output of all panning experiments following pIX excision. Fab clones were tested for binding to chimp and cyno PSMA expressing HEK cells, as well as to human PSMA on LNCaP cells. Briefly, PSMA expressing cells were aliquoted into a V-bottom plate (CoStar 3357) at a density of 200,000 per well and incubated with (100 µl) supernatants expressing Fab fragments for 1 hour on ice. Cells were washed twice with PBS containing 2%
25 FBS, and stained with a mouse anti-human kappa-RPE antibody (Life Technologies cat# MH10514) for 1 hour on ice. Cells were washed twice with PBS containing 2% FBS and resuspended in 100µL of the same wash buffer. Plates were read on a BD FACS Array flow cytometer. FACS data was analyzed in FlowJo software by live gating the healthy population of cells using forward scatter and side scatter, and then analyzing the cells within this gate for PE

staining. Mean fluorescence intensity (MFI) was calculated and exported into Microsoft Excel. Fab clones that exhibited binding ≥ 3 times background for all three species of PSMA (cyno, chimp and human), and exhibited no binding to the HEK293 cell line, were labeled as “preliminary positive”. Fabs were sequenced and moved forward for cloning into mammalian expression vector for rescreening. True positives were selected from the binding of mammalian cell expressed Fab supernatants to PSMA-expressing cell lines.

Preparation of Mammalian Fabs

For conversion of E.coli Fab to mammalian-expressed Fab, In-Fusion HD cloning (ClonTech cat#638918) was utilized according to the manufacturer’s protocol. Briefly, nucleotide sequences of clones that have passed the primary screen and are to be moved into mammalian Fab format, are loaded into the “InFu Primer Finder v1.2.3” program (software developed in-house), which generates a list of isotype-specific PCR primers used to generate PCR fragments for In-Fusion cloning into the huKappa_muIgGSP and huG1 Fab expression vectors. These vectors are in-house vectors with CMV promoters based off of pcDNA3.1. Following the In-fusion process, *E. coli* clones were isolated, sequence verified and transfected into HEK293 cells using standard protocols. Mammalian PSMA Fabs for confirming binding to PSMA expressing cell lines were prepared by harvesting 20 ml of supernatants from transfection after 5 days.

Rescreening hits from whole cell panning in mammalian sup format

Confirmation of mammalian expressed Fab supernatants was performed using the whole cell binding assay described previously. Binding of Fabs to human PSMA (LNCaP), chimpanzee, and cynomolgous monkey cells was tested, as well as counter screening for no binding to the parental HEK cell line. Table 19 shows the hit profile of mammalian Fab supernatant binding to PSMA-expressing cells. Many of the hits from E. coli supernatants did not confirm with mammalian expressed proteins. PSMM48 showed high binding to cyno PSMA-expressing cells and some binding to chimp-PSMA expressing cells, but no binding to LNCaP cells expressing human PSMA. PSMM56 showed a similar profile, but with some binding to LNCaP cells. PSMM69 – 80 bound to LNCaP cells, but not to chimp- or cyno-PSMA expressing cells. Mammalian Fab sups PSMM52, M56 and M57, bound all three cell lines.

PSMM50, M51, and M54, show more chimp or cyno binding. M58 showed slight chimp and cyno binding.

Table 19. Hit profile of Mammalian Fab protein binding to PSMA-expressing cells measured by Geo-MFI (Mean Fluorescent Intensity)

<u>Fab ID (Fab DNA ID)</u>	<u>cyno</u>	<u>chimp</u>	<u>LNCaP</u>	<u>Parent HEK</u>
PSMB10 (PSMM10)	244	81.6	-	248
PSMB11 (PSMM11)	19	6.6	-	8.14
PSMB12 (PSMM12)	31.6	8.05	-	12.6
PSMB13 (PSMM13)	57.8	18.2	-	50.5
PSMB14 (PSMM14)	32.6	13.1	-	22.2
PSMB15 (PSMM15)	40.4	18.5	-	38
PSMB16 (PSMM16)	175	220	-	6.39
PSMB17 (PSMM17)	34.9	22.4	-	40.1
PSMB18 (PSMM18)	696	439	-	8.71
PSMB19 (PSMM19)	53.7	-	5.15	4.47
PSMB20 (PSMM20)	5.75	-	5.85	41.3
PSMB21 (PSMM21)	94.4	-	20.7	372
PSMB22 (PSMM22)	9.07	-	7.92	54.9
PSMB23 (PSMM23)	16.4	-	6.66	164
PSMB24 (PSMM24)	14.6	9.6	4.09	3.96
PSMB25 (PSMM25)	15.2	11.3	16.9	4.09
PSMB26 (PSMM26)	9.48	-	7.26	114
PSMB27 (PSMM27)	20	-	7.56	136
PSMB28 (PSMM28)	29.7	-	8.88	302
PSMB29 (PSMM29)	6.87	-	5.7	72.8
PSMB30 (PSMM30)	5.16	-	4.58	45
PSMB31 (PSMM31)	5.99	-	-	25.5
PSMB32 (PSMM32)	4.81	-	-	27.1
PSMB33 (PSMM33)	5.14	-	-	40.1
PSMB34 (PSMM34)	17.9	-	-	107
PSMB35 (PSMM35)	58.5	-	-	231
PSMB36 (PSMM36)	5.05	-	-	6.96
PSMB37 (PSMM37)	23.4	-	-	178
PSMB38 (PSMM38)	4.05	-	-	7.7
PSMB39 (PSMM39)	10.2	-	-	166

PSMB40 (PSMM40)	66.9	-	-	348
PSMB41 (PSMM41)	5.39	-	-	12
PSMB42 (PSMM42)	7.35	-	-	25.8
PSMB43 (PSMM43)	8.73	-	-	7.18
PSMB44 (PSMM44)	12.6	-	-	48.9
PSMB45 (PSMM45)	22.4	-	-	43.1
PSMB46 (PSMM46)	3.88	-	-	5.29
PSMB47 (PSMM48)	101	25.5	3.46	2.85
PSMB48 (PSMM49)	2.72	3.18	2.68	2.72
PSMB49 (PSMM50)	51.6	22	3.22	3.48
PSMB51 (PSMM52)	285	231	41.5	2.68
PSMB52 (PSMM53)	39.2	6.89	2.67	2.56
PSMB53 (PSMM54)	27.6	17.8	4	2.6
PSMB54 (PSMM55)	2.7	2.75	2.65	2.79
PSMB55 (PSMM56)	226	180	17.2	2.58
PSMB56 (PSMM57)	95.6	34.7	24.5	2.52
PSMB57 (PSMM58)	19.8	11	3.26	2.68
PSMB58 (PSMM59)	121	192	25.3	2.67
PSMB59 (PSMM60)	4.96	9.69	6.04	3
PSMB60 (PSMM61)	2.28	3.07	87.3	4.64
PSMB61 (PSMM62)	2.1	3.16	135	2.98
PSMB62 (PSMM63)	7.17	4.43	54.9	9.09
PSMB63 (PSMM64)	2.07	2.95	27	2.82
PSMB64 (PSMM65)	2.39	3.26	70.5	3.05
PSMB65 (PSMM66)	2.3	3.13	32.4	4.25
PSMB66 (PSMM67)	2.14	3	24.6	2.83
PSMB67 (PSMM68)	2.23	2.95	21	2.95
PSMB68 (PSMM69)	5.44	-	134	35.3
PSMB69 (PSMM70)	2.29	3.38	25.5	3.35
PSMB70 (PSMM71)	2.22	3.49	15.5	3.26
PSMB71 (PSMM72)	2.54	4.4	18.5	3.07
PSMB72 (PSMM73)	2.13	3.53	227	3.02
PSMB73 (PSMM74)	2.97	4.13	125	11.1
PSMB74 (PSMM75)	120	-	178	132
PSMB75 (PSMM76)	2.99	3.04	173	7.89

PSMB76 (PSMM77)	3.75	3.99	138	3.95
PSMB77 (PSMM78)	4.68	3.96	144	4.71
PSMB78 (PSMM79)	25.2	-	378	24.4
PSMB79 (PSMM80)	38.4	-	512	157
PSMB80 (PSMM81)	19.6	18.6	20.9	6.61
PSMB81 (PSMM82)	2.63	2.06	4.07	2.69
PSMB82 (PSMM83)	2.79	2.23	4.11	2.76
PSMB83 (PSMM84)	2.59	2.28	4.09	2.74
PSMB84 (PSMM85)	750	729	192	3.15
PSMB85 (PSMM86)	2.84	2.59	2.33	3.24
PSMB86 (PSMM87)	224	176	31.7	2.82
PSMB87 (PSMM88)	2.63	2.27	4.23	2.91
PSMB88 (PSMM89)	37.7	29.7	30.3	7.6
PSMB89 (PSMM90)	27.1	27.3	53.2	39.5
PSMB90 (PSMM91)	26.7	24.7	47.1	36.4
PSMB91 (PSMM92)	8.97	6.16	13	6.63
PSMB92 (PSMM93)	20	16.5	57.1	50
PSMB93 (PSMM94)	5.13	9.62	2.5	3.66
PSMB94 (PSMM95)	5.12	2.67	2.22	3.57
PSMB95 (PSMM96)	8.9	8.82	13.4	11.4
PSMB96 (PSMM97)	2.4	3.25	2.53	4.03
PSMB97 (PSMM98)	2.57	4.73	2.52	3.7
PSMB99 (PSMM100)	9.95	2.4	2.39	4.03
PSMB100 (PSMM101)	4.03	2.52	2.33	3.37
PSMB100 (PSMM101)	3.5	2.86	2.48	4.57
PSMB101 (PSMM102)	5.49	3.18	2.23	3.33
PSMB102 (PSMM103)	2.4	2.42	2.16	3.2
PSMB103 (PSMM104)	3.52	3.26	2.58	4.44
PSMB104 (PSMM105)	2.15	2.5	2.34	3.95
PSMB105 (PSMM106)	2.03	2.39	2.18	3.39
PSMB106 (PSMM107)	2	2.4	2.27	3.59
PSMB107 (PSMM108)	2	2.47	2.33	3.49
PSMB108 (PSMM109)	2	2.58	2.28	3.46
PSMB109 (PSMM110)	321	326	34.9	6.11
PSMB110 (PSMM111)	2.3	2.31	2.31	3.4

PSMB111 (PSMM112)	2.32	2.31	-	3.21
PSMB112 (PSMM113)	6.28	5.7	2.71	3.28
PSMB113 (PSMM114)	2.82	2.95	2.32	3.29
PSMB114 (PSMM115)	2.78	2.47	4.3	3.14
PSMB115 (PSMM116)	2.66	2.59	2.2	3.14
PSMB46 (PSMM117)	4.54	3.18	2.21	4.79
PSMB67 (PSMM118)	3.95	4.3	3	6.13
PSMB74 (PSMM119)	7.94	13	3.16	12.5
PSMB78 (PSMM120)	5.08	4.79	22.3	6.82
PSMB81 (PSMM121)	3.66	3.83	3.05	5.11
PSMB82 (PSMM122)	15.1	28.4	10.8	24.3
PSMB83 (PSMM123)	37.5	42.1	3.04	4.88
PSMB85 (PSMM124)	34.6	52.9	20.7	46.8
PSMB87 (PSMM125)	4.23	3.74	2.26	4.73
PSMB89 (PSMM126)	51.8	53.1	11.7	6.27
PSMB90 (PSMM127)	42.8	30.2	7.74	5.99
PSMB91 (PSMM128)	3.9	27.6	2.37	4.32
PSMB92 (PSMM129)	45.7	37.3	12.1	7.4
PSMB93 (PSMM130)	5.13	7.85	4.11	7.82
PSMB94 (PSMM131)	3.67	3.23	2.32	4.72
PSMB95 (PSMM132)	4.05	3.64	2.56	5.57
PSMB96 (PSMM133)	3.91	4.54	2.37	4.65
PSMB97 (PSMM134)	3.22	3.16	4.08	4.22
PSMB98 (PSMM135)	15.6	12.7	2.22	4.21
PSMB99 (PSMM136)	4.08	3.26	2.22	5.04
PSMB100 (PSMM137)	5.24	3.82	2.16	4.83
PSMB101 (PSMM138)	3.84	3.14	2.23	4.52
PSMB102 (PSMM139)	4.51	3.82	2.23	4.59
PSMB103 (PSMM140)	6.81	4.27	2.21	5.41
PSMB104 (PSMM141)	7.52	4.35	2.26	4.39
PSMB105 (PSMM142)	5.03	11.2	4.87	7.28
PSMB106 (PSMM143)	3.87	3.8	2.73	4.9
PSMB107 (PSMM144)	3.3	3.35	2.3	4.64
PSMB108 (PSMM145)	6.78	3.83	2.33	4.98
PSMB110 (PSMM146)	4.03	3.23	2.28	5.3

PSMB111 (PSMM147)	3.71	3.26	2.36	5.11
PSMB112 (PSMM148)	4.54	3.26	2.26	4.86
PSMB113 (PSMM149)	84.3	104	51.7	94.2
PSMB114 (PSMM150)	3.31	3.26	2.21	5.14
PSMB115 (PSMM151)	3.55	3.43	2.3	4.21

Dose response curves of mammalian expressed Fabs

Once mammalian expressed Fab clones were confirmed for positive binding as neat Fab supernatants to PSMA expressing cell lines, the supernatants were normalized for protein concentration by Octet or protein gel, and dose-response curves were completed to confirm PSMA binding using the protocol described previously. **Fig. 23 – Fig. 25** show titration curves for hits that demonstrated binding to all three PSMA-expressing cells. **Figs. 23A, 23B, 23C and 23D** show the titration curves for anti-PSMA panning hits vs. LNCaP cells. **Figs. 24A, 24B, 24C, and 24D** show the titration curves for anti-PSMA panning hits vs chimp-PSMA HEK cells. **Figs. 25A, 25B, 25C, and 25D** show the titration curves for anti-PSMA panning hits vs Cyno-PSMA HEK cells. Binding profiles among hits were compared across cell lines expressing different species of PSMA. PSMM52 supernatant was used as a positive control across experiments. Several hits were deprioritized because of N-linked glycosylation sites in CDRs, binding to the PSMA negative parental HEK cell line, or lack of binding to PSMA positive cell lines. Eleven Fab hits remained and 10 hits were cloned into human IgG4-PAA heavy chain constructs and used to generate PSMA×CD3 bispecific antibodies. These hits showed cross-species binding within 3-fold of each other and were moved into a bispecific antibody format to be tested for T cell redirection killing of PSMA positive targets. The panning antigens for each hit is shown in Table 20.

Table 20. Antigen for each of the panning hits

Round 1 antigen	Round 2-3 antigen	Hits	Hit identification
Chimp PSMA ECD	Cyno PSMA ECD	2	PSMM18, PSMM25
Chimp PSMA ECD	Chimp PSMA HEK	9	PSMM50, PSMM52, PSMM57, PSMM59,

			PSMM110, PSMM56, PSMM85, PSMM84
LNCaP	Chimp PSMA HEK	2	PSMM87, PSMM81

Preparation of anti-PSMA mAbs

A total of 12 clones that demonstrated binding to all three PSMA-expressing cells were ultimately converted to mAb IgG4 having Fc substitutions S228P, F234A, and L235A (PAA) isotype by restriction cloning. Briefly, constructs corresponding to Fab clones that have passed
5 initial screens were digested with HindIII and ApaI. Gel purified fragments were ligated into an expression vector with CMV promoter vDR000215, a CMV driven expression vector containing the human IgG4-PAA Fc for full mAb expression. This allowed for rapid generation of bispecific antibodies. The expression vector previously described was used to express the Heavy and Light Chains for each PSMA mab, where both vectors were co-transfected transiently into
10 293Expi or CHO cell lines for expression of the mAb. CDR sequences of cross-species positive PSMA Fabs generated from phage panning are shown below in Table 21. VH and VL sequences of the selected Fabs are shown below in Table 22. Heavy and light chain sequences of mAbs generated from the Fabs are shown in Table 23.

Table 21. CDR sequences (defined according to Kabat) of FAbs from phage panning
15 (corresponding SEQ ID NOs are listed in parentheses)

FAB ID		CDRs (SEQ ID NO:)		
		CDR1	CDR2	CDR3
PSMB109	HC	NAWIS (62)	WINPESGRANYAQKFQG (63)	ELYLVYSTYYYAFDY (64)
	LC	RASQSIDRWLN (65)	AASSLQS (60)	QQSPRYPLT (66)
PSMB86	HC	SYDIS (67)	GIPIEGTANYAQKFQG (68)	DYPAGYGFDY (69)
	LC	RASQSVSSSYLA (70)	GASSRAT (71)	QQYGSSPLT (72)
PSMB84	HC	SDWMS (73)	AISGNGGSTHEYADSVKG (74)	DPYYYYDGDSYYGMDV (75)
	LC	RASQSISSYLN	AASSLQS	QQSYSTP

		(76)	(60)	(61)
PSMB83	HC	SDAMH (78)	EISGSGGYTNYADSVKG (79)	DSYDSSLYVG DYFDY (80)
	LC	RASQSVSSYLA (81)	DASNRAT (82)	QQRSNWPLT (83)
PSMB56	HC	SYAIS (84)	WISPYNGNANYAQKFQG (85)	DSDRSYNLDY (86)
	LC	RASQSIGWLN (87)	AASSLQS (60)	QQSYSTPLT (88)
PSMB55	HC	SYWIG (89)	IIYPGDS DTRYSPSFQG (90)	GLPIWYLDY (91)
	LC	RASQSVASDLA (92)	FASNRAT (93)	QQSITWPFT (94)
PSMB51	HC	SYAIS (95)	WIIPYNGNANYAQKFQG (96)	VNSAALVWERLDY (97)
	LC	RASQSIDRWLN (65)	AASSLQS (60)	QQSPRYPLT (66)
PSMB49	HC	SYAIS (84)	GIPIFGTANYAQKFQG (98)	ASRVWHASYGYLDY (99)
	LC	RASQSVSKWLA (100)	DASNRAT (82)	QQRFTAPWT (101)
PSMB25	HC	SYWIG (89)	IIYPGDS DTRYSPSFQG (90)	GWAYDRGLDY (102)
	LC	KSSQSVLYSSNNKNYLA (103)	WASTRES (104)	QQYYSTPLT (105)
PSMB18	HC	SYWIG (89)	IIYPGDS DTRYSPSFQG (90)	AYHYSKGLDY (106)
	LC	KSSQSVLYSSNNKNYLA (103)	WASTRES (104)	QQYYSTPLT (105)
PSMB80	HC	DY AIS (107)	RIDPIEGTANYAQKFQG (108)	DRYYDGVYWYSDYFDY (109)
	LC	RASQSISSYLN (76)	AASSLQS (60)	QQSYSTPLT (88)
PSMB58	HC	SYWIS (56)	IIYPGDSYTRYSPSFQG (57)	DYEWELFDSRLDY (58)
	LC	RASQSISSYLN	AASSLQS	QQSYSTP

	(59)	(60)	(61)

Table 22. VH and VL sequences of PSMA Fabs

FAB ID	VH Amino acid sequence	SEQ ID NO	VL Amino Acid Sequence	SEQ ID NO
PSMB109	QVQLVQSGAEVKKPGSSVKVSKASGGTF SSYAI SWVRQAPGQGLEWMGWISPYNGNA NYAQKFQGRVTITADESTSTAYMELSSLR SEDTAVYYCARVNSAALVWERLDYWGQGT LVTVSS	110	DIQMTQSPSSLSASVGDRV TITCRASQSIDRWLNWYQQ KPGKAPKLLIYAASSLQSG VPSRFGSGSGTDFTLTIS SLQPEDFATYYCQQSPRYP LTFGQGTKVEIK	111
PSMB86	QVQLVQSGAEVKKPGSSVKVSKASGGTF KSYDISWVRQAPGQGLEWMGGIIPIEGTA NYAQKFQGRVTITADESTSTAYMELSSLR SEDTAVYYCARDYPAGYGFYDWGQGT LVT VSS	112	EIVLTQSPGTLSPGERA TLSCRASQSVSSSYLAWYQ QKPGQAPRLLIYGASSRAT GIPDRFGSGSGTDFTLTIS SRLEPEDFAVYYCQQYGSS PLTFGQGTKVEIK	113
PSMB84	EVQLLESGGGLVQPGGSLRLSCAASGFTF DSDWMSWVRQAPGKGLEWVSAISGNGGST EYADSVKGRFTISRDN SKNTLYLQMNSLR AEDTAVYYCARDPYYYDGD SYYGMDVWG QGT LVTVSS	114	DIQMTQSPSSLSASVGDRV TITCRASQSISSYLNWYQQ KPGKAPKLLIYAASSLQSG VPSRFGSGSGTDFTLTIS SLQPEDFATYYCQQSYSTP LTFGQGTKVEIK	115
PSMB83	EVQLLESGGGLVQPGGSLRLSCAASGFTF KSDAMHWVRQAPGKGLEWVSEISGSGGYT NYADSVKGRFTISRDN SKNTLYLQMNSLR AEDTAVYYCARD SYDSSLVGDYFDYWGQ GT LVTVSS	116	EIVLTQSPATLSLSPGERA TLSCRASQSVSSSYLAWYQ KPGQAPRLLIYDASN RATG IPARFGSGSGTDFTLTIS SLEPEDFAVYYCQQRSNWP LTFGQGTKVEIK	117
PSMB80	QVQLVQSGAEVKKPGSSVKVSKASGGTF DDYAI SWVRQAPGQGLEWMGRIDPIEGTA NYAQKFQGRVTITADESTSTAYMELSSLR SEDTAVYYCARD RYYYDGVYWYSYFDYW GQGT LVTVS	118	DIQMTQSPSSLSASVGDRV TITCRASQSISSYLNWYQQ KPGKAPKLLIYAASSLQSG VPSRFGSGSGTDFTLTIS SLQPEDFATYYCQQSYSTP LTFGQGTKVEIK	119

PSMB58	EVQLVQSGAEVKKPGESLKISCKGSGYSF TSYWISWVRQMPGKGLEWMGIIYPGDSYT RYSPSFQGQVTISADKSI STAYLQWSSLK ASDTAMYYCARDYEWELFDSRLDYWGQGT LVTVSS	120	DIQMTQSPSSLSASVGDRV TITCRASQSISSYLNWYQQ KPGKAPKLLIYAASSLQSG VPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQSYSTP LTFGQGTKVEIK	115
PSMB56	QVQLVQSGAEVKKPGSSVKVCKASGGTF SSYAI SWVRQAPGQGLEWMGWISPYNNA NYAQKFQGRVTITADESTSTAYMELSSLR SEDTAVYYCARDSDRSYNLDYWGQGT LVT VSS	121	DIQMTQSPSSLSASVGDRV TITCRASQSI SGWLNWYQQ KPGKAPKLLIYAASSLQSG VPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQSYSTP LTFGQGTKVEIK	122
PSMB55	EVQLVQSGAEVKKPGESLKISCKGSGYSF TSYWI GWVRQMPGKGLEWMGIIYPGSDT RYSPSFQGQVTISADKSI STAYLQWSSLK ASDTAMYYCARGLPIWYLDYWGQGT LVT SSA	123	EIVLTQSPATLSLSPGERA TLSCRASQSVASDLAWYQQ KPGQAPRLLIYFASNATG IPARFSGSGSGTDFTLTIS SLEPEDFAVYYCQQSITWP FTFGQGTKVEIK	124
PSMB51	QVQLVQSGAEVKKPGSSVKVCKASGGTF SSYAI SWVRQAPGQGLEWMGWIIYPYNNA NYAQKFQGRVTITADESTSTAYMELSSLR SEDTAVYYCARVNSAALVWERLDYWGQGT LVTVSS	125	DIQMTQSPSSLSASVGDRV TITCRASQSIDRWLNWYQQ KPGKAPKLLIYAASSLQSG VPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQSPRYP LTFGQGTKVEIK	111
PSMB49	QVQLVQSGAEVKKPGSSVKVCKASGGTF SSYAI SWVRQAPGQGLEWMGGIIPIFGTA NYAQKFQGRVTITADESTSTAYMELSSLR SEDTAVYYCARASRVWHASYGYLDYWGQG TLVTVSS	126	EIVLTQSPATLSLSPGERA TLSCRASQSVSKWLAWYQQ KPGQAPRLLIYDASNATG IPARFSGSGSGTDFTLTIS SLEPEDFAVYYCQQRFTAP WTFGQGTKVEIK	127
PSMB25	EVQLVQSGAEVKKPGESLKISCKGSGYSF TSYWI GWVRQMPGKGLEWMGIIYPGSDT RYSPSFQGQVTISADKSI STAYLQWSSLK ASDTAMYYCARGWAYDRGLDYWGQGT LVT VSS	128	DIVMTQSPDSLAVSLGERA TINCKSSQSVLYSSNNKNY LAWYQQKPGQPPKLLIYWA STRESGVPDRFSGSGSGTD FTLTISLQAEDVAVYYCQ QYYSTPLTFGQGTKVEIK	129

PSMB18	EVQLVQSGAEVKKPGESLKISCKGSGYSF TSYWIGWVRQMPGKGLEWMGIIYPGSDST RYSPSFQGQVTISADKSI STAYLQWSSLK ASDTAMYYCARAYHYSKGLDYWGQGTTLVT VSS	130	DIVMTQSPDSLAVSLGERA TINCKSSQSVLYSSNNKNY LAWYQQKPGQPPKLLIYWA STRESGVPDRFSGSGSGTD FTLTISSLQAEDVAVYYCQ QYYSTPLTFGQGTKVEIK	131

Table 23 Heavy and Light chain sequences of PSMA monoclonal antibodies with corresponding SEQ ID NOs

mAb ID	Heavy Chain Amino acid sequence	SEQ ID NO	Light Chain Amino Acid Sequence	SEQ ID NO
PSMB129 (FAB PSMB109)	QVQLVQSGAEVKKPGSSVKVSCAS GGTFSSYAISWVRQAPQGGLWMMGW ISPYNGNANYAQKFQGRVTITADES TSTAYMELSSLRSEDTAVYYCARVN SAALVWERLDYWQGQTLVTVSSAST KGPSVFPLAPCSRSTSESTAALGCL VKDYFPEPVTVSWNSGALTSGVHTF PAVLQSSGLYSLSSVVTVPSSSLGT KTYTCNVDHKPSNTKVDKRVESKYG PPCPPCPAPEAAGGPSVFLFPPKPK DTLMI SRTPEVTCVVVDVSQEDPEV QFNWYVDGVEVHNAKTKPREEQFNS TYRVVSVLTVLHQDWLNGKEYKCKV SNKGLPSSIEKTIKAKGQPREPQV YTLPPSQEEMTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPVVL DSDGSFFLYSRLTVDKSRWQEGNVF SCSVMEALHNHYTQKSLSLGLGK	132	DIQMTQSPSSLSASVGDRVITIT CRASQSIDRWLNWYQQKPGKAP KLLIYAASSLQSGVPSRFSGSG SGTDFTLTISSLQPEDFATYYC QQSPRYPLTFGQGTKVEIKRTV AAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNAL QSGNSQESVTEQDSKDSSTYSL STLTLSKADYEKHKVYACEVTH QGLSSPVTKSFNREGC	133
PSMB130 (FAB PSMB86)	QVQLVQSGAEVKKPGSSVKVSCAS GGTFKSYDISWVRQAPQGGLWMMGG IPIEGTANYAQKFQGRVTITADES TSTAYMELSSLRSEDTAVYYCARDY PAGYGFYDWQGQTLVTVSSASTKGP SVFPLAPCSRSTSESTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAV LQSSGLYSLSSVVTVPSSSLGTKEY TCNVDHKPSNTKVDKRVESKYGP PPCPAPEAAGGPSVFLFPPKPKDTL MISRTPEVTCVVVDVSQEDPEVQFN WYVDGVEVHNAKTKPREEQFNSTYR VVSVLTVLHQDWLNGKEYKCKVSNK GLPSSIEKTIKAKGQPREPQVYTL PPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPVLDSD GSFFLYSRLTVDKSRWQEGNVFSCS VMHEALHNHYTQKSLSLGLGK	134	EIVLTQSPGTLTSLSPGERATLS CRASQSVSSSYLAWYQQKPGQA PRLLIYGASSRATGIPDRFSGS GSGTDFTLTISRLEPEDFAVYY CQYQGSPLTFGQGTKVEIKRT VAAPSVFIFPPSDEQLKSGTAS VCLLNNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKDSSTYSL SSTLTLSKADYEKHKVYACEVT HQGLSSPVTKSFNREGC	135

PSMB128 (FAB PSMB84)	EVQLLESGGGLVQPGGSLRLSCAAS GFTFDSWMSWVRQAPGKGLEWVSA ISGNGGSTHEYADSVKGRFTISRDN KNTLYLQMNSLRAEDTAVYYCARDP YYYYDGDSYYGMDVWGQGTlVTVSS ASTKGPSVFPLAPCSRSTSESTAAL GCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSS LGTKTYTCNVDHKPSNTKVDKRVES KYGPPCPPCPAPEAAGGPSVFLFPP KPKDTLMISRTPEVTCVVDVDSQED PEVQFNWYVDGVEVHNAKTKPREEQ FNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKGLPSSIEKTIKAKGQPRE PQVYTLPPSQEEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTP PVLDSGDSFFLYSRLTVDKSRWQEG NVFSCSVMEALHNHYTQKSLSLGL GK	136	DIQMTQSPSSLSASVGDRVITIT CRASQSISSYLNWYQQKPGKAP KLLIYAASSLQSGVPSRFSGSG SGTDFTLTISLQPEDFATYYC QQSYSTPLTFGQGTKVEIKRTV AAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNAL QSGNSQESVTEQDSKDYSTYSL STLTLSKADYEKHKVYACEVTH QGLSSPVTKSFNRRGEC	137
PSMB127 (FAB PSMB83)	EVQLLESGGGLVQPGGSLRLSCAAS GFTFKSDAMHWVRQAPGKGLEWVSE ISGSGGYTNYADSVKGRFTISRDN KNTLYLQMNSLRAEDTAVYYCARDS YDSSLYVGDFDYWGQGTlVTVSSA STKGPSVFPLAPCSRSTSESTAALG CLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSL GKTKTYTCNVDHKPSNTKVDKRVESK YGPCCPPCPAPEAAGGPSVFLFPPK PKDTLMISRTPEVTCVVDVDSQEDP EVQFNWYVDGVEVHNAKTKPREEQF NSTYRVVSVLTVLHQDWLNGKEYKC KVSNGKGLPSSIEKTIKAKGQPREP QVYTLPPSQEEMTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTTPP VLDSDGDSFFLYSRLTVDKSRWQEGN VFSCSVMEALHNHYTQKSLSLGLG K	138	EIVLTQSPATLSLSPGERATLS CRASQSVSSYLAWYQQKPGQAP RLLIYDASNRATGIPARFSGSG SGTDFTLTISLQPEDFAVYYC QQRSNWPLTFGQGTKVEIKRTV AAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNAL QSGNSQESVTEQDSKDYSTYSL STLTLSKADYEKHKVYACEVTH QGLSSPVTKSFNRRGEC	139
PSMB126 (FAB PSMB80)	QVQLVQSGAEVKKPGSSVKVSKCAS GGTFDDYAIWVRQAPGQGLEWMGR IDPIEGTANYAQKFQGRVTITADES TSTAYMELSSLRSEDTAVYYCARDR YYYDGVYWYSDFDYWGQGTlVTVS SASTKGPSVFPLAPCSRSTSESTA LGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVVTVPSS SLGKTKTYTCNVDHKPSNTKVDKRVE SKYGPPCPPCPAPEAAGGPSVFLFP PKPKDTLMISRTPEVTCVVDVDSQE DPEVQFNWYVDGVEVHNAKTKPREE QFNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKGLPSSIEKTIKAKGQPR EPQVYTLPPSQEEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTT PPVLDSDGDSFFLYSRLTVDKSRWQE GNVFSCSVMEALHNHYTQKSLSL LGK	140	DIQMTQSPSSLSASVGDRVITIT CRASQSISSYLNWYQQKPGKAP KLLIYAASSLQSGVPSRFSGSG SGTDFTLTISLQPEDFATYYC QQSYSTPLTFGQGTKVEIKRTV AAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNAL QSGNSQESVTEQDSKDYSTYSL STLTLSKADYEKHKVYACEVTH QGLSSPVTKSFNRRGEC	137

PSMB124 (FAB PSMB56)	QVQLVQSGAEVKKPGSSSVKVSCKAS GGTFSSYAISWVRQAPGQGLEWMGW ISPYNGNANYAQKFQGRVTITADES TSTAYMELSSLRSED TAVYYC ARDS DRSYNLDYWGQGLTVTVSSASTKGP SVFPLAPCSRSTSESTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAV LQSSGLYSLSSVTVPSSSLGKTKY TCNVDHKPSNTKVDKRVESKYGPPC PPCPAPEAAGGPSVFLFPPKPKDTL MISRTPEVTCVVVDVSQEDPEVQFN WYVDGVEVHNAKTKPREEQFNSTYR VVSVLTVLHQDWLNGKEYKCKVSNK GLPSSIEKTIKAKGQPREPQVYTL PPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPVLDSD GSFFLYSRLTVDKSRWQEGNVFSCS VMHEALHNHYTQKSLSLGLGK	141	DIQMTQSPSSLSASVGDRVITIT CRASQSI SGWLNWYQQKPGKAP KLLIYAASSLQSGVPSRFSGSG SGTDFTLTITSSLPEDFATYYC QQSYSTPLTFGQGTKVEIKRTV AAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNAL QSGNSQESVTEQDSKDYSTYSL STLTLSKADYEKHKVYACEVTH QGLSSPVTKSFNRGEC	142
PSMB123 (FAB PSMB55)	EVQLVQSGAEVKKPGESLKISCKGS GYSFTSYWIGWVRQMPGKGLEWMGI IYPGDS DTRYSPSFQGGVITISADKS ISTAYLQWSSLKASDTAMYYCARGL PIWYLDYWGQGLTVTVSSASTKGPS VFPLAPCSRSTSESTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVTVPSSSLGKTKYT CNVDHKPSNTKVDKRVESKYGPPCP PCPAPEAAGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSQEDPEVQFNW YVDGVEVHNAKTKPREEQFNSTYRV VSVLTVLHQDWLNGKEYKCKVSNK LPSSIEKTIKAKGQPREPQVYTL PSQEEMTKNQVSLTCLVKGFYPSDI AVEWESNGQPENNYKTTPVLDSDG SFFLYSRLTVDKSRWQEGNVFSCSV MHEALHNHYTQKSLSLGLGK	143	EIVLTQSPATLSLSPGERATLS CRASQSVASDLAWYQQKPGQAP RLLIYFASN RATGIPARFSGSG SGTDFTLTITSSLEPEDFAVYYC QQSITWPF TFGQGTKVEIKRTV AAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNAL QSGNSQESVTEQDSKDYSTYSL STLTLSKADYEKHKVYACEVTH QGLSSPVTKSFNRGEC	144
PSMB122 (FAB PSMB51)	QVQLVQSGAEVKKPGSSSVKVSCKAS GGTFSSYAISWVRQAPGQGLEWMGW IIPYNGNANYAQKFQGRVTITADES TSTAYMELSSLRSED TAVYYCARVN SAALVWERLDYWGQGLTVTVSSAST KGPSVFPLAPCSRSTSESTAALGCL VKDYFPEPVTVSWNSGALTSGVHTF PAVLQSSGLYSLSSVTVPSSSLGT KTYTCNVDHKPSNTKVDKRVESKYG PPCPPCPAPEAAGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSQEDPEV QFNWYVDGVEVHNAKTKPREEQFNS TYRVSVLTVLHQDWLNGKEYKCKV SNKGLPSSIEKTIKAKGQPREPQV YTLPPSQEEMTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPVLD SDSGSFFLYSRLTVDKSRWQEGNVF SCSV MHEALHNHYTQKSLSLGLGK	145	DIQMTQSPSSLSASVGDRVITIT CRASQSIDRWLNWYQQKPGKAP KLLIYAASSLQSGVPSRFSGSG SGTDFTLTITSSLPEDFATYYC QQSPRYPLTFGQGTKVEIKRTV AAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNAL QSGNSQESVTEQDSKDYSTYSL STLTLSKADYEKHKVYACEVTH QGLSSPVTKSFNRGEC	133
PSMB121 (FAB PSMB49)	QVQLVQSGAEVKKPGSSSVKVSCKAS GGTFSSYAISWVRQAPGQGLEWMGG IIPIFGTANYAQKFQGRVTITADES	146	EIVLTQSPATLSLSPGERATLS CRASQSVSKWLAWYQQKPGQAP RLLIYDASN RATGIPARFSGSG	147

	TSTAYMELSSLRSED TAVYYCARAS RVWHASYGYLDYWGQGT LVTVSSAS TKGPSVFPLAPCSRSTSESTAALGC LVKDYFPEPVT VSWNSGALTSGVHT FPAVLQSSGLYSLSSVVTVPSSSLG TKTYTCNV DHKPSNTKVDKRVESKY GPPCP CPAPEAAAGGPSVFLFPPKP KDTLMISRTPEVTCVVVDVSQEDPE VQFNWYVDGVEVHNAKTKPREEQFN STYRVVSVLTVLHQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQ VYTLPPSQEEMTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTT PPV LDSDGSFFLYSRLTVDKSRWQEGNV FSCSVMHEALHNHYTQKSLSLGLK		SGTDFTLT ISSLEPEDFAVYYC QQRFTAPWTFGQGTKVEIKRTV AAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNAL QSGNSQESVTEQDSKDYSTYLS STLTLSKADYEKHKVYACEVTH QGLSSPVT KSFNRGEC	
PSMB120 (FAB PSMB25)	EVQLVQSGAEVKKPGESLKISCKGS GYSFTSYWIGWVRQMPGKGLEWMGI IYPGDS DTRYSPSFQGVTTISADKS ISTAYLQWSS LKASDTAMYYCARGW AYDRGLDYWGQGT LVTVSSASTKGP SVFPLAPCSRSTSESTAALGCLVKD YFPEPVT VSWNSGALTSGVHTFPAV LQSSGLYSLSSVVTVPSSSLGT KTY TCNV DHKPSNTKVDKRVESKYGPPC PPCPAPEAAAGGPSVFLFPPKP KDTL MISRTPEVTCVVVDVSQEDPEVQFN WYVDGVEVHNAKTKPREEQFNSTYR VVS VLTVLHQDWLNGKEYKCKVSNK GLPSSIEKTISKAKGQPREPQVYTL PPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTT PPVLDSD GSFFLYSRLTVDKSRWQEGNVFSCS VMHEALHNHYTQKSLSLGLK	148	DIVMTQSPD SLAVSLGERATIN CKSSQSVLYSSNNKNYLAWYQQ KPGQPPKLLIYWASTRESGVPD RFGSGSGTDFTLT ISSLQAED VAVYYCQQYYSTPLTFGQGTKV EIKRTVAAPSVFIFPPSDEQLK SGTASV VCLLNNFYPREAKVQW KVDNALQSGNSQESVTEQDSK STYLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVT KSFNRGEC	149
PSMB119 (FAB PSMB18)	EVQLVQSGAEVKKPGESLKISCKGS GYSFTSYWIGWVRQMPGKGLEWMGI IYPGDS DTRYSPSFQGVTTISADKS ISTAYLQWSS LKASDTAMYYCARAY HYSKGLDYWGQGT LVTVSSASTKGP SVFPLAPCSRSTSESTAALGCLVKD YFPEPVT VSWNSGALTSGVHTFPAV LQSSGLYSLSSVVTVPSSSLGT KTY TCNV DHKPSNTKVDKRVESKYGPPC PPCPAPEAAAGGPSVFLFPPKP KDTL MISRTPEVTCVVVDVSQEDPEVQFN WYVDGVEVHNAKTKPREEQFNSTYR VVS VLTVLHQDWLNGKEYKCKVSNK GLPSSIEKTISKAKGQPREPQVYTL PPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTT PPVLDSD GSFFLYSRLTVDKSRWQEGNVFSCS VMHEALHNHYTQKSLSLGLK	150	DIVMTQSPD SLAVSLGERATIN CKSSQSVLYSSNNKNYLAWYQQ KPGQPPKLLIYWASTRESGVPD RFGSGSGTDFTLT ISSLQAED VAVYYCQQYYSTPLTFGQGTKV EIKRTVAAPSVFIFPPSDEQLK SGTASV VCLLNNFYPREAKVQW KVDNALQSGNSQESVTEQDSK STYLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVT KSFNRGEC	149

PSMB87 (FAB PSMB58)	EVQLVQSGAEVKKPGESLKISCKGS GYSFTSYWISWVRQMPGKGLEWMI IYPGDSYTRYSPSFQGVVTSADKS ISTAYLQWSSSLKASDTAMYYCARDY EWELFDSRLDYWGQGLTVTVSSAST KGPSVFPLAPCSRSTSESTAALGCL VKDYFPEPVTVSWNSGALTSGVHTF PAVLQSSGLYSLSSVTVPSSSLGT KTYTCNVDPKPSNTKVDKRVESKYG PPCPPCPAPEAAGGPSVFLFPPKPK DTLMI SRTPEVTCVVVDVSQEDPEV QFNWYVDGVEVHNAKTKPREEQFNS TYRVVSVLTVLHQDWLNGKEYKCKV SNKGLPSSIEKTIKAKGQPREPQV YTLPPSQEEMTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTTPVL DSDGSFFLYSRLTVDKSRWQEGNVF SCSVMEALHNHYTQKSLSLGLK	151	DIQMTQSPSSLSASVGDRVITIT CRASQSISSYLNWYQQKPGKAP KLLIYAASSLQSGVPSRFSGSG SGTDFTLTISLQPEDFATYYC QQSYSTPLTFGQGTKVEIKRTV AAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNAL QSGNSQESVTEQDSKSTYSL STLTLSKADYEKHKVYACEVTH QGLSSPVTKSFNRGEC	137

A monospecific anti-PSMA antibody PSMB119 was generated comprising the VH and VL regions having the VH of SEQ ID NO: 130 and the VL of SEQ ID NO: 131 and an IgG4 constant region with S228P, F234A, and L235A substitutions. A monospecific anti-PSMA antibody PSMB120 was generated comprising the VH and VL regions having the VH of SEQ ID NO: 128 and the VL of SEQ ID NO: 129 and an IgG4 constant region with S228P, F234A, and L235A substitutions. A monospecific anti-PSMA antibody PSMB121 was generated comprising the VH and VL regions having the VH of SEQ ID NO: 126 and the VL of SEQ ID NO: 127 and an IgG4 constant region with S228P, F234A, and L235A substitutions. A monospecific anti-PSMA antibody PSMB122 was generated comprising the VH and VL regions having the VH of SEQ ID NO: 125 and the VL of SEQ ID NO: 111 and an IgG4 constant region with S228P, F234A, and L235A substitutions. A monospecific anti-PSMA antibody PSMB123 was generated comprising the VH and VL regions having the VH of SEQ ID NO: 123 and the VL of SEQ ID NO: 124 and an IgG4 constant region with S228P, F234A, and L235A substitutions. A monospecific anti-PSMA antibody PSMB124 was generated comprising the VH and VL regions having the VH of SEQ ID NO: 121 and the VL of SEQ ID NO: 122 and an IgG4 constant region with S228P, F234A, and L235A substitutions. A monospecific anti-PSMA antibody PSMB126 was generated comprising the VH and VL regions having the VH of SEQ ID NO: 118 and the VL of SEQ ID NO: 119 and an IgG4 constant region with S228P, F234A, and L235A substitutions. A monospecific anti-PSMA antibody PSMB127 was generated comprising the VH and VL regions having the VH of SEQ ID NO: 116 and the VL of SEQ ID NO: 117 and an IgG4

constant region with S228P, F234A, and L235A substitutions. A monospecific anti-PSMA antibody PSMB128 was generated comprising the VH and VL regions having the VH of SEQ ID NO: 114 and the VL of SEQ ID NO: 115 and an IgG4 constant region with S228P, F234A, and L235A substitutions. A monospecific anti-PSMA antibody PSMB129 was generated comprising the VH and VL regions having the VH of SEQ ID NO: 110 and the VL of SEQ ID NO: 111 and an IgG4 constant region with S228P, F234A, and L235A substitutions. A monospecific anti-PSMA antibody PSMB130 was generated comprising the VH and VL regions having the VH of SEQ ID NO: 112 and the VL of SEQ ID NO: 113 and an IgG4 constant region with S228P, F234A, and L235A substitutions.

10

2-5 Crystal structure of human PSMA ECD bound to anti-PSMA Fab PSMB83 (aka PSMM84)

PSMA is a homodimeric protein expressed on the cell surface. PSMA is a type II integral glycoprotein of 750 residues per monomer, comprised of a large ECD domain (705 residues) with peptidase activity, a single pass TM domain, and a short 19 residue intracellular domain. The crystal structure of the extracellular region (ECD) of human PSMA bound to the anti-PSMA Fab arm of bispecific antibody PS3B27 was determined to 3.15 Å resolution to better understand the combining site between PSMA and the antibody.

The extracellular region of human PSMA (residues 44-750) was expressed in High Five™ insect cells with an N-terminal gp67 signal peptide followed by a cleavable hexahistidine tag (SEQ ID NO: 596). The secreted protein was purified from supernatant by a three-step procedure comprising of an initial Ni²⁺-NTA affinity capture, TEV-mediated cleavage of the histidine tag followed by an inverse affinity chromatography step, and a final size-exclusion chromatography step. Purified PSMA-ECD was flash-frozen in liquid nitrogen and stored at -80 °C in 10 mM HEPES pH 7.4, 150 mM NaCl, 2 mM CaCl₂, 0.1 mM ZnCl₂

The Fab of PSMB83 (aka PSMM84), which is the parental anti-PSMA Fab arm in bispecific antibody PS3B27, was expressed in HEK293 Expi cells with a hexahistidine tag (SEQ ID NO: 596) and purified using affinity (HisTrap, GE Healthcare) and size-exclusion chromatography (SEC-300, Phenomenex Yarra). The Fab was stored at 4 °C in 50 mM NaCl, 20 mM Tris pH 7.4

The human PSMA ECD/PSMB83 Fab complex was prepared by a three-step procedure. First, the Fab was buffer exchanged into 20mM MES pH 6.0, 150 mM NaCl. Then, the Fab and PSMA were mixed (1.5 molar excess Fab over PSMA monomer) and incubated overnight at 4 °C while dialyzing into 20 mM MES pH 6.0. Finally, the complex was bound to a monoS 5/50 column in 20 mM MES pH 6.0 and eluted with a NaCl gradient.

Crystals suitable for X-ray diffraction were obtained using the sitting drop vapor-diffusion method at 20 °C and a Mosquito LCP robot (TTP Labtech). Crystals of PSMB83 Fab bound to human PSMA ECD were grown from 18% PEG 3 kDa, 0.2 M (NH₄)₂SO₄, 0.1 M Tris pH 8.5 with micro-seeds and the PSMA/Fab complex initially at 7.3 mg/mL. Crystals of free PSMB83 Fab were obtained from 25% PEG 3 kDa, 0.2 M LiCl, 0.1 M acetate pH 4.5 with the Fab initially at 8.8 mg/mL.

The structures were solved by molecular replacement (MR) with Phaser (Phaser Crystallographic Software, University of Cambridge). The MR search model for the PSMB83 (aka PSMM84) Fab structure was PDB code 4M6O. The PSMA/Fab complex structure was solved using the crystal structures of PSMA (PDB code: 2C6G) and PSMB83 Fab (structure at 1.93 Å resolution; data not shown) as MR search models. The structures were refined with PHENIX (Adams, et al, 2004) and model adjustments were carried out using COOT (Emsley and Cowtan, 2004). All other crystallographic calculations were performed with the CCP4 suite of programs (Collaborative Computational Project Number 4, 1994). All molecular graphics were generated with PyMol (PyMOL Molecular Graphics System, Version 1.4.1, Schrödinger, LLC.) and complementarity determining regions (CDRs) were determined using the Kabat definition.

The PSMA/Fab structure includes Fab light chain residues 1-211, Fab heavy chain residues 1-224 (except for residues 138-146, which are disordered) and PSMA residues 56-750, which corresponds to the protease (residues 56-116 and 352-590), apical (residues 117-351) and helical (residues 591-750) domains, and seven of ten possible N-linked glycans (in Asn-76, -121, -140, -195, -459, -476, and -638) per PSMA dimer subunit. The PSMA active site is located at the interface between the three domains and it contains two zinc atoms coordinated by histidine (H377 and H553) and glutamate/aspartate (D387, catalytic E424, E425, and D453) residues and a water molecule. The crystal asymmetric unit contains one PSMA dimer with each subunit bound in a similar manner to a PSMB83 Fab. The Fab/PSMA combining site is well defined by

the electron density map, which allows reliable positioning of the binding residues. The Fab and PSMA molecules are numbered sequentially in **Fig. 26 – Fig. 31**.

The PSMB83 epitope, paratope and interactions. PSMB83, which is the parental anti-PSMA Fab arm in bispecific antibody PS3B27, recognizes a conformational and discontinuous epitope in the apical domain of PSMA (**Fig. 26**). The PSMA surface area buried by the Fab is around 700 Å². Specifically, the PSMB83 epitope residues are I138, F235, P237, G238, D244, Y299, Y300, Q303, K304, E307, and K324-P326. Helix α7 (residues Y299-E307) is a prevalent region of the epitope and binds across the Fab heavy and light chain CDRs. At one end of the helix, Y299 and Y300 form an aromatic cluster with Fab residues Y57^H, W94^L and PSMA residues F235 and P237, while E307, at the other helix end, forms a salt bridge with R91^L and hydrogen bonds Y32^L. **Fig. 27** and **Fig. 28** show the main interactions of PSMA with the PSMB83 light and heavy chains. The PSMB83 epitope residues are conserved between human and cynomolgus monkey (**Fig. 29**) and the bispecific antibody PS3B27 was demonstrated to bind with similar affinity to human and cyno PSMA. In contrast, the human to mouse G238A and, especially, Y300D epitope mutations are expected to lower PSMB83 binding affinity to mouse PSMA in comparison to human. The Y300D mutation disrupts a hydrogen bond contact with N59^H and a π stacking interaction with W94^L.

The PSMB83 paratope is composed of residues from all CDRs except CDR-L2 and CDR-H1 (**Fig. 30**). Specifically, the paratope residues are light chain S30^L, Y32^L, R91^L, S92^L, W94^L, and heavy chain G56^H-N59^H, K65^H, G66^H, Y101^H, V107^H, and D109^H. **Fig. 31** shows the interaction contacts between PSMA and PSMB83. The accessible location of the epitope facilitates binding of the PSMB83 Fab arm in the PS3B27 bispecific antibody to membrane-bound PSMA, while the other Fab arm is still bound to CD3 in the T-cell membrane. PSMB83 is not expected to inhibit PSMA enzymatic activity since the antibody binds away from the active site and does not cause any significant structural changes in PSMA that could affect enzymatic function, such as loop movements that close the active site or displacement of catalytic residues (RMSD of 0.3 Å for Cα superposition of PSMA molecules in Fab bound and unbound (Barinka et al, 2007) structures).

2-6 Anti-PSMA Affinity Maturation

Affinity maturation was performed on anti-PSMA Fab phage clones from two PSMA affinity maturation libraries to identify an antibody with increased binding affinity compared to the parental PSMB127 (fab ID = PSMB83, aka PSMM84). Two libraries were generated for affinity maturation of PSMB127). In the first library heavy chain CDR1 and CDR2 were randomized according to the design in Table 24 (PH9H9L1). The H-CDR3 fragment was PCR amplified from pDR000024032 and digested with SacII + XhoI. This fragment was cloned into the PH9H9L1/PH9L3 library. This was transformed into *E.coli* MC1061F' cells and phage was generated displaying this Fab library. In the second library light chain CDRs were randomized according to the design in Table 25 (PH9L3L3). The heavy chain from PSMB83 (PSMH360) was PCR amplified and digested with NcoI + XhoI. This fragment was cloned into the PH9L3L3 library DNA (ELN: De Novo 2010 phage library SRI-021). This was transformed into *E.coli* MC1061F' cells and phage was generated displaying this Fab library.

Table 24: PH9H9L1 Library design

Position	Parent AA	Library AA
30	S	D, K, S
31	S	D, N, S, T
32	Y	A, D, S, Y
33	A	A, D, G, S, W, Y
35	S	H, N, S
50	A	A, E, L, N, R, T, W, Y
52	S	A, D, L, N, R, S
54	S	A, E, N, S, Y
57	S	D, N, R, S, T, Y
59	Y	E, G, N, Q, R, Y

Table 25: PH9L3L3 Library design

Position	Parent AA	Library AA
30	S	D, N, R, S
31	S	N, S, T
32	Y	D, N, R, S, Y
49	Y	E, H, K, Y
50	D	D, G, S, W, Y
53	N	D, N, S, T, Y

91	R	A, D, E, G, H, N, R, S, W, Y
92	S	A, D, E, G, H, N, R, S, W, Y
93	N	A, D, E, G, H, N, R, S, W, Y
94	W	A, D, E, G, H, N, R, S, W, Y
96	L	F, I, L, N, R, W, Y

A solution panning of the PSMA affinity maturation Fab-pIX libraries was performed against biotinylated human PSMA ECD for three rounds. The phage-bound antigen was captured on neutravidin beads (GE HealthCare Life Science Cat# 78152104011150) according to the manufacturer's protocol, followed by extensive washes in 1x PBST (0.05% tween 20) and an hour-long incubation with unlabeled PSMA ECD in 500-fold molar excess of the biotinylated antigen. This panning yielded the clones, PSMXP46R3_59H09, PSMXP46R3_59H06, PSMXP46R3_59E03, PSMXP46R3_59C09, PSMXP46R3_59H01, PSMXP46R3_59F11, and PSMXP46R3_59F07.

10 To determine the expression level of the anti-PSMA fab clones, 96 well Maxisorb plates were coated overnight at 4C with anti-human Fd IgG, washed, and blocked with 3% milk-PBS-0.05% Tween for 1 hour. The phage supernatant samples were serially diluted 2-fold for 11 dilutions in blocking buffer with the final well blank. 100ul of these solutions were captured on the coated plates for 1 hour. The plates were washed and 100ul of anti-F(ab')₂-HRP antibody
15 was added for 1 hour. Plates were washed and developed with 100ul of peroxidase reagent and luminescence was read on the Envision (**Fig. 32**).

To determine the binding of the anti-PSMA fab clones to human and cynomolgus recombinant protein, 96 well Maxisorb plates were coated with 100ul of 5ug/ml neutravidin overnight at 4C. The plates were washed and blocked with 3% milk-PBS-0.05% Tween for 1
20 hour. Recombinant biotinylated human and cynomolgus PSMA proteins were captured at 2.5ug/ml for 1 hour at room temperature. The plates were washed and 100ul of 2-fold serially diluted fab supernatant was capture for 1 hour at RT. The plate was washed and then there was a 2.5-hour incubation with 200ul 0.3% milk in PBST to wash away some of the weak affinity fabs. Then there was another 30 minutes incubation with fresh 200ul 0.3% milk in PBST to
25 remove more weak affinity fabs. The plates were washed and 100ul of anti-F(ab')₂-HRP antibody was added for 1 hour. Plates were washed and developed with 100ul of peroxidase reagent and luminescence was read on the Envision (**Fig. 33** and **Fig. 34**).

Fig. 32 demonstrates that the protein expression of the parental Fab and affinity matured Fabs were similar. The y axis values represent the luminescence of the detection reagent which equates to the abundance of fab protein over the dilution curve; the higher the luminescence reading, the more protein in the well which decreased with successive two-fold dilutions. There was more protein in the wells with affinity mature fabs but the increase over the parental is at most five times greater as demonstrated by the EC50 values (which is the concentration of protein that gives half of the maximal response). These data demonstrate the difference in PSMA binding profiles in **Fig. 33** and **Fig. 34** is not due to a difference in Fab concentration.

Fig. 33 demonstrates improved binding of the affinity matured Fabs to the human recombinant antigen over the parental anti-PSMA Fab (PSMB83). Again, the y axis of the graph represents luminescence values. In this case the larger the value means more Fab bound to the human PSMA protein. This is a measure of binding as increased concentrations of Fab (along the x axis) generate higher luminescence values. There was negligible binding of the parental Fab under these conditions as demonstrated by the absence of signal even at high concentrations (open circles along the x axis). Binding of the affinity matured fabs was observed over the concentrations tested which equates to stronger binding capacity to the human PSMA protein. Given that parental Fab binding to human PSMA protein was zero, no EC50 could be generated.

Fig. 34 demonstrates improved binding of the affinity matured Fabs to the cynomolgus recombinant antigen over the parental anti-PSMA Fab (PSMB83). Again, the y axis of the graph represents luminescence values. In this case the larger the value means more Fab bound to the cynomolgus PSMA protein. This is a measure of binding as increased concentrations of Fab (along the x axis) generate higher luminescence values. There was negligible binding of the parental Fab under these conditions as demonstrated by the absence of signal even at high concentrations (open circles along the x axis). Binding of the affinity matured Fabs was observed over the concentrations tested which equates to stronger binding capacity to the human PSMA protein. Given that parental Fab binding to human PSMA protein was zero, no EC50 could be generated for direct comparison.

Overall, the phages' Fab binding profiles demonstrate improved binding to the human and cynomolgus recombinant antigen over the parental anti-PSMA mAb (PSMB127). This improvement is not a result of differences in Fab expression profiles, as demonstrated by Fig. 34 and Fig. 35, showing binding of affinity mature Fabs normalized to Fab expression levels. The

top five Fab candidates identified from the ELISA screen were produced in monoclonal antibody format on IgG4 PAA. Table 26 lists the subsequent Mab identifiers and Tables 27 and 28 depict sequences for their variable regions and the sequences for the heavy and light chains, respectively.

5

Table 26: Top five affinity mature antibodies identified based on the ELISA

Well ID	HC SEQ ID	LC SEQ ID	MAB protein IDs
PSMXP46R3_59C09	PSMH859	PSML160	PSMB346
PSMXP46R3_59E03	PSMH859	PSML159	PSMB345
PSMXP46R3_59F07	PSMH862	PSML158	PSMB349
PSMXP46R3_59H01	PSMH860	PH9L3	PSMB347
PSMXP46R3_59H06	PSMH859	PH9L3	PSMB344

Table 27. VH and VL sequences of top five PSMA Fab candidates

MAB ID	VH Amino acid sequence	SEQ ID NO	VL Amino Acid Sequence	SEQ ID NO
PSMB344	EVQLLES GGGLVQP GGS LRLSCAASG FTFKSDAMHWVRQAPGKGLEWVSEIS GSGGYTNYADSMKGRFTISRDN SKNT LYLQMNSLRAEDTAVYYCARDSDYSS LYVGDYFDYWGQGT LTVTVSS	6	EIVLTQSPATLSLSPGE RATLSCRASQSVSSYLA WYQQKPGQAPRLLIYDA SNRATGIPARFSGSGSG TDFTLTISSELPEDFAV YYCQQRN WPLTFGQGT KVEIK	117
PSMB345	EVQLLES GGGLVQP GGS LRLSCAASG FTFKSDAMHWVRQAPGKGLEWVSEIS GSGGYTNYADSMKGRFTISRDN SKNT LYLQMNSLRAEDTAVYYCARDSDYSS LYVGDYFDYWGQGT LTVTVSS	6	EIVLTQSPATLSLSPGE RATLSCRASQSVSNYLA WYQQKPGQAPRLLIHDA SNRATGIPARFSGSGSG TDFTLTISSELPEDFAV YYCQQRN WPLTFGQGT KVEIK	9
PSMB346	EVQLLES GGGLVQP GGS LRLSCAASG FTFKSDAMHWVRQAPGKGLEWVSEIS GSGGYTNYADSMKGRFTISRDN SKNT LYLQMNSLRAEDTAVYYCARDSDYSS LYVGDYFDYWGQGT LTVTVSS	6	EIVLTQSPATLSLSPGE RATLSCRASQSVSSYLA WYQQKPGQAPRLLIYDA SYRATGIPARFSGSGSG TDFTLTISSELPEDFAV YYCQQRN WPLTFGQGT KVEIK	682

PSMB347	EVQLLES GGGLVQP GGS LRLSCAASG FTFKSDAMHWVRQAPGKGLEWVSEIS GSGGYTNYADSMKSRFTISRDN SKNT LYLQMNSLRAEDTAVYYCARDSDSS LYVGDYFDYWGQGLTVTVSS	7	EIVLTQSPATLSLSPGE RATLSCRASQSVSSYLA WYQQKPGQAPRLLIYDA SNRATGIPARFSGSGSG TDFTLTISSLEPEDFAV YYCQQRSNWPLTFGQGT KVEIK	117
PSMB349	EVQLLES GGGLVQP GGS LRLSCAASG FTFKSDAMHWVRQAPGKGLEWVSEIS GSGGYTNYADSLKGRFTISRDN SKNT LYLQMNSLRAEDTAVYYCARDSDSS LYVGDYFDYWGQGLTVTVSS	8	EIVLTQSPATLSLSPGE RATLSCRASQSVSSYLA WYQQKPGQAPRLLIYDA SNRATGIPARFSGSGSG TDFTLTISSLEPEDFAV YYCQQRGNWPLTFGQGT KVEIK	10

Table 28. Heavy Chain and Light Chain sequences of top five PSMA candidates in monoclonal antibody format on IgG4 PAA

mAb ID	Heavy Chain Amino acid sequence	SEQ ID NO	Light Chain Amino Acid Sequence	SEQ ID NO
PSMB344	EVQLLES GGGLVQP GGS LRLSCAA SGFTFKSDAMHWVRQAPGKGLEWV SEISGSGGYTNYADSMKGRFTISR DNSKNTLYLQMNSLRAEDTAVYYC ARDSYDSSLYVGDYFDYWGQGLTV TVSSASTKGPSVFPLAPCSRSTSE STAALGCLVKDYFPEPVTWNSG ALTSGVHTFPAVLQSSGLYSLSSV VTVPSSSLGKTYTCNV DHKPSNT KVDKRVESKYGPPCPPCPAPEAAG GPSVFLFPPKPKDTLMISRTPEVT CVVVDVSQEDPEVQFNWYVDGVEV HNAKTKPREEQFNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKGLPSSI EKTISKAKGQPREPQVYTLPPSQE EMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPVLDSDGSF FLYSRLTVDKSRWQEGNVFSCSVM HEALHNHYTQKSLSLSLGK	11	EIVLTQSPATLSLSPGERATLS CRASQSVSSYLAWYQQKPGQAP RLLIYDASN RATGIPARFSGSG SGTDFTLTISSLEPEDFAVYYC QQRSNWPLTFGQGT KVEI KRTV AAPSVFI FPPSDEQLKSGTASV VCLLNNFY PREAKVQWKVDNAL QSGNSQESVTEQDSKDSTYSLS STLTLSKADYEKHKVYACEVTH QGLSSPVT KSFNRGEC	139
PSMB345	EVQLLES GGGLVQP GGS LRLSCAA SGFTFKSDAMHWVRQAPGKGLEWV SEISGSGGYTNYADSMKGRFTISR DNSKNTLYLQMNSLRAEDTAVYYC ARDSYDSSLYVGDYFDYWGQGLTV TVSSASTKGPSVFPLAPCSRSTSE STAALGCLVKDYFPEPVTWNSG ALTSGVHTFPAVLQSSGLYSLSSV VTVPSSSLGKTYTCNV DHKPSNT KVDKRVESKYGPPCPPCPAPEAAG GPSVFLFPPKPKDTLMISRTPEVT	11	EIVLTQSPATLSLSPGERATLS CRASQSVSNYLAWYQQKPGQAP RLLIHDASN RATGIPARFSGSG SGTDFTLTISSLEPEDFAVYYC QQRN WPLTFGQGT KVEI KRTV AAPSVFI FPPSDEQLKSGTASV VCLLNNFY PREAKVQWKVDNAL QSGNSQESVTEQDSKDSTYSLS STLTLSKADYEKHKVYACEVTH QGLSSPVT KSFNRGEC	14

	CVVVDVSQEDPEVQFNWYVDGVEV HNAKTKPREEQFNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKGLPSSI EKTISKAKGQPREPQVYTLPPSQE EMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPVLDSGGSF FLYSRLTVDKSRWQEGNVFSCSVM HEALHNHYTQKSLSLGLGK			
PSMB346	EVQLLESGGGLVQPGGSLRLSC AASGFTFKSDAMHWVRQAPGKG LEWVSEISGSGGYTNYADSMKG RFTISRDNKNTLYLQMNSLRA EDTAVYYCARDSDSSLYVGDY FDYWGQGTlTVSSASTKGPSV FPLAPCSRSTSESTAALGCLVK DYFPEPVTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVTVPS SLGTKTYTCNVDHKPSNTKVDK RVESKYGPPCPPCPAPEAAGGP SVFLFPPKPKDTLMISRTPEVT CVVVDVSQEDPEVQFNWYVDG EVHNAKTKPREEQFNSTYRVV VLTVLHQDWLNGKEYKCKVSNK GLPSSIEKTISKAKGQPREPQV YTLPPSQEEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYK TTPVLDSGGSFFLYSRLTVDK SRWQEGNVFSCSVMHEALHNHY TQKSLSLGLGK	11	EIVLTQSPATLSLSPGERAT LSCRASQSVSSYLAWYQQKP GQAPRLLIYDASYRATGIPA RFSGSGSGTDFTLTISLLEP EDFAVYYCQQRNWPLTFGQ GTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQ ESVTEQDSKDYSLSSSTLT LSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC	680
PSMB347	EVQLLESGGGLVQPGGSLRLSC AASGFTFKSDAMHWVRQAPGKG LEWVSEISGSGGYTNYADSMKS RFTISRDNKNTLYLQMNSLRA EDTAVYYCARDSDSSLYVGDY FDYWGQGTlTVSSASTKGPSV FPLAPCSRSTSESTAALGCLVK DYFPEPVTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVTVPS SLGTKTYTCNVDHKPSNTKVDK RVESKYGPPCPPCPAPEAAGGP SVFLFPPKPKDTLMISRTPEVT CVVVDVSQEDPEVQFNWYVDG EVHNAKTKPREEQFNSTYRVV VLTVLHQDWLNGKEYKCKVSNK GLPSSIEKTISKAKGQPREPQV YTLPPSQEEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYK TTPVLDSGGSFFLYSRLTVDK SRWQEGNVFSCSVMHEALHNHY TQKSLSLGLGK	12	EIVLTQSPATLSLSPGERAT LSCRASQSVSSYLAWYQQKP GQAPRLLIYDASNATGIPA RFSGSGSGTDFTLTISLLEP EDFAVYYCQQRNWPLTFGQ GTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQ ESVTEQDSKDYSLSSSTLT LSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC	139

PSMB349	EVQLLESGGGLVQPGGSLRLSC AASGFTFKSDAMHWVRQAPGKG LEWVSEISGSGGYTNYADSLKG RFTISRDN SKNTLYLQMNSLRA EDTAVYYCARDSDYSSLYVGDY FDYWGQGT LVT VSSASTKGPSV FPLAPCSRSTSESTAALGCLVK DYFPEPVT VSWNSGALTSGVHT FPAVLQSSGLYSLSSVVTVPSS SLGTKTYTCNV DHKPSNTKV DK RVESKYGPPCPPCPAPEAAGGP SVFLFPPKPKDTLMISRTPEVT CVVVDV SQEDPEVQFNWYVDGV EVHNAKTKPREEQFNSTYRVVS VLT V LHQDWLNGKEYKCKVSNK GLPSSIEKTI SKAKGQPREPQV YTLPPSQEEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSRLTVDK SRWQEGNVFSCSVMHEALHNHY TQKSLSLSLGK	13	EIVLTQSPATLSLSPGERAT LSCRASQSVSSYLAWYQQKP GQAPRLLIYDASN RATGIPA RFSGSGSGTDFTLT ISSLEP EDFAVYYCQQRGNWPLTFGQ GTKVEIKRTVAAPSVFI FPP SDEQLKSGTASVVC LLNNFY PREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLT LSKADYEKHKVYACEVTHQG LSSPVT KSFNRGEC	15

The 3 different HC and 4 different LC were combined in a matrix format to expand the diversity of hits (Table 29). Given that the methionine in the CDR2 of PSMH860 is a posttranslational risk, a new sequence was generated with M64L and identified as PSMH865.

5 PSMH865 was paired with PSML160 to generate Mab PSMB365.

Table 29: Matrix format of the 3 heavy chains and 4 light chains combined

	PSMH859	PSMH860	PSMH862
PH9L3	PSMB344	PSMB347	PSMB358
PSML158	--	PSMB361	PSMB349
PSML159	PSMB345	PSMB362	PSMB359
PSML160	PSMB346	PSMB363	PSMB360

10 Tables 30 and 31 depict the sequences for the matrix recombined variable regions and the sequences for the heavy and light chains, respectively.

Table 30. VH and VL sequences of matrix recombined PSMA hits

MAB ID	VH Amino acid sequence	SEQ ID NO	VL Amino Acid Sequence	SEQ ID NO

PSMB358	EVQLLES GGGLVQP GGS LRLSCAASG FTFKSDAMHWVRQAPGKGLEWVSEIS GSGGYTNYADSLKGRFTISRDN SKNT LYLQMNSLRAEDTAVYYCARDSDSS LYVGDYFDYWGQGLTVTVSS	8	EIVLTQSPATLSLSPGE RATLSCRASQSVSSYLA WYQQKPGQAPRLLIYDA SNRATGIPARFSGSGSG TDFTLTISSLEPEDFAV YYCQQRSNWPLTFGQGT KVEIK	117
PSMB359	EVQLLES GGGLVQP GGS LRLSCAASG FTFKSDAMHWVRQAPGKGLEWVSEIS GSGGYTNYADSLKGRFTISRDN SKNT LYLQMNSLRAEDTAVYYCARDSDSS LYVGDYFDYWGQGLTVTVSS	8	EIVLTQSPATLSLSPGE RATLSCRASQSVSNYLA WYQQKPGQAPRLLIHDA SNRATGIPARFSGSGSG TDFTLTISSLEPEDFAV YYCQQRNWNWPLTFGQGT KVEIK	9
PSMB360	EVQLLES GGGLVQP GGS LRLSCAASG FTFKSDAMHWVRQAPGKGLEWVSEIS GSGGYTNYADSLKGRFTISRDN SKNT LYLQMNSLRAEDTAVYYCARDSDSS LYVGDYFDYWGQGLTVTVSS	8	EIVLTQSPATLSLSPGE RATLSCRASQSVSSYLA WYQQKPGQAPRLLIYDA SYRATGIPARFSGSGSG TDFTLTISSLEPEDFAV YYCQQRNWNWPLTFGQGT KVEIK	682
PSMB361	EVQLLES GGGLVQP GGS LRLSCAASG FTFKSDAMHWVRQAPGKGLEWVSEIS GSGGYTNYADSMKS RFTISRDN SKNT LYLQMNSLRAEDTAVYYCARDSDSS LYVGDYFDYWGQGLTVTVSS	7	EIVLTQSPATLSLSPGE RATLSCRASQSVSSYLA WYQQKPGQAPRLLIYDA SNRATGIPARFSGSGSG TDFTLTISSLEPEDFAV YYCQQRGNWPLTFGQGT KVEIK	10
PSMB362	EVQLLES GGGLVQP GGS LRLSCAASG FTFKSDAMHWVRQAPGKGLEWVSEIS GSGGYTNYADSMKS RFTISRDN SKNT LYLQMNSLRAEDTAVYYCARDSDSS LYVGDYFDYWGQGLTVTVSS	7	EIVLTQSPATLSLSPGE RATLSCRASQSVSNYLA WYQQKPGQAPRLLIHDA SNRATGIPARFSGSGSG TDFTLTISSLEPEDFAV YYCQQRNWNWPLTFGQGT KVEIK	9
PSMB363	EVQLLES GGGLVQP GGS LRLSCAASG FTFKSDAMHWVRQAPGKGLEWVSEIS GSGGYTNYADSMKS RFTISRDN SKNT LYLQMNSLRAEDTAVYYCARDSDSS LYVGDYFDYWGQGLTVTVSS	7	EIVLTQSPATLSLSPGE RATLSCRASQSVSSYLA WYQQKPGQAPRLLIYDA SYRATGIPARFSGSGSG TDFTLTISSLEPEDFAV YYCQQRNWNWPLTFGQGT KVEIK	682

PSMB365	EVQLLES GGGLVQP GGSRLRLSCAASG FTFKSDAMHWVRQAPGKGLEWVSEIS GSGGYTNYADSLKSRFTISRDN SKNT LYLQMNSLRAEDTAVYYCARDSDSS LYVGDYFDYWGQGLTVTVSS	681	EIVLTQSPATLSLSPGE RATLSCRASQSVSSYLA WYQQKPGQAPRLLIYDA SYRATGIPARFSGSGSG TDFTLTISSLEPEDFAV YYCQRRNWPLTFGQGT KVEIK	682

Table 31. Heavy Chain and Light Chain sequences of matrix recombined PSMA hits

MAB ID	Heavy Chain Amino acid sequence	SEQ ID NO	Light Chain Amino Acid Sequence	SEQ ID NO
PSMB358	EVQLLES GGGLVQP GGSRLRLSCAASG FTFKSDAMHWVRQAPGKGLEWVSEIS GSGGYTNYADSLKGRFTISRDN SKNT LYLQMNSLRAEDTAVYYCARDSDSS LYVGDYFDYWGQGLTVTVSSASTKGP SVFPLAPCSRSTSESTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVTVPSSSLGKTKYTCN VDHKPSNTKVDKRVESKYGPCPPCP APEAAGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSQEDPEVQFNWYVDGV EVHNAKTKPREEQFNSTYRVSVLTV LHQDWLNGKEYKCKVSNKGLPSSIEK TISKAKGQPREPQVYTLPPSQEEMTK NQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTTPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCSVMEALHNHYTQ KSLSLSLGK	13	EIVLTQSPATLSLSPGE RATLSCRASQSVSSYLA WYQQKPGQAPRLLIYDA SNRATGIPARFSGSGSG TDFTLTISSLEPEDFAV YYCQQRNWPLTFGQGT KVEIKRTVAAPSVFIFP PSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKD STYLSSTLTLSKADYE KHKVYACEVTHQGLSSP VTKSFNRGEC	139
PSMB359	EVQLLES GGGLVQP GGSRLRLSCAASG FTFKSDAMHWVRQAPGKGLEWVSEIS GSGGYTNYADSLKGRFTISRDN SKNT LYLQMNSLRAEDTAVYYCARDSDSS LYVGDYFDYWGQGLTVTVSSASTKGP SVFPLAPCSRSTSESTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVTVPSSSLGKTKYTCN VDHKPSNTKVDKRVESKYGPCPPCP APEAAGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSQEDPEVQFNWYVDGV EVHNAKTKPREEQFNSTYRVSVLTV LHQDWLNGKEYKCKVSNKGLPSSIEK TISKAKGQPREPQVYTLPPSQEEMTK NQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTTPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCSVMEALHNHYTQ KSLSLSLGK	13	EIVLTQSPATLSLSPGE RATLSCRASQSVSNYLA WYQQKPGQAPRLLIHDA SNRATGIPARFSGSGSG TDFTLTISSLEPEDFAV YYCQRRNWPLTFGQGT KVEIKRTVAAPSVFIFP PSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKD STYLSSTLTLSKADYE KHKVYACEVTHQGLSSP VTKSFNRGEC	14

PSMB360	EVQLLES GGGLVQP GGSRLRLSCAASG FTFKSDAMHWVRQAPGKGLEWVSEIS GSGGYTNYADSLKGRFTISRDN SKNT LYLQMNSLRAEDTAVYYCARDSDSS LYVGDYFDYWGQGLTVTVSSASTKGP SVFPLAPCSRSTSESTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSSLGKTKYTCN VDHKPSNTKVDKRVESKYGPCCPPCP APEAAGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSQEDPEVQFNWYVDGV EVHNAKTKPREEQFNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKGLPSSIEK TISKAKGQPREPQVYTLPPSQEEMTK NQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTTPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCSVMEALHNHYTQ KSLSLSLGK	13	EIVLTQSPATLSLSPGE RATLSCRASQSVSSYLA WYQQKPGQAPRLLIYDA SYRATGIPARFSGSGSG TDFTLTISSLEPEDFAV YYCQQRNWPLTFGQGT KVEIKRTVAAPSVFIFP PSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKD STYLSSTLTLSKADYE KHKVYACEVTHQGLSSP VTKSFNRGEC	680
PSMB361	EVQLLES GGGLVQP GGSRLRLSCAASG FTFKSDAMHWVRQAPGKGLEWVSEIS GSGGYTNYADSMKSRFTISRDN SKNT LYLQMNSLRAEDTAVYYCARDSDSS LYVGDYFDYWGQGLTVTVSSASTKGP SVFPLAPCSRSTSESTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSSLGKTKYTCN VDHKPSNTKVDKRVESKYGPCCPPCP APEAAGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSQEDPEVQFNWYVDGV EVHNAKTKPREEQFNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKGLPSSIEK TISKAKGQPREPQVYTLPPSQEEMTK NQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTTPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCSVMEALHNHYTQ KSLSLSLGK	12	EIVLTQSPATLSLSPGE RATLSCRASQSVSSYLA WYQQKPGQAPRLLIYDA SNRATGIPARFSGSGSG TDFTLTISSLEPEDFAV YYCQQRNWPLTFGQGT KVEIKRTVAAPSVFIFP PSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKD STYLSSTLTLSKADYE KHKVYACEVTHQGLSSP VTKSFNRGEC	15
PSMB362	EVQLLES GGGLVQP GGSRLRLSCAASG FTFKSDAMHWVRQAPGKGLEWVSEIS GSGGYTNYADSMKSRFTISRDN SKNT LYLQMNSLRAEDTAVYYCARDSDSS LYVGDYFDYWGQGLTVTVSSASTKGP SVFPLAPCSRSTSESTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSSLGKTKYTCN VDHKPSNTKVDKRVESKYGPCCPPCP APEAAGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSQEDPEVQFNWYVDGV EVHNAKTKPREEQFNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKGLPSSIEK TISKAKGQPREPQVYTLPPSQEEMTK NQVSLTCLVKGFYPSDIAVEWESNGQ	12	EIVLTQSPATLSLSPGE RATLSCRASQSVSNYLA WYQQKPGQAPRLLIHDA SNRATGIPARFSGSGSG TDFTLTISSLEPEDFAV YYCQQRNWPLTFGQGT KVEIKRTVAAPSVFIFP PSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKD STYLSSTLTLSKADYE KHKVYACEVTHQGLSSP VTKSFNRGEC	14

	PENNYKTTTPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCSVMHEALHNHYTQ KSLSLSLGK			
PSMB363	EVQLLES GGGLVQP GGSLRLSCAASG FTFKSDAMHWVRQAPGKGLEWVSEIS GSGGYTNYADSMKSRFTISRDN SKNT LYLQMNSLRAEDTAVYYCARDSDSS LYVGDYFDYWGQGLTVTVSSASTKGP SVFPLAPCSRSTSESTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVTVPSSSLGTKTYTCN VDHKPSNTKVDKRVESKYGPCPPCP APEAAGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSQEDPEVQFNWYVDGV EVHNAKTKPREEQFNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKGLPSSIEK TISKAKGQPREPQVYTLPPSQEEMTK NQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTTPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCSVMHEALHNHYTQ KSLSLSLGK	12	EIVLTQSPATLSLSPGE RATLSCRASQSVSSYLA WYQQKPGQAPRLLIYDA SYRATGIPARFSGSGSG TDFTLTISSELEPEDFAV YYCQQRNWPLTFGQGT KVEIKRTVAAPSVFIFP PSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKD STYLSSTLTLSKADYE KHKVYACEVTHQGLSSP VTKSFNRGEC	680
PSMB365	EVQLLES GGGLVQP GGSLRLSCAASG FTFKSDAMHWVRQAPGKGLEWVSEIS GSGGYTNYADSLKSRFTISRDN SKNT LYLQMNSLRAEDTAVYYCARDSDSS LYVGDYFDYWGQGLTVTVSSASTKGP SVFPLAPCSRSTSESTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVTVPSSSLGTKTYTCN VDHKPSNTKVDKRVESKYGPCPPCP APEAAGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSQEDPEVQFNWYVDGV EVHNAKTKPREEQFNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKGLPSSIEK TISKAKGQPREPQVYTLPPSQEEMTK NQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTTPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCSVMHEALHNHYTQ KSLSLSLGK	679	EIVLTQSPATLSLSPGE RATLSCRASQSVSSYLA WYQQKPGQAPRLLIYDA SYRATGIPARFSGSGSG TDFTLTISSELEPEDFAV YYCQQRNWPLTFGQGT KVEIKRTVAAPSVFIFP PSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKD STYLSSTLTLSKADYE KHKVYACEVTHQGLSSP VTKSFNRGEC	631

Table 32 shows the CDR sequences for all affinity-matured PSMA hits.

Table 32. CDR sequences of affinity-matured PSMA hits

MAB ID		CDRs (SEQ ID NO:)		
		CDR1	CDR2	CDR3
PSMB344	HC	SDAMH (78)	EISGSGGYTNYADSMKG (1)	DSYDSSLYVG DYFDY (80)
	LC	RASQSVSSYLA (81)	DASNRAT (82)	QQRNWLPT (83)
PSMB345	HC	SDAMH (78)	EISGSGGYTNYADSMKG (1)	DSYDSSLYVG DYFDY (80)
	LC	RASQSVSNYLA (4)	DASNRAT (82)	QQRNWLPT (686)
PSMB346	HC	SDAMH (78)	EISGSGGYTNYADSMKG (1)	DSYDSSLYVG DYFDY (80)
	LC	RASQSVSSYLA (81)	DASYRAT (684)	QQRNWLPT (686)
PSMB347	HC	SDAMH (78)	EISGSGGYTNYADSMKS (2)	DSYDSSLYVG DYFDY (80)
	LC	RASQSVSSYLA (81)	DASNRAT (82)	QQRNWLPT (83)
PSMB349	HC	SDAMH (78)	EISGSGGYTNYADSLKG (3)	DSYDSSLYVG DYFDY (80)
	LC	RASQSVSSYLA (81)	DASNRAT (82)	QQRNWLPT (5)
PSMB358	HC	SDAMH (78)	EISGSGGYTNYADSLKG (3)	DSYDSSLYVG DYFDY (80)
	LC	RASQSVSSYLA (81)	DASNRAT (82)	QQRNWLPT (83)
PSMB359	HC	SDAMH (78)	EISGSGGYTNYADSLKG (3)	DSYDSSLYVG DYFDY (80)
	LC	RASQSVSNYLA (4)	DASNRAT (82)	QQRNWLPT (686)
PSMB360	HC	SDAMH (78)	EISGSGGYTNYADSLKG (3)	DSYDSSLYVG DYFDY (80)
	LC	RASQSVSSYLA (81)	DASYRAT (684)	QQRNWLPT (686)
PSMB361	HC	SDAMH (78)	EISGSGGYTNYADSMKS (2)	DSYDSSLYVG DYFDY (632)
	LC	RASQSVSSYLA (81)	DASNRAT (82)	QQRNWLPT (5)
PSMB362	HC	SDAMH (78)	EISGSGGYTNYADSMKS (2)	DSYDSSLYVG DYFDY (80)
	LC	RASQSVSNYLA (4)	DASNRAT (685)	QQRNWLPT (686)
PSMB363	HC	SDAMH (78)	EISGSGGYTNYADSMKS (2)	DSYDSSLYVG DYFDY (80)
	LC	RASQSVSSYLA (630)	DASYRAT (684)	QQRNWLPT (686)
PSMB365	HC	SDAMH (78)	EISGSGGYTNYADSLKS (683)	DSYDSSLYVG DYFDY (80)
	LC	RASQSVSSYLA (81)	DASYRAT (684)	QQRNWLPT (686)

3 Preparation and Functional Evaluation of PSMA×CD3 Bispecific Antibodies

3-1 Generation of PSMA×CD3 Bispecific Antibodies

Two types of affinity-matured PSMA×CD3 bispecific antibodies were generated: one specific for the targeting arm (e.g. affinity matured anti-PSMA) recombined with a high affinity
5 CD3 arm CD3B376 (VH SEQ ID NO:652, VL SEQ ID NO:661; HC SEQ ID NO:640, LC SEQ ID NO:676) CD3 arm or low affinity CD3B450 (VH SEQ ID NO: 657, VL SEQ ID NO: 678, HC SEQ ID NO:675, LC SEQ ID NO:677) arm.

These parental mAbs are in the GenMab format (Labrijn et al, 2013) where the targeting parent (PSMA) contains the 409R GenMab mutation (native amino acid for IgG4), while the
10 killing parent (CD3) contains the F405L GenMab mutation and R409K mutation. The monospecific anti-CD3 antibody was expressed as IgG4, having Fc substitutions S228P, F234A, L235A, F405L, and R409K (CD3 arm) (numbering according to EU index) in their Fc regions. The targeting parent (PSMA) is on human IgG4 with Fc substitutions S228P, F234A, L235A. The monospecific antibodies were expressed in HEK cell lines under CMV promoters.

15 The parental PSMA and CD3 antibodies were purified using a protein A column with an elution buffer of 100mM NaAc pH3.5 and a neutralization buffer of 2.5M Tris, pH 7.2. The neutralized parental mAbs were used to make PSMA×CD3 bispecific antibodies. A portion of parental mabs were further buffer exchanged into D-PBS, pH 7.2 buffer for analytical measurements and assays.

20 Post purification, controlled Fab-arm exchange was performed to make bispecific antibodies. The parental PSMA antibodies were mixed with the desired parental CD3 antibody under reducing conditions in 75mM -2-MEA (2-Mercaptoethylamine) and incubated at 31°C for 4h or at room temperature overnight. The recombination reactions were based on molar ratios, where 6% excess PSMA parental mAbs was used to minimize the CD3 parental mAb remaining
25 after recombination. The recombinations were subsequently dialyzed against 1×DPBS, pH 7.2 to remove the reductant.

The final bispecific antibodies produced, along with the parental mAbs (i.e. PSMA, CD3, or Null) used in the recombination reactions are listed in Table 33.

Selected PSMA hits were also paired with a non-killing arm (Null) to create negative controls for
30 testing purposes. For control bispecific antibodies, B2M1, an RSV antibody in the IgG4 PAA

format (VH SEQ ID NO:610, VL SEQ ID NO:611) was generated, purified and, combined with either the CD3 arm CD3B219 -F405L, R409K to generate CD3B288 (CD3×null) or PSMA arms, PSMB122, PSMB126, PSMB130 to generate PS3B37, PS3B39 and PS3B40 respectively (PSMA×null). These PSMA specific affinity matured Mabs were crossed (as in methods above) to CD3B219 and CD3B376 to generate the bispecific antibodies shown in Table 32.

Table 33. Generation of affinity-matured PSMA×CD3 bispecific antibodies generated from affinity matured PSMA hits

ID	Arm 1	HC	LC	Arm 2	HC	LC
PS3B60	PSMB344	PSMH859	PH9L3	CD3B219	CD3H141	CD3L66
PS3B61	PSMB345	PSMH859	PSML159	CD3B219	CD3H141	CD3L66
PS3B62	PSMB346	PSMH859	PSML160	CD3B219	CD3H141	CD3L66
PS3B63	PSMB347	PSMH860	PH9L3	CD3B219	CD3H141	CD3L66
PS3B64	PSMB349	PSMH862	PSML158	CD3B219	CD3H141	CD3L66
PS3B70	PSMB358	PSMH862	PH9L3	CD3B219	CD3H141	CD3L66
PS3B71	PSMB359	PSMH862	PSML159	CD3B219	CD3H141	CD3L66
PS3B72	PSMB360	PSMH862	PSML160	CD3B219	CD3H141	CD3L66
PS3B73	PSMB361	PSMH860	PSML158	CD3B219	CD3H141	CD3L66
PS3B74	PSMB362	PSMH860	PSML159	CD3B219	CD3H141	CD3L66
PS3B75	PSMB363	PSMH860	PSML160	CD3B219	CD3H141	CD3L66
PS3B76	PSMB358	PSMH862	PH9L3	CD3B376	CD3H219	CD3L150
PS3B77	PSMB349	PSMH862	PSML158	CD3B376	CD3H219	CD3L150
PS3B78	PSMB359	PSMH862	PSML159	CD3B376	CD3H219	CD3L150
PS3B79	PSMB360	PSMH862	PSML160	CD3B376	CD3H219	CD3L150
PS3B80	PSMB347	PSMH860	PH9L3	CD3B376	CD3H219	CD3L150
PS3B81	PSMB361	PSMH860	PSML158	CD3B376	CD3H219	CD3L150
PS3B82	PSMB362	PSMH860	PSML159	CD3B376	CD3H219	CD3L150
PS3B83	PSMB363	PSMH860	PSML160	CD3B376	CD3H219	CD3L150
PS3B84	PSMB344	PSMH859	PH9L3	CD3B376	CD3H219	CD3L150
PS3B85	PSMB345	PSMH859	PSML159	CD3B376	CD3H219	CD3L150
PS3B86	PSMB346	PSMH859	PSML160	CD3B376	CD3H219	CD3L150
PS3B90	PSMB365	PSMH865	PSML160	CD3B376	CD3H219	CD3L150

3-2 Evaluation of PSMA×CD3 affinity matured bispecific abs in LNCAP cell binding

PSMA×CD3 bispecific antibodies were tested for binding to PSMA positive cell line, LNCAP, to PSMA negative cell line, PC3. To assess the binding capabilities of the PSMA bispecific antibodies, the cell-binding assay was utilized (described previously). Bispecific antibodies were normalized for protein concentration and then incubated with the same number of cells expressing either human or cyno PSMA. The MFI at each concentration was collected by flow cytometry and plotted as a function of concentration. Data was transformed via log10 and then plotted. Nonlinear regression of binding curves was done to determine EC50s.

These relative values were used for ranking PSMA binding to target cells. **Figs. 14-16** show LNCAP binding of all bispecific antibodies prepared. In **Fig. 16**, none of the constructs demonstrated binding to the PSMA negative cell line. In **Fig. 14** and **Fig. 15**, all of the affinity matured hits demonstrated increased binding affinity through left shifted curves and increased cMax as compared to the parental Mab, PS2B27.

The interactions of the affinity matured bispecific antibodies with recombinant Cyno PSMA ECD and Human PSMA ECD were studied by Surface Plasmon Resonance (SPR) using a ProteOn XPR36 system (BioRad) as described previously for recombinant chimp PSMA ECD. All of the bispecific antibodies bind both targets with substantially the same affinity, KDs ranging from 0.05 nM to 0.27 nM for human PSMA ECD and from 0.05 nM to 0.23 nM from cyno PSMA ECD.

3-3 Evaluation of PSMA x CD3 Affinity Matured Bispecific Abs in Functional Cell Killing Assay

Based on the above data, affinity measurements, and sequence identity, three PSMA antibodies, PSMB347, PSMB360 and PSMB365 as bispecifics with either CD3B219 or CD3B376, were further characterized for the ability to mediate PSMA specific, redirected T cell

cytotoxicity. T-cell mediated killing was measured using a caspase cytotoxicity assay, which indirectly measures cell killing via cleavage of a fluorescent substrate by active caspase 3/7. Cleavage of the substrate results in a fluorescent DNA dye, with fluorescence restricted to the cell nucleus. Repeated fluorescence measurements are taken in each well throughout the course
5 of the assay, using a motorized 10X objective, capable of precisely imaging well(s) at the same coordinates. Target cell populations are identified based on defined size restrictions and/or through the use of a secondary label. Frozen Pan CD3⁺ T-cells (purchased from Biological Specialty Corporation, Colmar, PA) were isolated by negative selection from normal healthy donors. Prostate cancer cells, expressing PSMA, (LNCaP, C42) were cultured in RPMI 1640
10 with 10% HI FBS + supplements (purchased from Life Technologies).

T-cells and target cells were combined at an effector to target ratio (E:T) of 3:1 in Phenol Red free RPMI + 10% FBS and supplements (Life Technologies), without selection reagents, and 0.6uL of NucView caspase reagent (Essen Bioscience) was added to each mL of cells, per manufacturer guidelines. A total volume of 0.1mL cells were added to appropriate wells of a
15 clear, 96-well flat-bottom plate (BD Falcon). PS3B27 (CD3xPSMA), CD3B288 (CD3xNull) or PS3B46 (PSMAxNull) Bispecific antibodies were prepared at 2X final concentration in Phenol Red free RPMI, prepared as indicated above, and 0.1mL of compounds were added to each well. After 30 minute incubation at room temperature to minimize cell aggregation at the edge of wells, plates were transferred to the Zoom Incucyte instrument (Essen Bioscience). The Incucyte
20 Instrument resides in a humidified incubator set at 37°C, 5% CO₂.

Processing definitions on the Incucyte were designed for each cell line tested, per manufacture guidelines. Measurements were taken every six hours, until a plateau in the caspase signal was observed, and followed by three or more successive decreases from the maximum signal in the well(s) containing the highest concentration of the test compound(s). As the data
25 shows in **Fig. 17**, the curves for PS3B80, PS3B79, PS3B89, PS3B90, PS3B63, and PS3B72 are left shifted indicating increased potency over PS3B27. The null arm controls did not induce cell death as expected.

3-4 Anti-tumor efficacy in tumorigenesis prevention of LnCaP xenografts in humanized NSG mice

Efficacy of PS3B79 and PS3B90 was evaluated in established 3D LnCaP AR.TB human prostate cancer xenografts in male NOD.Cg-Prkdc^{scid} Il2rg^{tm1Wjl}/SzJ (NSG) mice humanized intraperitoneally (*ip*) with human T cells. PS3B79 and PS3B90 at 2.5 and 5 mg/kg or Null×CD3B376 antibody control was dosed *q3d-q4d* on Days 36, 39, 43, 47, 50, 53, 56, 60, and 63 for a total of 8 doses. On day 53 post-tumor implant, which was the last date of the study when nine (9) animals remained per group, tumor growth inhibition (%TGI) was calculated. Statistically significant tumor growth inhibition was observed for PS3B79 at 5 mg/kg with 42% TGI (Two-way ANOVA with Bonferroni test, **p*<0.0001, **Fig. 21**), and for PS3B90 at 2.5 and 5 mg/kg with 53% and 33% respectively compared to Null×CD3 control (Two-way ANOVA with Bonferroni test, **p*<0.001, **Fig. 22**). Thus, CD3B376 is able to induce T cell activation and cytotoxicity in vivo and result in tumor growth inhibition in a bispecific format with high affinity PSMA binding arms, PSMB360 and PSMB365.

4 Preparation and Functional Evaluation of IL1RAP×CD3 Bispecific Antibodies

IL1RAP monoclonal antibodies used in and suitable for use in the bispecific antibodies of the present disclosure are described in U.S. Patent Application Publication No. 20170121420A1, the disclosure of which is hereby incorporated by reference in its entirety. Fifteen monospecific IL1RAP antibodies (see Table 6 of US20170121420A1) were expressed as IgG4, having Fc substitutions S228P, L234A, and L235A. CD3 parental mAbs were expressed as IgG4 with S228P, L234A, L235A, F405L, and R409K (numbering according to EU index). A monospecific anti-CD3 antibody CD3B220 was also generated comprising the VH and VL regions having the VH of SEQ ID NO: 92 and the VL of SEQ ID NO: 93 and IgG4 constant region with S228P, L234A, L235A, F405L, and R409K substitutions.

The monospecific antibodies were purified using standard methods using a Protein A column. After elution, the pools were neutralized to pH 7 and dialyzed into 1xD-PBS, pH 7.2.

Bispecific IL1RAP×CD3 antibodies were generated by combining a monospecific CD3 mAb (CD3B376: VH of SEQ ID NO: 652 and VL of SEQ ID NO: 661; or CD3B450: VH of

SEQ ID NO: 657 and VL of SEQ ID NO: 678) and a monospecific IL1RAP mAb through controlled Fab-arm exchange (as described in WO2011/131746). Briefly, at about 1-20 mg/mL at a molar ratio of 1.08:1 of anti-IL1RAP/anti-CD3 antibody in DPBS, pH 7-7.4 and 75 mM 2-mercaptoethanolamine (2-MEA) were mixed together and incubated at 25-37° C. for 2-6 hours, followed by removal of the 2-MEA via dialysis, diafiltration, tangential flow filtration to remove the reductant and enable bispecific antibody formation.

Heavy and light chains for the IL1RAP×CD3 bispecific antibodies are shown below in Table 34.

Table 34. CDR sequences of 15 IL1RAP mAbs selected for generation of IL1RAP×CD3 bispecific antibodies (SEQ ID NOs in parentheses).

ID	HC-CDR1	HC-CDR2	HC-CDR3	LC-CDR1	LC-CDR2	LC-CDR3
IAPB47	GYSFTSYW	IYPSDSYT	ARRNSAENY ADLDY	QSIEND	YAS	QQSFTAPLT
	(152)	(153)	(154)	(155)	(156)	(157)
IAPB38	GFTFSNYA	INYGGGSK	AKDYGPFAL DY	QSVDDW	TAS	QQYHHWPL T
	(158)	(159)	(160)	(161)	(162)	(163)
IAPB57	GGSISSSTY Y	IYFTGST	AKEDDSSGY YSFDY	QGISSY	AAS	QQVNSYPLT
	(164)	(165)	(166)	(167)	(168)	(169)
IAPB61	GVSISSTY Y	IYFTGNT	GSLFGDYGY FDY	QFISSN	GAS	QQYNNWPS T
	(170)	(171)	(172)	(173)	(174)	(175)
IAPB62	GYTFNTYA	INTNTGNP	ARRYFDWLL GAFDI	QGISSW	AAS	QQANSFPLT
	(176)	(177)	(178)	(179)	(168)	(180)
IAPB3	GGTFSSYA	ISAIFGTA	ARGNSFHAL WDYAFDY	QSVLYSS NNKNY	WAS	QQYYSTPLT
	(181)	(182)	(183)	(184)	(185)	(186)
IAPB17	GGTFSSYA	IPIFGNA	ARTIYLDYV HILDY	QSVLYSS NNKNY	WAS	QQYYSTPLT
	(181)	(187)	(188)	(184)	(185)	(186)

IAPB23	GFTFSNYW	IRYDGGSK	AKDAYPPYS FDY	QSVSSY	DAS	QQRSNWPL T
	(189)	(190)	(191)	(192)	(193)	(194)
IAPB25	GFTFSSYA	ISGSGGST	AKGDEYYY DPLDY	QSISSY	AAS	QQSYSTPLT
	(195)	(196)	(197)	(198)	(168)	(199)
IAPB29	GFTFSNYA	ISGSGGST	AKEWSSYFG LDY	QSISSY	AAS	QQSYSTPLT
	(158)	(196)	(200)	(198)	(168)	(199)
IAPB9	GGTFSSYA	ISPIFGTA	ARRYDNFAR SGDL DY	QSISSY	AAS	QQSYSTPLT
	(181)	(201)	(202)	(198)	(168)	(199)
IAPB55	GVSISSTY Y	IYFTGNT	GSLFGDYGY FDY	QFISSN	GAS	QQYNNWPF T
	(170)	(171)	(172)	(173)	(174)	(203)
IAPB63	GYTFNTYA	INTNTGNP	ARRYFDWLL GAFDI	SSDVGDY NY	DVS	ASYAGNYN VV
	(176)	(177)	(178)	(204)	(205)	(206)
IAPB64	GYTFNTYA	INTNTGNP	ARRYFDWLL GAFDI	SSDVGDY NY	DVS	SSYAGNYN VV
	(176)	(177)	(178)	(204)	(205)	(207)
IAPB65	GGTFSSYA	ISAIFGTA	ARHLHNAIH LDY	QSVSNF	GAS	QQGKHWPW T
	(181)	(182)	(208)	(209)	(174)	(210)

VH and VL sequences of the 15 IL1RAP mAbs are shown below in Table 35.

Table 35. VH and VL sequences of IL1RAP mAbs for generation of IL1RAP×CD3 bispecific antibodies.

ID	VH Amino Acid Sequence	SEQ ID NO:	VL Amino Acid Sequence	SEQ ID NO.
IAPB47	EVQLVQSGAEVKKPGESLK ISCKGSGYSFTSYWIGWVR QMPGKGLEWMGIIYPSDSY TRYSPSFQGQVTISADKSIST	211	EIVLTQSPGTLSPGERA TLSCRASQSI SNDLNWYQ QKPGKAPKLLIYYASSLQ SGVPSRFSGSGSGTDFTLT	212

	AYLQWSSLKASDTAMYCY ARRNAENYADLDYWGQG TLVTVSSASTKGPSVFPLAP CSRSTSESTAALGCLVKDYF PEPVTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVVTVP SSSLGKTKYTCNVDPKPSN TKVDKRVESKYGPPCPPCP APEAAGGPSVFLFPPKPKDT LMISRTPEVTCVVVDVSQ DPEVQFNWYVDGVEVHNA KTKPREEQFNSTYRVVSVL TVLHQDWLNGKEYKCKV NKGLPSSIEKTISKAKGQPR EPQVYTLPPSQEEMTKNQV SLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDG SFFLYSRLTVDKSRWQEGN VFSCSVMEALHNHYTQKS LSLSLGK		INSLQPEDFATYYCQQSFT APLTFGQGTKVEIKRTVA APSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVT EQDSKDYSLSSSTLTLSK ADYEEKHKVYACEVTHQG LSSPVTKSFNRGEC	
IAPB38	EVQLLESGGGLVQPGGSLR LSCAASGFTFSNYAMNWV RQAPGKGLEWVSGINYGG GSKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAV YYCAKDYGPFALDYWGQG TLVTVSSASTKGPSVFPLAP CSRSTSESTAALGCLVKDYF PEPVTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVVTVP SSSLGKTKYTCNVDPKPSN TKVDKRVESKYGPPCPPCP APEAAGGPSVFLFPPKPKDT LMISRTPEVTCVVVDVSQ DPEVQFNWYVDGVEVHNA KTKPREEQFNSTYRVVSVL TVLHQDWLNGKEYKCKV NKGLPSSIEKTISKAKGQPR EPQVYTLPPSQEEMTKNQV SLTCLVKGFYPSDIAVEWES	213	EIVLTQSPATLSLSPGERA TLSCRASQSVDDWLAWY QQKPGQAPRLLIYTASNR ATGIPARFSGSGSGTDFTL TISSLEPEDFAVYYCQQY HHWPLTFGQGTKVEIKRT VAAPSVFIFPPSDEQLKSG TASVVCLLNNFYPREAKV QWKVDNALQSGNSQESV TEQDSKDYSLSSSTLTLS KADYEEKHKVYACEVTHQ GLSSPVTKSFNRGEC	214

	NGQPENNYKTTTPVLDSGDG SFFLYSRLTVDKSRWQEGN VFSCSVMHEALHNHYTQKS LSLSLGK			
IAPB57	QLQLQESGPGLVKPSETLSL TCTVSGGSISSSTYYWGWIR QPPGKGLEWIGSIYFTGSTD YNPSLKSRSISVDTSKNQF SLKLSSVTAADTAVYYCAK EDDSSGYYSFDYWGGQGNL VTVSSASTKGPSVFPLAPCS RSTSESTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFP AVLQSSGLYSLSSVVTVPSS SLGTKTYTCNVDPHKPSNTK VDKRVESKYGPPCPPCPAPE AAGGSPVFLFPPKPKDTLMI SRTPEVTCVVVDVSQEDPE VQFNWYVDGVEVHNAKTK PREEQFNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKGL LPSSIEKTISKAKGQPREPQV YTLPPSQEEMTKNQVSLTC LVKGFYPSDIAVEWESNGQ PENNYKTTTPVLDSGDG SFFLYSRLTVDKSRWQEGN VFSCSVMHEALHNHYTQKS LSLSLGK	215	DIQLTQSPSFLSASVGDRV TITCRASQGISSYLAWYQ QKPGKAPKLLIYAASLTQ SGVPSRFSGSGSGTEFTLT ISSLQPEDFATYYCQQVN SYPLTFGGGKVEIKRTV AAPS VFIFPPSDEQLKSGT ASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVT EQDSKDSTYSLSTLTLSK ADYEKHKVYACEVTHQG LSSPVTKSFNRGEC	216
IAPB61	QLQLQESGPGLVKPSETLSL TCTVSGVSISSSTYYWGWL RQPPGMGLEWTGSIYFTGN TYYNPSLKSRSVTISVDTSRN QFSLKLSSVTAADTAVYYC GSLFGDYGFDYWGGQTL VTVSSASTKGPSVFPLAPCS RSTSESTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFP AVLQSSGLYSLSSVVTVPSS SLGTKTYTCNVDPHKPSNTK	217	EIVMTQSPATLSVPPGERA TLSCRASQFISSNLAWYQ QKPGQAPRLLIYGASTRA TGIPARFSGSGSGTDFTLTI SSLQSEDFAVYYCQQYNN WPSTFGPGTKVDIKRTVA APSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVT EQDSKDSTYSLSTLTLSK ADYEKHKVYACEVTHQG	218

	VDKRVESKYGPPCPPCPAPE AAGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSQEDPE VQFNWYVDGVEVHNAKTK PREEQFNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKG LPSSIEKTISKAKGQPREPQV YTLPPSQEEMTKNQVSLTC LVKGFYPSDIAVEVVESNGQ PENNYKTPPVLDSDGSFFL YSRLTVDKSRWQEGNVFSC SVMHEALHNHYTQKSLSLS LGK		LSSPVTKSFNRGEC	
IAPB62	QVQLVQSGSELKKPGASVK VSCKASGYTFNTYAMNWV RQAPGQGLEWMGWINTNT GNPTYAQGFTGRFVFSLDT SVSTAYLQISSLKAEDTAVY YCARRYFDWLLGAFDIWG QGTMVTVSSASTKGPSVFP LAPCSRSTSESTAALGCLVK DYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVV TVPSSSLGKTYTCNVDPHK PSNTKVDKRVESKYGPPCP PCPAPEAAGGPSVFLFPPKP KDTLMISRTPEVTCVVVDV SQEDPEVQFNWYVDGVEV HNAKTKPREEQFNSTYRVV SVLTVLHQDWLNGKEYKC KVSNGKLPSSIEKTISKAKG QPREPQVYTLPPSQEEMTK NQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTPPVLD SDGSFFLYSRLTVDKSRWQ EGNVFSCSVMHEALHNHYT QKSLSLSLGK	219	DIQMTQSPSSVSASVGDR VTITCRASQGISSWLAWY QQKPGKAPKLLIYAASSL QSGVPSRFSGSGSGTDFTL TISSLQPEDFATYYCQQA NSFPLTFGGGTKVEIKRTV AAPSVFIFPPSDEQLKSGT ASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVT EQDSKDISTYLSSTLTLSK ADYEEKHKVYACEVTHQG LSSPVTKSFNRGEC	220
IAPB3	QVQLVQSGAEVKKPGSSVK VSCKASGGTFSSYAISWVR	221	DIVMTQSPDSLAVSLGER ATINCKSSQSVLYSSNNK	222

	QAPGQGLEWMGGISAIFGT ANYAQKFQGRVTITADEST STAYMELSSLRSEDVAVYY CARGNSFHALWDYAFDYW GQGTLLTVSSASTKGPSVFP LAPCSRSTSESTAALGCLVK DYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVV TVPSSSLGKTYTCNVDPHK PSNTKVDKRVESKYGPPCP PCPAPEAAGGPSVFLFPPKP KDTLMISRTPEVTCVVVDV SQEDPEVQFNWYVDGVEV HNAKTKPREEQFNSTYRVV SVLTVLHQDWLNGKEYKC KVSNGKLPSSIEKTISKAKG QPREPQVYTLPPSQEEMTK NQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTPPVLD SDGSFFLYSRLTVDKSRWQ EGNVFSCSVMEALHNHYT QKSLSLSLGK		NYLAWYQQKPGQPPKLLI YWASTRESGVPDRFSGSG SGTDFTLTISSLQAEDVAV YYCQQYYSTPLTFGQGTK VEIKRTVAAPSVFIFPPSD EQLKSGTASVCLLNNFY PREAKVQWKVDNALQSG NSQESVTEQDSKDYSL SSTLTLSKADYEKHKVYA CEVTHQGLSSPVTKSFNR GEC	
IAPB17	QVQLVQSGAEVKKPGSSVK VSCKASGGTFSSYAISWVR QAPGQGLEWMGGIPIFGN ANYAQKFQGRVTITADEST STAYMELSSLRSEDVAVYY CARTIIYLDYVHILDYWGQ GTLTVTVSSASTKGPSVFPLA PCSRSTSESTAALGCLVKDY FPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVTV PSSSLGKTYTCNVDPHKPS NTKVDKRVESKYGPPCPPC PAPEAAGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSQ EDPEVQFNWYVDGVEVHN AKTKPREEQFNSTYRVVSV LTVLHQDWLNGKEYKCKV SNKGLPSSIEKTISKAKGQP	223	DIVMTQSPDSLAVSLGER ATINCKSSQSVLYSSNNK NYLAWYQQKPGQPPKLLI YWASTRESGVPDRFSGSG SGTDFTLTISSLQAEDVAV YYCQQYYSTPLTFGQGTK VEIKRTVAAPSVFIFPPSD EQLKSGTASVCLLNNFY PREAKVQWKVDNALQSG NSQESVTEQDSKDYSL SSTLTLSKADYEKHKVYA CEVTHQGLSSPVTKSFNR GEC	222

	REPQVYTLPPSQEEMTKNQ VSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTTPVLDS DGSFFLYSRLTVDKSRWQE GNVFSCSVMHEALHNHYT QKSLSLSLGK			
IAPB23	EVQLLESGGGLVQPGGSLR LSCAASGFTFSNYWMNW RQAPGKGLEWVSAIRYDGG SKYYADSVKGRFTISRDN KNTLYLQMNSLRAEDTAV YYCAKDAYPPYSFDYWGQ GTLVTVSSASTKGPSVFPLA PCSRSTSESTAALGCLVKDY FPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVTV PSSSLGKTYTCNVDHKPS NTKVDKRVESKYGPPCPPC PAPEAAGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSQ EDPEVQFNWYVDGVEVHN AKTKPREEQFNSTYRVVSV LTVLHQDWLNGKEYKCKV SNKGLPSSIEKTISKAKGQP REPQVYTLPPSQEEMTKNQ VSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTTPVLDS DGSFFLYSRLTVDKSRWQE GNVFSCSVMHEALHNHYT QKSLSLSLGK	224	EIVLTQSPATLSLSPGERA TLSCRASQSVSSYLAWYQ QKPGQAPRLLIYDASNRA TGIPARFSGSGSGTDFTLTI SSLEPEDFAVYYCQQRSN WPLTFGQGGTKVEIKRTVA APSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVT EQDSKDYSTYLSSTLTLSK ADYEEKHKVYACEVTHQG LSSPVTKSFNRGEC	225
IAPB25	EVQLLESGGGLVQPGGSLR LSCAASGFTFSSYAMSWVR QAPGKGLEWVSAISGSGGS TYYADSVKGRFTISRDN NTLYLQMNSLRAEDTAVY YCAKGDEYYYPDPLDYWG QGTLVTVSSASTKGPSVFPL APCSRSTSESTAALGCLVKD YFPEPVTVSWNSGALTSGV	226	DIQMTQSPSSLSASVGDR VTITCRASQSISSYLNWYQ QKPGKAPKLLIYAASSLQ SGVPSRFSGSGSGTDFTLT ISSLPEDFATYYCQQSYS TPLTFGQGGTKVEIKRTVA APSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVT	227

	HTFPAVLQSSGLYSLSSVVT VPSSSLGTKTYTCNVDPHKP SNTKVDKRVESKYGPPCPP CPAPEAAGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVS QEDPEVQFNWYVDGVEVH NAKTKPREEQFNSTYRVYS VLTVLHQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQ PREPQVYTLPPSQEEMTKN QVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLD SDGSFFLYSRLTVDKSRWQ EGNVFSCSVMEALHNHYT QKSLSLSLGK		EQDSKDYSLSSSTLTLTK ADYEKHKVYACEVTHQG LSSPVTKSFNRGEC	
IAPB29	EVQLLESGGGLVQPGGSLR LSCAASGFTFSNYAMSWVR QAPGKGLEWVSAISGSGGS TYYADSVKGRFTISRDNK NTLYLQMNSLRAEDTAVY YCAKEWSSYFGLDYWGQG TLVTVSSASTKGPSVFPLAP CSRSTSESTAALGCLVKDYF PEPVTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVVTVP SSSLGTKTYTCNVDPHKPSN TKVDKRVESKYGPPCPPCP APEAAGGPSVFLFPPKPKDT LMISRTPEVTCVVVDVSQE DPEVQFNWYVDGVEVHNA KTKPREEQFNSTYRVVSVL TVLHQDWLNGKEYKCKVVS NKGLPSSIEKTISKAKGQPR EPQVYTLPPSQEEMTKNQV SLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDG SFFLYSRLTVDKSRWQEGN VFSCSVMEALHNHYTQKS LSLSLGK	228	DIQMTQSPSSLSASVGDR VTITCRASQSISSYLNWYQ QKPGKAPKLLIYAASSLQ SGVPSRFSGSGSGTDFTLT ISSLPEDFATYYCQSYS TPLTFGGGTKVEIKRTVA APSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVT EQDSKDYSLSSSTLTLTK ADYEKHKVYACEVTHQG LSSPVTKSFNRGEC	227

IAPB9	QVQLVQSGAEVKKPGSSVK VSCKASGGTFSSYAISWVR QAPGQGLEWMGWISPIFGT ANYAQKFQGRVTITADEST STAYMELSSLRSEDNAVYY CARRYDNFARSGDLDYWG QGTLVTVSSASTKGPSVFPL APCSRSTSESTAALGCLVKD YFPEPYTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVT VPSSSLGTKTYTCNVDHKP SNTKVDKRVESKYGPPCPP CPAPEAAGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVS QEDPEVQFNWYVDGVEVH NAKTKPREEQFNSTYRVVS VLTVLHQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQ PREPQVYTLPPSQEEMTKN QVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLD SDGSFFLYSRLTVDKSRWQ EGNVFSCSVMHEALHNHYT QKSLSLSLGK	229	DIQMTQSPSSLSASVGDR VTITCRASQSISSYLNWYQ QKPGKAPKLLIYAASSLQ SGVPSRFSGSGSGTDFLT ISSLPEDFATYYCQQSYS TPLTFGQGTKVEIKRTVA APSVFIFPPSDEQLKSGTA SVVCLLNNFYPPREAKVQ WKVDNALQSGNSQESVT EQDSKDYSTYLSSTLTLSK ADYEKHKVYACEVTHQG LSSPVTKSFNRGEC	227
IAPB55	QLQLQESGPGLVKPSSETLSL TCTVSGVSISSSTYYWGWL RQPPGMGLEWTGSIYFTGN TYYNPSLKSRTISVDTSRN QFSLKLSSVTAADNAVYYC GSLFGDYGYFDYWQGTL VTVSSASTKGPSVFPLAPCS RSTSESTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFP AVLQSSGLYSLSSVVTVPSS SLGTKTYTCNVDHKPSNTK VDKRVESKYGPPCPPCPAPE AAGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSQEDPE VQFNWYVDGVEVHNAKTK PREEQFNSTYRVVSVLTVL	633	EIVMTQSPATLSVSPGERA TLSCRASQFISSNLAWYQ QKPGQAPRLLIYGASTRA TGIPARFSGSGSGTDFLTI SSLQSEDFAVYYCQQYNN WPFTFGPGHCVDIKRTVA APSVFIFPPSDEQLKSGTA SVVCLLNNFYPPREAKVQ WKVDNALQSGNSQESVT EQDSKDYSTYLSSTLTLSK ADYEKHKVYACEVTHQG LSSPVTKSFNRGEC	230

	HQDWLNGKEYKCKVSNKG LPSSIEKTISKAKGQPREPQV YTLPPSQEEMTKNQVSLTC LVKGFYPSDIAVEWESNGQ PENNYKTTTPVLDSDGSFFL YSRLTVDKSRWQEGNVFSC SVMHEALHNHYTQKSLSLS LGK			
IAPB63	QVQLVQSGSELKKPGASVK VSCKASGYTFNTYAMNWV RQAPGQGLEWMGWINTNT GNPTYAQGFTGRFVFSLD SVSTAYLQISSLKAEDTAVY YCARRYFDWLLGAFDIWG QGTMTVTVSSASTKGPSVFP LAPCSRSTSESTAALGCLVK DYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVV TVPSSSLGTKTYTCNV DHKPSNTKVDKRVESKYGPPCP PCPAPEAAGGPSVFLFPPKP KDTLMISRTPEVTCVVVDV SQEDPEVQFNWYVDGVEV HNAKTKPREEQFNSTYRVV SVLTVLHQDWLNGKEYKC KVSNGKLPSSIEKTISKAKG QPREPQVYTLPPSQEEMTK NQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTTPVLD SDGSFFLYSRLTVDKSRWQ EGNVFSCSVMHEALHNHYT QKSLSLSLGK	219	QSALTQPRSVSGSPGHSV TISCTGTSSDVGDYNYVS WYQQRPGKVPKLLIYDVS KRPSGVPDRFSGSKSGNT ASLTISGLQAEDEAIYFCA SYAGNYNVVFGGGTKLT VLGQPKAAPSVTLFPPSSE ELQANKATLVCLISDFYP GAVTVAWKADSSPVKAG VETTTPSKQSNKYAASS YLSLTPEQWKSHRSYSCQ VTHEGSTVEKTVAPTECS	231
IAPB64	QVQLVQSGSELKKPGASVK VSCKASGYTFNTYAMNWV RQAPGQGLEWMGWINTNT GNPTYAQGFTGRFVFSLD SVSTAYLQISSLKAEDTAVY YCARRYFDWLLGAFDIWG QGTMTVTVSSASTKGPSVFP	219	QSALTQPRSVSGSPGHSV TISCTGTSSDVGDYNYVS WYQQRPGKVPKLLIYDVS KRPSGVPDRFSGSKSGNT ASLTISGLQAEDEAIYFCS SYAGNYNVVFGGGTKLT VLGQPKAAPSVTLFPPSSE	232

	LAPCSRSTSESTAALGCLVK DYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVV TVPSSSLGKTYTCNVDP PSNTKVDKRVESKYGPPCP PCPAPEAAGGPSVFLFPPKP KDTLMISRTPEVTCVVVDV SQEDPEVQFNWYVDGVEV HNAKTKPREEQFNSTYRVV SVLTVLHQDWLNGKEYKC KVSNGKLPSSIEKTISKAKG QPREPQVYTLPPSQEEMTK NQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLD SDGSFFLYSRLTVDKSRWQ EGNVFSCSVMHEALHNHYT QKSLSLSLGK		ELQANKATLVCLISDFYP GAVTVAWKADSSPVKAG VETTTPSKQSNNKYAASS YLSLTPEQWKSHRSYSCQ VTHEGSTVEKTVAPTECS	
IAPB65	QVQLVQSGAEVKKPGSSVK VSCKASGGTFSSYAISWVR QAPGQGLEWMGGISAIFGT ANYAQKFQGRVTITADEST STAYMELSSLRSEDYAVYY CARHLHNAIHLDYWGQGT LVTVSSASTKGPSVFPLAPC SRSTSESTAALGCLVKDYFP EPVTVSWNSGALTSGVHTF PAVLQSSGLYSLSSVTVPS SSLGKTYTCNVDPKPSNT KVDKRVESKYGPPCPPCPA PEAAGGPSVFLFPPKPKDTL MISRTPEVTCVVVDVSQED PEVQFNWYVDGVEVHNAK TKPREEQFNSTYRVVSVLT VLHQDWLNGKEYKCKVSN KGLPSSIEKTISKAKGQPREP QVYTLPPSQEEMTKNQVSL TCLVKGFYPSDLAVEWESN GQPENNYKTTPPVLDSDGS FFLYSRLTVDKSRWQEGNV FSCSVMHEALHNHYTQKSL	233	EIVLTQSPATLSLSPGERA TLSCRASQSVSNFLAWYQ QKPGQAPRLLIYGASNRA TGIPARFSGSGSGTDFTLTI SSLEPEDFAVYYCQQGKH WPWTFGQGTKVEIKRTV AAPSVFIFPPSDEQLKSGT ASVVCLLNNFYPPREAKVQ WKVDNALQSGNSQESVT EQDSKDSYSLSTLTLSK ADYEKHKVYACEVTHQG LSSPVTKSFNRGEC	234

	SLSLGK			

4-1 Evaluation of IL1RAP bispecific antibodies in a whole blood T cell cytotoxicity assay

Methods: Tumor cell line LAMA-84 was washed with DPBS before incubation with CFSE (resuspended in 150 μ L DMSO and diluted 1:10,000) at 10×10^6 cells/mL of CFSE for 8 minutes at room temperature. Staining was quenched with HI FBS and washed in media before resuspension in complete media at 2×10^5 cells/mL. Equal volumes of whole blood and CFSE-stained tumor cells were combined in each well of a 96-well plate. After the addition of antibody (resuspended in 10 μ L of DPBS) in respective wells, all plates were incubated at 37°C with 5% CO₂ for 48 hours. Undiluted CD25-PE was added directly to each well of whole blood and incubated for 30 minutes at room temperature, protected from light. Cells were then centrifuged at 1500 rpm for 5 minutes and lysed with 200 μ L of multi-specie red lysis buffer, repeated 4 more times. Cells were washed in DPBS once and stained with Live/Dead Near-IR (diluted in DPBS) for 15 minutes (Table 36). Each well was washed and resuspended in FACS buffer before the cells were acquired on a BD FACS CANTO II.

Table 36. Whole Blood T cell cytotoxicity staining panel

Antigen	Channel	Clone	Dilution	Source	Catalog #
CD25	PE	BC96	1:100	Biolegend	302606
CD4	PerCP	RPA-T4	1:100	Biolegend	300528
CD8	APC	HIT8a	1:100	Biolegend	300912
Live/Dead	APC-Cy7	NA*	1:200	Invitrogen	L34976

*NA = not applicable

The cell acquisition on the FACS CANTO II (Becton, Dickinson and Company, Franklin Lakes, NJ) was limited to 1×10^4 tumor cells. Tumor cell death was assessed by gating on FSC and SSC to identify cell populations, then CFSE positive tumor events, and finally Live/Dead Near-IR to assess tumor cytotoxicity. T-cell activation was assessed by gating on FSC and SSC to identify cell populations, CFSE negative events, Near-IR negative events to assess live cells, then CD25 positive cells. The percentage of either dead tumor cells or CD25 positive cells were graphed using GraphPad Prism 6 and analyzed with a non-linear curve fit. Additional statistical

analysis was evaluated in the program “R” to determine population EC₅₀ values using a nonlinear mixed-effects model.

Results: To mimic physiological peripheral whole blood conditions containing sIL1RAP, IC3B19 (IAPB57×CD3B219) and IC3B34 (IAPB57×CD3B376) were evaluated in an *ex vivo* T cell redirection assay utilizing whole blood. Exogenously added IL1RAP⁺ LAMA-84 cell line (2×10⁴ cells/well) was added to healthy control human peripheral whole blood (n=15 donor samples) with IC3B19, IC3B34, and null arm control bispecific antibodies for 48 hours. As shown in **Fig. 53**, IC3B19 and IC3B34 induced similar T-cell mediated cytotoxicity of IL1RAP⁺ LAMA-84 cell line *ex vivo* after 48 hours. The EC₅₀ values for IC3B19 and IC3B34 cytotoxicity, represented **Fig. 53** were 2.097 and 2.762, respectively (Table 37). Similarly, the EC₅₀ values for T-cell activation (CD25) by IC3B19 and IC3B34 represented by **Fig. 54** were 4.237 and 7.825 nM, respectively (Table 38). All of the null arm control bispecific antibodies did not induce detectable levels of cytotoxicity or T-cell activation as shown in **Fig. 53** and **Fig. 54**. The general level of cytotoxicity and T-cell activation were similar between both IC3B19 and IC3B34.

Table 37. IC3B19 and IC3B34 Cytotoxicity EC₅₀ (nM) Concentrations in the LAMA-84 cell line

Effective Concentration (nM)	IC3B19	IC3B34
EC ₅₀	2.097	2.762

Table 38. IC3B19 and IC3B34 T-cell Activation EC₅₀ (nM) Concentrations in the LAMA-84 cell line

Effective Concentration (nM)	IC3B19	IC3B34
EC ₅₀	4.237	7.825

4-2 Evaluation of Cytokine Release by IL1RAP×CD3 Bispecific Abs in a Whole Blood T cell Cytotoxicity Assay at 24 and 48 hours

Methods: Frozen supernatants from 24 hour and 48 hour samples from Example 4-1 were thawed on wet ice. Prior to use, plates were centrifuged at 500 g for 5 minutes at 4°C, then placed back on wet ice. Serial dilutions were prepared in U-bottom 96-well plates (Falcon), using MSD Diluent 2 at 1:2, 1:25, and 1:1000 dilution ratios for ELISA.

While supernatants were being centrifuged, MSD Assay Plates (ProInflammatory Panel I V-Plex, Catalog # K15049G-4, Lot# K008572) were pre-washed per manufacturer's protocol. A standard curve was prepared by reconstituting the provided calibrator in 1.0 mL of MSD Diluent 2. Fifty microliters of each sample or standard was added directly to pre-washed MSD plates.

5 Subsequent incubations and washes were all carried out per manufacturer's protocol. Assay plates were read on the MSD Sector Imager.

Two methods were used to compare response between IC3B19 and IC3B34:

Linear regression with mixed effects

In this method, a linear regression model with fixed effects for compound, dose, and
10 compound by dose interaction and random effects that take into account the paired donors was constructed. Post-hoc comparisons were then between IC3B19 and IC3B34 were made at each concentration and p-values were appropriately adjusted for multiple comparisons.

Non-linear (four-parameter) regression with mixed effects

IC3B19 and IC3B34 were modeled together using a non-linear regression model, with
15 fixed effect parameters for minimum, maximum, logEC50, and slope for each compound, and a random effect term that takes into account paired donor effect. Point estimates and their confidence intervals were extracted and plotted for visual comparison from these separate models. Testing significant differences for each parameter was done by constructing a model that used a joint estimate for the parameter of interest, then comparing that model to the original
20 model using a log-likelihood test. To elaborate, there is a model with parameters for IC3B19 minimum, IC3B19 maximum, IC3B19 logEC50, IC3B19 slope, IC3B34 minimum, IC3B34 maximum, IC3B34 logEC50, and IC3B34 slope. To check whether the minimums are the significantly different, a second model is constructed that has all the same parameter except that there is a single shared parameter for the minimum. The log likelihood (an overall measure of
25 how well the model fits the data) of the first model is compared to the log likelihood of the second model. If they are not significantly different from each other, then we can conclude that the minimums are not significantly different from each other. Similarly, if the log likelihoods are significantly different from one another, then we would conclude that the minimums are significantly different.

30 In a number of cases, models or parameter comparisons were inestimable for one of two reasons: 1. the data was too intractable to calculate the four-parameter logistic regression itself, or

2. the difference between the parameter estimates was so large that is caused the joint model to fail. In the first case, results are not reported and in the summary table they are indicated with "NA". In the second, results are also not reported, but they are indicated in the summary table as "Sig.", as short-hand for significant. As the 95% confidence intervals around these parameters
5 are individually estimable and do not overlap, we can consider them significantly different but the exact p-value is unknown.

Differences are considered statistically significant at p-value less than or equal to 0.05. All analyses were conducted in R, version 3.3.2.

Results: IC3B19 and IC3B34 mediated engagement of T cells and IL1RAP+ target cell
10 line LAMA-84 (endogenous and exogenously added tumor cells) resulted in T cell cytokine release. To determine cytokine release difference between IC3B19 and IC3B34, supernatants were evaluated for 10 pro-inflammatory cytokines from whole blood (n=15 donors) cytotoxicity and T-cell activation assays with exogenous LAMA-84 IL1RAP+ tumor cell line added, as discussed in section example 1. Of the 10 cytokines evaluated, most cytokines resulted in a
15 measurable dose dependent release in response to both IC3B19 and IC3B34, except for IL-8 and IL-12p70. As shown in Table 39, IL-10, IL-2, TNF- α , and INF- γ resulted in the most potent EC50 (nM) release. In addition, the majority of cytokines and at both time points, the IC3B34 molecule resulted in a less potent EC50 (nM) that was statistically significant. The exception were, IL-4 (24 hours), IL-6 (24 and 48 hours), IL-8 (24 and 48 hours), IL-12p70 (24 and 48
20 hours), IL-13 (24 hours), INF- γ (24 and 48 hours), and TNF- α (24 hours), which did not have a statistically significant difference in EC50 (nM) values between IC3B19 and IC3B34.

Table 39. IC3B19 and IC3B34 Four Parameter Logistic Regression Summary Table. Bold text denotes statistical significant difference in EC50 (nM) values between IC3B19 and IC3B34. Results of individual cytokine release experiments are shown in the **Fig. Nos.** indicated.

Cytokine	Fig. No.	Experiment	EC50	Slope	Minimum	Maximum
IL-1beta	Fig. 37	24 hours	0.0027	0.3046	0.0268	0.2033
IL-1beta	Fig. 38	48 hours	0.0010	0.3951	0.2543	0.0528
IL-2	Fig. 39	24 hours	0.0001	0.0256	0.3103	0.6466
IL-2	Fig. 40	48 hours	Sig.	0.2079	0.0158	0.0008
IL-4	Fig. 41	24 hours	0.2415	0.4668	0.2942	0.0043
IL-4	Fig. 42	48 hours	NA	NA	NA	NA
IL-6	Fig. 43	24 hours	Sig.	0.0819	0.1151	0.5224
IL-6	Fig. 44	48 hours	NA	NA	NA	NA

IL-8	Fig. 45	24 hours	NA	NA	NA	NA
IL-8	Fig. 46	48 hours	NA	NA	NA	NA
IL-10	Fig. 47	24 hours	<0.0001	0.0010	0.3406	0.7036
IL-10	Fig. 48	48 hours	<0.0001	0.2702	0.0011	0.0004
IL-12p70	Fig. 49	24 hours	NA	NA	NA	NA
IL-12p70	Fig. 50	48 hours	NA	NA	NA	NA
IL-13	Fig. 51	24 hours	NA	NA	NA	NA
IL-13	Fig. 52	48 hours	0.0106	0.8268	<0.0001	<0.0001
IFN-gamma	Fig. 53	24 hours	0.0065	0.6920	0.4644	0.3179
IFN-gamma	Fig. 54	48 hours	0.0266	0.1678	0.2695	0.0319
TNF-alpha	Fig. 55	24 hours	0.0016	0.0128	0.1443	0.7895
TNF-alpha	Fig. 56	48 hours	0.0004	0.5553	0.0043	0.5216

4-3 Evaluation of IL1RAP bispecific antibodies in a caspase cytotoxicity assay

T-cell mediated killing of IC3B19 and IC3B34 was measured using a second type of cell toxicity assay. The caspase cytotoxicity assay indirectly measures cell killing via cleavage of a fluorescent substrate by active caspase 3/7. Cleavage of the substrate results in a fluorescent DNA dye, with fluorescence restricted to the cell nucleus. Repeated fluorescence measurements are taken in each well throughout the course of the assay, using a motorized 10X objective, capable of precisely imaging well(s) at the same coordinates. Target cell populations are identified based on defined size restrictions.

Frozen Pan CD3+ T-cells (purchased from Biological Specialty Corporation, Colmar, PA) were isolated by negative selection from normal healthy donors. Target cells (NCI-H1975 cells, a human lung adenocarcinoma cell line expressing IL1RAP), were cultured in RPMI 1640/Glutamax (25 mM HEPES buffer) medium supplemented with 10% heat inactivated FBS, 1mM sodium pyruvate, and 0.1 mM non-essential amino acids (Life Technologies).

Target cells were plated at 20,000 cells/well in 50 ul of phenol-red free RPMI media containing supplements 16 hours prior to experiment initiation into tissue culture-treated, clear flat bottom plates (Costar). The cells were allowed to incubate at room temperature (RT) for 20 min to allow for even distribution of cells in the wells, and then the cells were allowed to incubate at 37°C and 5% CO₂ overnight.

On the day of the experiment, T-cells were counted and diluted to 1.0×10^6 cells/ml in phenol red free RPMI media containing supplements and combined with Nuc-View TM488 Caspase-3/7 Substrate (Essen Biosciences) for a working concentration of 10 uM. 100 ul of the combined T-cells and the Caspase-3/7 substrate were added to each well for a final concentration of 5 uM of the Caspase-3/7 substrate.

IC3B19 (IAPB57×CD3B219), IC3B34 (IAPB57×CD3B376), CD3B288 (Null×CD3B219), and IAPB57×Null (IAPB101) bispecific antibodies were prepared at 4X final concentration in phenol red free RPMI media containing supplements and 50 uL of the antibodies were added to each well. After a 20 min incubation at RT to allow for even distribution in the wells, plates were transferred to the Zoom Incucyte instrument (Essen Bioscience). The Incucyte Instrument resides in a humidified incubator set at 37°C, 5% CO₂.

A processing definition on the Incucyte was designed for the NCI-H1975 cells. This processing definition clearly identifies caspase activity of target cells, while excluding the T-cells by size. Measurements were taken at T0 and every six hours for up to 120 hours. The maximum signal was determined to be at 72 hours post treatment at which time the data was analyzed.

After the assay was complete, each plate was analyzed using the NCI-H1975 processing definition. Raw fluorescent data was exported from the Incucyte Zoom software, and pasted into GraphPad Prism (GraphPad Software, Inc., La Jolla, CA). Caspase 3/7 activity was determined by calculating the area under the curve (AUC) for each well in GraphPad. AUC values were plotted as a function of Log₁₀ nM antibody concentrations. The EC₅₀ for each concentration response curve, in nanomolar (nM), was reported following non-linear regression (Sigmoidal dose-response-variable slope). Each assay contained two technical replicates and four measurements within each technical replicate.

Both IC3B19 and IC3B34, but not the bispecific antibodies with null arms (IAPB57×B23B49 or B23B39×CD3B219), induced target specific cytotoxicity in NCI-H1975 cells (**Fig. 57**). In this assay, the cytotoxicity EC₅₀s vary three-fold between IC3B19 and IC3B34, with values of 0.018 and 0.057 nM, respectively.

4-4 Efficacy of IAPB57×CD3B376 in H1975 Human NSCLC Xenografts in T Cell Humanized NSG Mice

Efficacy of IAPB57×CD3B376 bispecific antibody IC3B34 was evaluated in established H1975 human Non-small cell lung cancer (NSCLC) xenografts in female NOD.Cg-Prkdcscid Il2rgtm1 Wjl/SzJ (NSG) mice humanized with human T cells. IAPB57×CD3B376 at 0.1, 0.35 or 1 mg/kg or Null×CD3 antibody control was dosed on Days 14, 18, 21 and 25 for a total of 4 doses. On day 29 post-tumor implant, which was the last date of the study when ten animals remained per group, tumor growth inhibition (% TGI) was calculated. Statistically significant tumor growth inhibition was observed with IAPB57×CD3B376 at 0.35 and 1 mg/kg with 63% and 89% TGI, respectively compared to Null×CD3 control (Two-way ANOVA with Bonferroni test, $p < 0.0001$, **Fig. 58**).

5 CD33 Antibodies

5-1 Antigen Generation

The human and cyno CD33 proteins were produced with or without a mutated monomeric form of human serum albumin (HSA), Uniprot P02768 with a C58S mutation, fused at the C-terminus for immunizations and assays. The cDNAs encoding the CD33 protein antigens with a six-histidine tag (SEQ ID NO: 596) were synthetically synthesized and cloned into a mammalian secretion expression vector under the Actin promoter using standard molecular biology techniques.

The full-length human CD33 extracellular domain (ECD) derived from Uniprot P20138 (SEQ ID NO:235) (human CD33 ECD) was fused at the N-terminus with a signal sequence and with or without the HSA, followed by a six histidine tag (SEQ ID NO: 596) at the C-terminus, (hCD33 ECD with HSA and hCD33 ECD only). The human CD33 ECD expression construct was transiently transfected into HEK293 derived cells, Expi293 (Gibco/Thermo Fisher Scientific; Waltham, MA) using Expifectamine according to manufacturer protocol. Cells were incubated 5 days at 37°C with 8% CO₂ on an orbital shaker before harvesting. The expressed cells were removed by centrifugation and the soluble CD33 was purified from the media using immobilized metal affinity chromatography using Ni Sepharose 6 Fast Flow resin (GE Healthcare; Little Chalfont, United Kingdom) followed by Superdex 200 preparative size

exclusion chromatography (SEC) (GE Healthcare) in Dubelcco's Phosphate Saline buffer pH 7.2 (1x DPBS). SEC elution fractions excluding any disulfide aggregates were combined and sterile filtered to yield the final protein for immunization and CD33 assays. Protein concentration was determined by A280 and quality of purified protein was assessed by SDS-PAGE and analytical SEC (Phenomenex; Torrance, CA). Endotoxin measurements were performed using EndoSafe-PTS Cartridges, a chromogenic LAL assay (Charles River; Wilmington, MA).

The human CD33 ECD subdomain proteins, hCD33 V-domain-HSA, hCD33 V-domain-his, hCD33 C2 domain-HSA, and hCD33 C2 domain-His, were similarly constructed, expressed and purified as the full-length human CD33 ECD.

10 Cyno CD33 constructs for immunization and cross selectivity assays, cyno CD33 ECD-HSA, cyno CD33-His, were also generated based on the Genbank sequence XP_005590138.1. Cyno CD33 protein expression and purification were same as the human CD33 proteins.

The CD33 antigens for screening were biotinylated in 50mM Na Phosphate pH 7.2 using SureLink Chromagenic Biotin Labeling kit (SeraCare KPL) according to manufacturer conditions. Briefly, a biotin stock of 25 mM was added to the CD33 protein at a 4:1 molar ratio of biotin to protein and incubated at room temperature for 30 minutes with gentle rotation and then switched to 4°C for 2 more hours. Unincorporated biotin was removed by buffer exchange into 1x DPBS. Protein concentration and biotin incorporation was determined by measuring at A280 nm and A354 nm using NanoDrop. See Table 40 for the sequences of each of the antigens described above.

Table 40: Antigen Sequences

Protein Name	Protein ID	SEQ ID NO
Cyno CD33 ECD-HSA	C33W1	236
Human CD33 ECD-HSA	C33W2	237
Human CD33-V-HSA	C33W3	238
Human CD33-C2-HSA	C33W4	239
Human CD33-V-His	C33W8	240
Human CD33 C2-His	C33W9	241
Human CD33 ECD-His	C33W49	242
Cyno CD33 ECD-His	C33W50	243

Human CD33 full length		244
Cyno CD33 full length		245

5-2 Generation of CD33 expressing isogenic cell lines

Human and cyno CD33 expressing cell lines were generated using lentivirus (Genecopoeia; Rockville, MD) containing full length human CD33 or cyno CD33 and puromycin for selection of CD33 positive cells. HEK293F cells (ATCC), negative for CD33, were transduced with lentiviral particles to overexpress human CD33 and cyno CD33. Following transduction, cells positively expressing CD33 and the resistance marker, were selected by treating pooled cells, grown in DMEM + 10% HI FBS (Life Technologies; Carlsbad, CA) and supplemented with varying concentrations of Puromycin (Life Technologies).

In addition to the HEK generated cell lines, several commercial cell lines were used for binding and cellular toxicity assays. These included MOLM13, KG1, SH2, OCIAML3 and MV411 and were obtained from either American Type Culture Collection or Deutsche Sammlung von Mikroorganismen und Zellkulturen, and cultured at 37°C, 5% CO₂ in complete RPMI culture media with 10% FBS.

5-3 Immunization Campaigns

OmniRat

A human immunoglobulin transgenic rat strain (OmniRat®; Ligand Pharmaceuticals; San Diego, CA) was used to develop human CD33 monoclonal antibody expressing hybridoma cells. The OmniRat® contains a chimeric human/rat IgH locus (comprising 22 human V_{HS}, all human D and J_H segments in natural configuration linked to the rat C_H locus) together with fully human IgL loci (12 V_{KS} linked to J_K-C_K and 16 V_{LS} linked to J_L-C_L) (see e.g., Osborn, et al. (2013) J Immunol 190(4): 1481-1490). Accordingly, the rats exhibit reduced expression of rat immunoglobulin, and in response to immunization, the introduced human heavy and light chain transgenes undergo class switching and somatic mutation to generate high affinity chimeric human/rat IgG monoclonal antibodies with fully human variable regions. The preparation and

use of OmniRat®, and the genomic modifications carried by such rats, is described in PCT Publication WO 2014/093908 to Bruggemann et al.

When immunized with recombinant human and cynomolgus CD33 (huCD33 ECD-HSA and cyno CD33 ECD-HSA respectively), this transgenic rat produces chimeric human-rat IgG
5 antibodies to human CD33, some of which also bind to cynomolgus CD33.

Eight OmniRats were immunized alternately with huCD33 ECD-HSA and cyno CD33 ECD-HSA. Following a 46 day immunization regimen, lymph nodes from all eight OmniRats were harvested and used to generate hybridomas. Eighty-one 96-well plates of hybridoma supernatants were screened via binding ELISA and AlphaLISA using standard techniques, of
10 which 128 hybridoma supernatants were selected for specific binding to huCD33 ECD-HSA and cyno CD33 ECD-HSA. Most of the 128 supernatants were also positive for binding to cells over-expressing huCD33 or cyCD33.

Six additional OmniRats were immunized with rhuCD33 only. Following a 31 day immunization regimen, lymph nodes from all six OmniRats were harvested and used to generate
15 hybridomas. Thirty 96-well plates of hybridoma supernatants were screened via binding ELISA using standard techniques, of which 94 hybridoma supernatants were selected for specific binding to huCD33 ECD-HSA and cyno CD33 ECD-HSA. Hybridoma lysates were prepared from the positive clones and progressed to v region cloning described below.

OmniMouse

20 A human immunoglobulin transgenic mouse strain (OmniMouse ®; Ligand Pharmaceuticals) was used to develop human CD33 monoclonal antibody expressing hybridoma cells. The OmniMouse® contains chimeric human/rat IgH loci together with fully human IgL loci. The mice exhibit reduced expression of mouse immunoglobulin, and in response to immunization, the introduced human heavy and light chain transgenes undergo class switching
25 and somatic mutation to generate high affinity chimeric human/rat IgG monoclonal antibodies with fully human variable regions.

When immunized with recombinant human and cynomolgus CD33 (huCD33 ECD-HSA and cyno CD33 ECD-HAS respectively), this transgenic mouse produces chimeric human/rat IgG antibodies to human CD33, some of which also bind to cynomolgus CD33.

Four OmniMice were immunized alternately with huCD33 ECD-HSA and cyno CD33 ECD-HSA. Following a 53 day immunization regimen, spleens and lymph nodes from all four OmniMice were harvested and used to generate hybridomas. Forty-eight 96-well plates of hybridoma supernatants were screened via binding ELISA and AlphaLISA, of which 8
5 hybridoma supernatants were selected for specific binding to huCD33 ECD-HSA and cyno CD33 ECD-HSA. Hybridoma lysates were prepared from the positive clones and progressed to v region cloning described below.

V Region Cloning

Total RNA from hybridoma cell lysates was purified using RNeasy 96 kit (Qiagen;
10 Hilden, Germany) following the manufacturer's protocol, and the resulting RNA was quantitated using Drop Sense and stored at -80°C or cDNA was synthesized using Invitrogen SuperScript III First-Strand Synthesis System for RT-PCR (Invitrogen; Carlsbad, CA). The first strand cDNA Synthesis was carried out using gene specific primers annealed to the constant regions of heavy, kappa, and lambda chains, respectively. The RT-PCR reaction mixture is comprised of up to 3
15 µg of purified RNA, gene specific primer, dNTP mix, reaction buffer, 25 mM MgCl₂, DTT, RNaseOUT™ (40 U/µl, Invitrogen), and SuperScript™ III RT (200 U/µl, Invitrogen Cat# 18080-051), and incubate at 50°C for 50 minutes and 85°C for 5 minutes. The resulting single-stranded cDNA was stored at -20°C, or the single-stranded DNA was PCR amplified. The PCR reaction was carried out using Platinum Pfx polymerase (Invitrogen). The v-region fragments
20 were amplified by forward and reverse primers annealing to the leader sequences and constant regions of heavy, kappa and lambda chains, respectively, using optimized PCR conditions. The resulting PCR fragments were run on the gel and sequenced using pre-designed primers to obtain v-region sequences. The resulting .abi files of v-region sequences were collected and analyzed by the Sanger v-region sequence analysis program created at Janssen Biologics Discovery. The
25 AA sequences of the recovered v-regions were registered in the internal database, codon optimized and cloned into the pUnder-based expression vector carrying the appropriate constant region of the desired human antibody isotype: IgG1 F405L and IgG4 PAA. A total of 76 OMNIRat antibodies and 8 OMNIMouse antibodies were successfully cloned and proceeded for further characterization. The tables below summarize the sequences from the top 32 identified in
30 the OMNIRat campaigns (see Table 41) and the 8 identified in the OMNIMouse campaign (see

Table 42) with several of the OMNIRat antibodies cloned into IgG1 as well as IgG4 PAA and all from the OMNIMouse campaign were cloned into both IgG1 and IgG 4 PAA.

Table 41: Antibody sequences identified via CD33 immunization in OMNIRat

mAb	HC ID	HC Isotype	LC ID
C33B46	C33H108	hulgG1F405L	C33L74
C33B48	C33H80	hulgG1F405L	C33L73
C33B52	C33H42	hulgG1F405L	C33L8
C33B54	C33H44	hulgG1F405L	C33L10
C33B55	C33H45	hulgG1F405L	C33L11
C33B56	C33H46	hulgG1F405L	IAPL24
C33B61	C33H48	hulgG1F405L	C33L58
C33B62	C33H49	hulgG1F405L	C33L59
C33B63	C33H51	hulgG1F405L	C33L34
C33B64	C33H52	hulgG1F405L	N46L109
C33B66	C33H55	hulgG1F405L	C33L42
C33B72	C33H65	hulgG1F405L	C33L47
C33B73	C33H66	hulgG1F405L	C33L60
C33B75	C33H70	hulgG1F405L	N46L109
C33B77	C33H72	hulgG1F405L	C33L40
C33B79	C33H74	hulgG1F405L	C33L38
C33B80	C33H76	hulgG1F405L	C33L39
C33B82	C33H78	hulgG1F405L	C33L57
C33B83	C33H81	hulgG1F405L	C33L53
C33B87	C33H87	hulgG1F405L	C33L35
C33B88	C33H88	hulgG1F405L	C33L61
C33B89	C33H90	hulgG1F405L	C33L51
C33B94	C33H98	hulgG1F405L	C33L69
C33B95	C33H98	hulgG1F405L	IAPL24
C33B96	C33H99	hulgG1F405L	C33L37
C33B101	C33H69	hulgG1F405L	C4LL152
C33B107	C33H68	hulgG1F405L	C33L17
C33B120	C33H87	hulgG1F405L	C33L41
C33B122	C33H92	hulgG1F405L	C33L30
C33B123	C33H91	hulgG1F405L	C33L44
C33B124	C33H73	hulgG1F405L	C33L32
C33B125	C33H84	hulgG1F405L	C33L66
C33B760	C33H45	hulgG4 PAA	C33L11
C33B777	C33H65	hulgG4 PAA	C33L47
C33B778	C33H66	hulgG4 PAA	C33L60
C33B782	C33H72	hulgG4 PAA	C33L40
C33B792	C33H87	hulgG4 PAA	C33L35
C33B799	C33H98	hulgG4 PAA	C33L69
C33B806	C33H69	hulgG4 PAA	C4LL152
C33B830	C33H84	hulgG4 PAA	C33L66
C33B836	C33H80	hulgG4 PAA	C33L73
C33B937	C33H66	hulgG4 PAA	C33L132

HC: Heavy Chain; LC: Light Chain

Table 42: Antibody sequences identified via CD33 immunization in OMNIMouse

mAb	HC ID	LC ID
C33B901	C33H249	C33L115
C33B902	C33H250	C33L116
C33B903	C33H251	C33L117
C33B904	C33H252	C33L118
C33B905	C33H253	C33L119
C33B906	C33H254	C33L120
C33B907	C33H255	C33L121
C33B908	C33H256	C33L122
C33B909	C33H249	C33L115
C33B910	C33H250	C33L116
C33B911	C33H251	C33L117
C33B912	C33H252	C33L118
C33B913	C33H253	C33L119
C33B914	C33H254	C33L120
C33B915	C33H255	C33L121
C33B916	C33H256	C33L122

HC: Heavy Chain; LC: Light Chain

5-4 Expi293 Small Scale Transfection and Purification

Antibodies identified in the immunization campaigns and subsequent v region cloning
 5 (into IgG1 F405L and IgG4 PAA) were expressed and purified via small 2 ml scale. Expi293™
 cells (ThermoFisher Scientific) were seeded at $1.25 \times 10^5 - 2.25 \times 10^5$ viable cells/mL density in
 Expi293™ Expression Medium and cultured in polycarbonate, disposable, sterile, vented, non-
 baffled Erlenmeyer shake flasks in a 37°C, 7% CO₂ shaker incubator (INFORS HT Multitron
 Pro). For routine cell growth in 125 mL – 2L shake flasks, the shake speed was set to 130 rpm
 10 for shakers with a 19mm shaking diameter. Cells were sub-cultured when density reached log
 phase growth at $3 \times 10^6 - 5 \times 10^6$ viable cells/mL with a 98-99% viability.

On day of transfection, the viable cell density and percent viability was determined. Cells
 were transfected at a density of 3×10^6 viable cells/mL. For optimal transfection, sterile Heavy
 and Light Chain plasmid DNA at 0.1 mg/mL concentration in TE buffer (10mM Tris-HCl, 1mM
 15 EDTA, pH 8.0) is used.

Expi293™ cells were transfected following manufacturer's Transfection protocol
 (ThermoFisher Publication Number MAN0007814). Transfection was performed in 24-well
 deepwell plates (GE Healthcare). Briefly, plasmid DNA was diluted with 0.1mL OptiMEM™
 medium (ThermoFisher Scientific) at the following ratio: 0.250 µg Heavy Chain DNA: 0.750 µg

Light Chain DNA : 0.5 µg pAdvantage. 5µL of ExpiFectamine™ 293 Transfection Reagent was diluted and mixed gently with 95µL OptiMEM™ medium and incubated for 1 min. The diluted ExpiFectamine™ 293 Reagent was added to the diluted DNA, mixed gently and the ExpiFectamine™ 293/plasmid DNA complexes were incubated at room temperature for 40
5 minutes. Post-incubation, 1.8mL Expi293™ cells were added to the complexes incubated overnight in a 37°C, 7% CO₂ shaker incubator.

On Day 1 post-transfection, 10µL ExpiFectamine™ 293 Enhancer 1 and 100µL Expifectamine 293™ Enhancer 2 were added and the plates were returned to the incubator for an additional 5 days. The culture was harvested on day 6 post-transfection by centrifugation at
10 850xG for 15 minutes before purification.

1.7 mls of clarified expression supernatants prepared above were transferred to a new 96
2ml deepwell plate. Purification plates were prepared by pipetting 800 µl of a 1:4 mix of
MabSelect SuRe (GE Healthcare) and DPBS +/- slurry into every well of a 96 well Acroprep
Advance 1 µm glass filter plate (Pall). 200 mbar of vacuum pressure was applied to the plate to
15 remove excess PBS and subsequently washed with 800 µl fresh PBS. 200 mbar vacuum
pressure was applied to remove the wash buffer. The clarified supernatants were then transferred
to the PBS washed resin, mixed gently and incubated for 15 minutes. Following the incubation,
200 mbar vacuum pressure was applied to remove the supernatant. The MabSelect SuRe was
washed three times with PBS and once with 25 mM Sodium Acetate, pH 5 (TEKNOVA;
20 Hollister, CA) with 200 mbar vacuum pressure applied between washes to remove excess buffer.
mAbs bound to the resin were eluted using 0.1 M Sodium Acetate, pH 3.5 and incubated for 10
minutes for effective dissociation. The filter plate was placed atop a 96 deepwell plate and the
eluted mAbs were collected in the bottom plate via centrifugation at 1000 g for 2 minutes. 80 µl
of 2.5 M Tris-Acetate, pH 7.2 was added to neutralize the mAbs. The mAbs were dialyzed into
25 PBS overnight in a 96 well DispoDIALYZER plate (Harvard Apparatus; Holliston, MA),
transferred to a 96 well Acroprep Advance 0.2 µm Supor filter plate (Pall; Port Washington,
NY), placed atop a 96 deepwell plate and the protein solutions filtered via centrifugation at 1,500
g for 15 minutes in a desktop centrifuge. Protein concentrations were determined by A280
measurement on the filtrate using a DropSense Instrument (Trinean).

Table 43: CD33 mAb Heavy Chain and Light Chain Variable Regions

HC ID	SEQ ID NO	AMINO ACID SEQUENCE
B23H1	246	QITLKESGPTLVKPTQTLTLTCTFSGFSLSTSGMGVSWIRQPPGKALEWLAHIYWDDDKRYNPS LKSRLTITKDTSKNQVVL TMTNMDPVD TATYYCARLYGFTYGFAYWGQGLTVTVSS
CD3H141	247	EVQLVESGGGLVQPGGSLRLSCAASGFTFTNYAMNWVRQAPGKGLEWVARIRSKYNNYATY YAASVKGRFTISRDDSKNSLYLQMNSLKTEDTAVYYCARHGNFGNSYVSWFAYWGQGLTV VSS
CD3H219	20	QVQLQQSGPRLVRPSQTLSTCAISGDSVFNNNAAWSWIRQSPSRGLEWLGRITYYRSKWLYD YAVSVKSRITVNPDTSRNQFTLQLNSVTPEDTALYYCARGYSSSFYWGQGLTVTVSS
C33H42	248	QLQLQESGPGLVNPSETLSHTCTVSGGSISSSSHYWGWRQPPGKGLEWIGKIYYSGNTYYNPS LKSRVTISIDTSKNQFSLKMSSVTAADTAVYYCARLADV VV VPAARYFDSWGQGLTVTVSS
C33H44	249	QVQLQQSGPGLVKPSQTLSTCAISGDSVSSNSAAWNWIRQSPSRGLEWLGRITYYRSKWYND YAVSVRSRITINPDTSKNQFSLQLNSVTPEDTAVYHCARETMFRGLMDYWGQGLTVTVSS
C33H45	250	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQSPGKGLEWVAVISYDGSNKYCAD SVKGRFTISRDNKSTLYLQMNSLRAEDTAVYYCAKDFRSLDWLPDSTSYDGMVDVWGQGT TVVSS
C33H46	251	QVQLVQSGSELKKPGASVKVSKASGYTFTNYAMNWVRQAPGQGLEWMGWINTNTGNPTY AQFTGRFVFSLDTSVSTAYLQISSLKAEDTAVYYCARDREVRDYWGQGLTVTVSS
C33H48	252	QLQLQESGPGLVKPSETLSLTCTVSGGSIRSTNYWGWRQPPGKGLEWIGTIYYSGNTYYNPS LKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARLADV VV VPAARYFDYWGQGLTVTVSS
C33H49	253	QLQLQESGPGLVKPSETLSLTCTVSGGSIRSSGFYWGWRQPPRKGLEWIGTIYYSGNTYYNPSL KSRVTISVDTSKNQFSLKLSSVTAADTAVYFCARLADV VV VPAARYFDN WGQGLTVTVSS
C33H51	254	QLQLQESGPGLVKPSETLSLTCTVSGGSISTGRYYWGWRQPPGKGVWIGNIYYSGNTYYNPS LKSRVTISVDTSKNQFSLKLNSVTAADTAVYYCARLGS LVV VPAAMSFYWGQGLTVTVSS
C33H52	255	QLQLQESGPGLVKPSETLSLTCTVSGGSIRGSSYYGWVVRQPPGKGLEWIGSIYSSGNTYYNPS LKSRVTISVDTSKNQFSLKLSSVTAADTALYYCARLGS LVV VPAAMSFYWGQGLTVTVSS
C33H55	256	QVQLQESGPGLVKPSGTLSTCAVSGGSISSSNWWSWVRQPPGRGLEWIGEIIYHSGNTNNSPSL KSRVTISADKSKNQFSLKLSSVTAADTAVYFCARIIAVARYFDSWGQGLTVTVSS
C33H65	257	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVVVISYDGSNKYYA DSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKDFRDFDWLPDSTSYHGMDVWGQG TTVTVSS
C33H66	258	QVQLVESGGGVVQPGRSLRLSCVASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYA DSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKDFRSFDWLPPDSASYHGMDVWGQG TTVTVSS
C33H68	259	EVQLLES GGGLVQPGGSLGLSCAASGFTFSGYAMSWVRQAPGKGLNWVSAIDYSGNDTYAD SVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKESQLLHGLFEHWGQGILTVTVSS
C33H69	26	QLQLQESGPGLVKPSETLSLTCTVSGGSISSSSYYWGWRQPPGKGLDWIGSINYSYSTYYNPSL KSRVTISVDTSKIQFSLKLRSVTAADTAVYYCARLDGYESPFDYWGQGLTVTVSS
C33H70	261	QLQLQESGPGLVKPSETLSLTCTVSGGSIRGSSYYWGWRQPPGKGLEWIGSIYSSGNTYYNPSL KSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARLGS LVV VPAAMSFYWGQGLTVTVSS
C33H72	262	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVANIKQHGEKYYV DSVKGRFTISRDNKNSLYLQMNSLRAEDTAVYYCARDRLGYFDYWGQGLTVTVSS
C33H73	263	EVQLLES GGGLVQPGGSLRLSCAASRFTFSSYAMTWVRQAPGKGLEWVSTINISGGSTYYADS VKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCTKGGYSSGPFYWGQGLTVSVSS
C33H74	264	QVQLVESGGGVVQPGRSLRLSCAASRFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYA DSVKGRFTISRDNKNTLYLQMNSLRAEDTAVHYCAKDFRSFDWLPPDSASYHGMDVWGQG TTVTVSS

C33H76	265	EVQLLESGGGLVQPGGSLRLSCAASGFTFNYAMSWVRQAPGKGLEWVSAISGGGSTYYADS VKGRFTISRDISKNTLYLQMNSLRAEDTAVYYCARTYNSGYDGDYFDYWGQGLTVTVSS
C33H78	266	QVQLVESGGGVVQPGSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYA DSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKDFRYFDWLPDSSSYGMDVWGQGT TVTVSS
C33H80	267	QVQLVQSGSELRKPGASVKVSKASGYTFTNYAMNWVRQAPGQGLEWMGWINTNTGNPTY AQGFTGRFVFLDTSVSSAYLQISSLKAEDTAMYYCATDRDRGTDYWGQGLTVTVSS
C33H81	268	QVQLVESGGGVVQPGSLRLSCAASGFTFSA YGMHWVRQAPGKGLEWVAVISYDGSNKYYA DSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKDFRSFDWLPDSTSYHGMDVWGQG TTTVTVSS
C33H84	269	QVQLVESGGGVVQPGSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYA DSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKDFRSFDWLPDSTSYHGMDVWGQGT TVTVSS
C33H87	270	EVQLVESGGGFVQPGGSLRLSCAASGFTFSSYWSWVRQAPGKGLEWVANIKQHGESEKYYV DSVKGRFTISRDNVKNLSYLQMNSLRTEDTAVYYCARDRLGYFDYWGQGLTVTVSS
C33H88	271	QVQLVQSGSELKKPGASVKVSKASGYTLTRSAMNWVRQAPGQGLEWMGWINTNTGNPTYA QGFTGRFVFLDTSVNTAYLLISSLKTEDTAVYYCASDILPGYHEDYWGQGLTVTVSS
C33H90	272	QVQLQQSGPGLVKPSQTLSTCAISGDSVSSNSAAWNWRQSPSRGLEWLGRTYRYSKYYND YALSVQSRITINPDTSKNQFSLQLNSVTPEDTAVYYCAREVAVAASFYDWGQGLTVTVSS
C33H91	273	QLQLQESGPGLVKPSETLSLTCTVSGGSISSRSHYWGWIQPPGVGLEWIGSIYYTGSTYYNPSL KSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARLADIVVPAARYFDYWGQGLTVTVSS
C33H92	274	QLQLQESGPGLVKPSETLSLTCTVSGGSIRSSSYWGWIQPPGKGPWEWIGSIYSSGNTYYNPSL KSRVTISVDTSKNQFSLKLISMTAADTAVFYCARLAATIVVPAARYFDCWGQGLTVTVSS
C33H98	275	EVQLVESGGGFVQPGGSLRLSCAASGFTFSSYWSWVRQAPGKGLEWVANIKQHGESEKYYV DSVKGRFTISRDNKNSLYLQMNSLRAEDTAVYYCARDRLGYFDYWGQGLTVTVSS
C33H99	276	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMTWVRPAPGKGLEWVANIKRDGGEKYYV DSVKGRFTISRDNAANSYLQMNSLRVEDTAVYYCARPFYDHFYDWGQGLTVTVSS
C33H108	277	QVQLVQSGSELKKPGASVKVSKASGYTFSTYAMNWVRQAPGQGLEWMGWINTNTGNPTYA QGFTGRFVFLDTSVSTAYLQISSLKAEDTAVYYCARDRDRGTDYWGQGLTVTVSS
C33H249	278	EVQLVESGGGLVQPGSLRLSCVASGFTFDDYAIHWVRQAPGKGLEWVSGLSWNGGNIGYAD SVKGRFTISRDNKNSLYLQMNSLKTEDTAFYYCTKDTPTYGDYFDYWGQGLTVTVSS
C33H250	279	EVQLVESGGGLVQPGSLRLSCAGSGFTFDDYAIHWVRQAPGKGLEWVSGLSWNGGNIGYAD SVKGRFTISRDNKNSLYLQLNSLKTEDTAFYYCAKDSPLYGDYFDYWGQGLTVTVSS
C33H251	280	EVQLVESGGGLVQPGSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGIGWSGGSIVYAD SVKGRFKISRDNKNSLYLQMNSLRAEDTALYYCAKDSPLYGDFDYWGQGLTVTVSS
C33H252	281	EVQLVESGGGLVQPGSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGIGWSGGSIVYAD SVKGRFTISRDNKNSLYLQMNSLRAEDTALYYCAKDSPLYGDFDYWGQGLTVTVSS
C33H253	282	EVQLLESGGGLVQPGGSLKLCTASGFTFRSYAMSWVRQAPGKGLEWVSAINGYGDGRYYAD SVKGRFTISRDNKNTLYLQMNSLRAEDTAVYSCAKDQGFELFFDYWGQGLTVTVSS
C33H254	283	QVQLVESGGGVVQPGSLRLSCAASGFTFSYGMHWVRQAPDKGLEWVAVIWFDGNNKYY ADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCARDRELLFDYWGQGLTVTVSS
C33H255	284	EVQLVESGGGLVQPGSLRLSCAASGFTFDDYAMHWVRQVPGEGLWVSGISWNGGDMVYA DSVKGRFTISRDNKNSLYLQMNSLRPEDTALYYCVKDMPLYFDFTGSDYYYGMDVWGQG TTTVTVSS
C33H256	285	QVQLVESGGGVVQPGSLRLSCATSGFTFSNYGMHWVRQAPGKGLEWVAVIWYVGSHKYYA DSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCARDGSLCFDYWGQGLTVTVSS
LC ID	SEQ ID NO	AMINO ACID SEQUENCE

B23L3	286	DIVMTQSPDSLAVSLGERATINCRASQSVVDYNGISYMHWYQQKPGQPPKLLIYAASNPESGVP DRFSGSGSGTDFTLTISSLQAEDVAVYYCQQIIEDPWTFGQGTKVEIK
CD3L66	287	QTVVTQEPSLTVSPGGTVLTCRSSTGAVTTSNYANWVQQKPGQAPRGLIGGTNKRAPGTPAR FSGSLLGGKAALTL SGVQPEDEAEYYCALWYSNLWVFGGGTKLTVL
CD3L150	52	QSALTQPASVSGSPGQSITISCTGTSSNIGTYKFVSWYQQHPDKAPKVLLYEVS KRPSGVSSRFS GSKSGNTASLTISGLQAEDQADYHCVS YAGSGTLLFGGGTKLTVL
C33L8	288	SYELTQPPSVSVSPGQTASITCSGDKLGDKYACWYQQKPGQSPVLVIYQDSKRPSGIPERFSGSN SGNTATLTISGTQAVDEADYYCQAWDSSTYVFGTGTKVTVL
C33L10	289	SYVLTQPPSVSVAPGQTARITCGGSNIGSKSVHWYQQKPGQAPVMVYDDSDRPSGIPERFSGS NSGNTATLTISRVEAGDEADYYCQVWDSSSDVVFVFGGGTKLTVL
C33L11	290	SYELTQPPSVSVSPGQTASITCSGDKLGDKYACWYQQKPGQSPVVVIYKDSKRPSGIPERFSGS NFGNTATLTISGTQAMDEADYYCQAWDSSTVVFVFGGGTKLTVL
IAPL24	291	SYELTQPPSVSVSPGQTASITCSGDKLGDKYACWYQQKPGQSPVLVIYQDSKRPSGIPERFSGSN SGNTATLTISGTQAMDEADYYCQAWDSSTVVFVFGGGTKLTVL
C33L58	292	SYELTQPPSVSVSPGQTASITCSGDKLGDKYACWYQQKPGQSPVLVIYQDYKRPSGIPERFSGS NSGNTATLTISGTQAMDEADYYCQAWDSSTYVFGTGTKVTVL
C33L59	293	SYELTQPPSVSVSPGQTASITCSGDKLGDKYACWYQQKPGQSPVLVIYQDYKRPSGIPERFSGS NSGNTATLTISGTQTMDEADYYCQAWDISTYVFGTGTKVTVL
C33L34	294	SYELTQPPSVSVSPGQTASITCSGDKLGDKYACWYQLRPGQSPILVIYQDSNRPSGIPERFSGSNS GNTATLTISGTQAMDEADYYCQAWDSSTWVFVFGGGTKLTVL
N46L109	295	SYELTQPPSVSVSPGQTASITCSGDKLGDKYACWYQQKPGQSPVLVIYQDSKRPSGIPERFSGSN SGNTATLTISGTQAMDEADYYCQAWDSSTWVFVFGGGTKLTVL
C33L42	296	SYVLTQPPSVSVAPGQTARITCGGNIGIKSVHWYQQKPGQAPVLVYDDSDRPPGIPERFSGS NSGNTATLTITRVEAGDEADYYCQVWDSSSDHVVFVFGGGTKLTVL
C33L47	297	SYELTQPPSVSVSPGQTASITCSGDKLGDKYACWYQQKPGQSPVVVIYQDRKRPSGIPERFSGS NFGNTATLTISGTQAMDEADYYCQAWDSSTVVFVFGGGTKLTVL
C33L60	298	SYELTQPPSVSVSPGQTASITCSGDKLGDKYACWYQQKPGQSPVLVIYQDGKRPSGIPERFSGS NFGNKATLTISGTQAMDEADYYCQAWDRNTVVFVFGGGTKLTVL
C33L17	299	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKAGQPPKLLIYWASTRESG VPDRFSGSGSGTDFILISSLQAEDVAVYYCQQYYGTPWTFGQGTKVEIK
C4LL152	300	DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIYAASSLQSGVPSRFSG SGSGTDFTLTISSLQPEDFATYYCQANSFPFTFGPGTKVDIK
C33L40	301	SYELTQPPSVSVSPGQTASITCSGNKLGAKFASWYQQKPGQSPVLVIYQDNKRPSGIPERFSGSN SGNTATLTISGTQAVDEADYYCQAWDSSTVVFVFGGGTKLTVL
C33L32	302	SYELTQPPSVSVSPGQTASITCSGDKLGDKYVRWYQQKTGQSPVLVMIYQDSKRPSGIRERFYG SNSGNTATPTISGTQAVDEAEYYCQAWDSSTGVVFVFGGGTKLTVL
C33L38	303	SYELTQPPSVSVPPGQTASITCSGDKLGDKYACWYQQKPGQSPVLVIYQDNKRPSGIPERFSGS NSGNTATLTISGTQAMDEADYYCQAWGRNTVVFVFGGGTKLTVL
C33L39	304	QSALTQPASVSGSPGQSIPISTGTSSDDGKNNIVSWYQQHPGKAPKLMYKDSKRPSGVSNRFS GSKSGNTASLTISGLQAEDDEADYHCCSYAGASNHVVFVFGGGTKLTVL
C33L57	305	SYELTQPPSVSVSPGQTASITCSGDELGNKYACWYQQKPGQSPVVVVYQDRKRPSGIPERFSGS NFGNTATLTISGTQAMDEADYYCQAWDSSTVVFVFGGGTKLTVL
C33L73	306	QSALTQPASVSGSPGQSITISCTGTSSDVGDNYSWYQQHPGKVPKLMYDVSNRPSGVSNRF SGMSGNTASLTISGLQAEDDEADYYCSSYSSSALEVFVFGGGTKLTVL
C33L53	307	SYELTQPPSVSVSPGQTASITCSGDKLGDKYACWYQQKPGQSPVLVIYQDNKRPSGIPERFSGS NSGNTATLTISGTQAMDEADYYCQAWDSNTVVFVFGGGTKLTVL

C33L66	308	SYELTQPPSVSVSPGQTASITCSGDKLGDKYVCWYQQKPGQSPVVIHQDRKRPSGIPERFSGS NFGNTATLTISGTQAMDEADYYCQAWDSSTVVFGGGTKLTVL
C33L35	309	SYELTQPPSVSVSPGQTASITCSGDKLGDKYASWYQQKPGQSPVLVIYQDTRKPSGIPERFSGS NSGNTATLTISGTQAMDEADYHCQAWDSSTVVFGGGTKLTVL
C33L61	310	QSALTQPASVSGSPGQSITISCTGINSVGSYDLVSWYQQHPGKAPKLLIYDGSERPSGVFGRFS GSKSDNTTSLTISGLQAEDAAAYCCSYEVTTTYVVFGGGTKLTVL
C33L51	311	SYVLTQPPSVSVAPGQTARITCGGNNIGSKSVHWSQQKPGQAPVLVYVDDSDRPSGIPERFSGS NSGNTATLTISRVEAGDEADYYCQVWDSNSDHVVFGGGTKLTVL
C33L44	312	SYELTQPPSVSVSPGQTASITCSGDKLGDKYACWYQQKPGQSPVLVIYQDSNRPSGIPERFSGSN SGNTATLTISETQAMDEADYYCQAWDSSTYVFGTGKTVL
C33L30	313	SYELTQPPSVSVSPGQTVSISCSGDRLGDKYACWYQQKPGQSPVLVIYQDSKRPSGIPERFSGSN SGNTATLTISGTQAMDEADYYCQAWDSSTYVFGTGKTVL
C33L69	314	SYELTQPPSVSVSPGQTASITCSGDKLGSKFACWYQQKPGQSPVLVIYQDSKRPSGIPERFSGSN SGNTATLTISGTQAMDEADYYCQAWDSSTVVFGGGTKLTVL
C33L37	315	SYVLTQPPSVAVAPGQTARITCGGSNIGKISVHWYQQKAGQAPVLVHDDRARPSGIPERLSGS NSGTTATLTISRVEVGDEADYYCQVWNSSSVHPVVFGGGTKLTVL
C33L74	316	QSALTQPASVSGSPGQSITISCTGTSSDVGGDNYVSWYQQHPGKAPKLLMIYDVSNRPSGVSNRF SGSKSGNTASLTISGLQSEDEADYYCSSYSSSTTLEVFGGGTKLTVL
C33L115	317	DIQMTQSPSSVWASVGDRTITCRASQGISSWLAWYQQPGKAPNLLIYRSSLQSGVPSRFSG SGSGTDFTLTISSLQPEDFATYYCQQDNSFPYTFGQGTKLEIK
C33L116	318	DIQMTQSPSSEWASVGDRTITCRASQGISSWLAWYQQPGKAPKLLIYGASSWQSGVPSRFS SGSGTDFTLTISSLQPEDFATYYCQQDNSFPYTFGQGTKLEIK
C33L117	319	DIVMTQSPDSLAVSLGERATINCKSSQTVLYSSNNKNYLAWYQQKPGQPPKLLISWASTRKSG VPDRFSGSGSGTDFTLTVSSLQAEDVAVYYCQHYYSTPYTFGQGTKLEIK
C33L118	320	DIVMTQSPDSLAVSLGERATINCKSSQTVFYSSNNKNYLAWYQQKPGQPPKLLISWASTRKSG VPDRFSGSGSGTDFTLTVSSLQAEDVAVYYCQHYYSTPYTFGQGTKLEIK
C33L119	321	DIQMTQSPSTLSASVGDRTITCRASQSISSWLAWYQQKPGKAPKLLIYKASSLESQVPSRFSGS GSGTEFTLTISLQPDFFATYCCQYNSYPWTFGQGTKVEIK
C33L120	322	SYELTQPPSVSVSPGQTASITCSGDELGDYACWYQQKPGQSPVLVIYQDSKRPSGIPERFSGSN SGNTATLTISGTQAMDEAAAYCQTDWTRIAVFGGGTNLTVL
C33L121	323	SYELTQPPSVSVSPGQTASITCSGDNLGNEHVCWYHQKPGQSPVLVIYQNNKRPSGIPERFSGSN SGNTATLSISGTQATDEADYYCQAWDSSTAVFGGGTKLTVL
C33L122	324	SYELTQPPSVSVSPGQTANISCSGVTLGYNAYWYQQKPGQSPILVISQDTQRPSGIPERFSGSN SGNTATLTISGTQAMDEAAAYCQAWDITVLFGGGTKLTVL
C33L132	325	SYELTQPPSVSVSPGQTASITCSGDKLGDKYASWYQQKPGQSPVLVIYQDGKRPSGIPERFSGSN FGNKATLTISGTQAMDEADYYCQAWDRNTVVFGGGTKLTVL
C33L41	326	SYELTQPPSVSVSPGQTASITCSGDKLGDKYASWYQQKPGQSPVLVIYQDSKRPSGIPERFSGSN SGNTATLTISGTQAMDEADYYCQAWDSSTVVFGGGTKLTVL

Table 44: CD33 mAb Heavy Chain CDR1-3 sequences

HC ID	CDR1	ID	CDR2	ID	CDR3	ID
B23H1	GFSLSSTSGMG	327	IYWDDDK	368	ARLYGFTYGFAY	409
CD3H141	GFTFNTYA	328	IRSKYNNYAT	369	ARHGNFGNSYVSWFAY	410
CD3H219	GDSVFNNNA	329	TYYSKWL	370	ARGYSSFDY	411
C33H42	GGSISSSHY	330	IYYSNT	371	ARLADVVPVPAARYFDS	412
C33H44	GDSVSSNSAA	331	TYYSKWYN	372	ARETMFRGLMDY	413
C33H45	GFTFSSYG	332	ISYDGSNK	373	AKDFRSLDWLPDSTSYDGMVDV	414
C33H46	GYTFTNYA	333	INTNTGNP	374	ARDREVRDY	415

C33H48	GGsirSTNYY	334	IYySGNT	375	ARLADVVPVPAARYFDY	416
C33H49	GGsirSSGFY	335	IYySGNT	376	ARLADVVPVPAARYFDN	417
C33H51	GGsISTGRYY	336	IYySGNT	377	ARLGSLVVVPAAMSFY	418
C33H52	GGsirGSSYY	337	IYySGNT	378	ARLGSLVVVPAAMSFY	419
C33H55	GGSISSSNW	338	IYHSGNT	379	ARIIVARYFDS	420
C33H65	GFTFSSYG	339	ISYDGSNK	380	AKDFRFDWLPPDSTSYHGMDV	421
C33H66	GFTFSSYG	340	ISYDGSNK	381	AKDFRSFDWLPPDSASYHGMDV	422
C33H68	GFTFSGYA	341	IDYSGNDT	382	AKESQLLHGLFEH	423
C33H69	GGSISSSSYY	342	INySGST	383	ARLDGYESPFYD	424
C33H70	GGsirGSSYY	343	IYySGNT	384	ARLGSLVVVPAAMSFY	425
C33H72	GFTFSSYW	344	IKQHGESEK	385	ARDRDLGYFDY	426
C33H73	RFTFSSYA	345	INISGGST	386	TKGGYSSGPFYD	427
C33H74	RFTFSSYG	346	ISYDGSNK	387	AKDFRSFDWLPPDSASYHGMDV	428
C33H76	GFTFNYA	347	ISGSGGST	388	ARTYNSGYDGDYD	429
C33H78	GFTFSSYG	348	ISYDGSNK	389	AKDFRYFDWLPPDSSSYGMDV	430
C33H80	GYTFTNYA	349	INTNTGNP	390	ATDRDRGTDY	431
C33H81	GFTFSAYG	350	ISYDGSNK	391	AKDFRSFDWLPPDSASYHGMDV	432
C33H84	GFTFSSYG	351	ISYDGSNK	392	AKDFRSFDWLPPDSTSYGMDV	433
C33H87	GFTFSSYW	352	IKQHGESEK	393	ARDRDLGYFDY	434
C33H88	GYTLTRSA	353	INTNTGNP	394	ASDILPGYHEDY	435
C33H90	GDSVSSNSAA	354	TYYSKWN	395	AREVAVASFDY	436
C33H91	GGSISSRSHY	355	IYYTGST	396	ARLADIVVPVPAARYFDY	437
C33H92	GGsirSSSYY	356	IYySGNT	397	ARLAATIVVPVPAARYFDC	438
C33H98	GFTFSSYW	357	IKQHGESEK	398	ARDRDLGYFDY	439
C33H99	GFTFSSYW	358	IKRDGGEK	399	ARPFYDHFYD	440
C33H108	GYTFSTYA	359	INTNTGNP	400	ARDRDRGTDY	441
C33H249	GFTFDDYA	360	LSWNGGNI	401	TKDTPYGDYFDY	442
C33H250	GFTFDDYA	361	LSWNGGNI	402	AKDSPYGDYFDY	443
C33H251	GFTFDDYA	362	IGWSGGSI	403	AKDSPYGDFFDY	444
C33H252	GFTFDDYA	363	IGWSGGSI	404	AKDSPYGDFFDY	445
C33H253	GFTFRSYA	364	INGYGDGR	405	AKDQGFGLFFDY	446
C33H254	GFTFSYYG	365	IWFDGNK	406	ARDRELLFDY	447
C33H255	GFTFDDYA	366	ISWNGGDM	407	VKDMPYFDLTGSDYYYGMDV	448
C33H256	GFTFSNYG	367	IWYVGSBK	408	ARDGSLCFDY	449

Table 45: CD3 mAb Light Chain CDR1-3 sequences

LC ID	CDR1	ID	CDR2	ID	CDR3	ID
B23L3	QSVYDNGISY	450	AAS	492	QQIIEDPWT	534
CD3L66	TGAVTTSNY	451	GTN	493	ALWYSNLWV	535
CD3L150	SSNIGTYKF	452	EVS	494	VSYAGSGTLL	536
C33L8	KLGNKY	453	QDS	495	QAWDSSTYV	537
C33L10	NIGSKS	454	DDS	496	QVWDSSTDVV	538
C33L11	KLGDY	455	KDS	497	QAWDSSTVV	539
IAPL24	KLGDY	456	QDS	498	QAWDSSTVV	540
C33L58	KLGDY	457	QDY	499	QAWDSSTYV	541
C33L59	KLGDY	458	QDY	500	QAWDISTYV	542
C33L34	KLGDY	459	QDS	501	QAWDSSTWV	543
N46L109	KLGDY	460	QDS	502	QAWDSSTWV	544
C33L42	NIGIKS	461	DDS	503	QVWDSSTDHV	545
C33L47	KLGDY	462	QDR	504	QAWDSSTVV	546
C33L60	KLGDY	463	QDG	505	QAWDRNTVV	547
C33L17	QSVLYSSNNKNY	464	WAS	506	QYYGTPWT	548
C4LL152	QGISSW	465	AAS	507	QQANSFPT	549
C33L40	KLGAKF	466	QDN	508	QAWDSSTVV	550
C33L32	KLGDY	467	QDS	509	QAWDSSTGVV	551
C33L38	KLGDY	468	QDN	510	QAWGRNTVV	552
C33L39	SSDDGKNNI	469	KDS	511	CSYAGASNHVV	553
C33L57	ELGNKY	470	QDR	512	QAWDSSTVV	554
C33L73	SSDVGDYNY	471	DVS	513	SSYSSSSALEV	555
C33L53	KLGDY	472	QDN	514	QAWDSNTVV	556
C33L66	KLGDY	473	QDR	515	QAWDSSTVV	557
C33L35	KLGNKY	474	QDT	516	QAWDSSTVV	558
C33L61	NSDVGSYDL	475	DGS	517	CSYEVTITYV	559

C33L51	NIGSKS	476	DDS	518	QVWDSNSDHVV	560
C33L44	KLGDY	477	QDS	519	QAWDSSTYV	561
C33L30	RLGDY	478	QDS	520	QAWDSSSYV	562
C33L69	KLGSKF	479	QDS	521	QAWDSSTVV	563
C33L37	NIGKIS	480	DDR	522	QVWSSSVHPV	564
C33L74	SSDVGGDDNY	481	DVS	523	SSYSSSTLEV	565
C33L115	QGISSW	482	RSS	524	QODNSFPYT	566
C33L116	QGISSW	483	GAS	525	QODNSFPYT	567
C33L117	QTVLYSSNNKNY	484	WAS	526	QHYYSTPYT	568
C33L118	QTVFYSSNNKNY	485	WAS	527	QHYYSTPYT	569
C33L119	QSISSW	486	KAS	528	QQYNSYPWT	570
C33L120	ELGDMY	487	QDS	529	QTWDTRIAV	571
C33L121	NLGNEH	488	QNN	530	QAWDSTTAV	572
C33L122	TLGYNY	489	QDT	531	QAWDITTVL	573
C33L132	KLGDY	490	QDG	532	QAWDRNTVV	574
C33L41	KLGNKY	491	QDS	533	QAWDSSTVV	634

5-5 Characterization of anti-CD33 mAbs

OMNIRat antibodies identified via immunization, v-region cloned and subsequently expressed and purified were characterized further for binding to CD33 expressing cells and binding to recombinant antigens. The purified antibodies were assessed for binding to stably transfected HEK293F cells expressing human CD33 or cyno CD33 (generation described above) along with the parental HEK293F as negative control. Cells were harvested from tissue culture flasks using non-enzymatic dissociation buffer (Thermo Scientific). The flasks were rinsed twice with PBS and dissociation buffer was added to the flask, and the flask was incubated for 10 minutes at 37°C until the cells became non-adherent. The cells were centrifuged at 300 g for 5 minutes and resuspended at 1.0×10^6 cells/ml in staining buffer (Becton Dickinson; Franklin Lakes, NJ). 50,000 cells/well of each cell type was plated in 50 μ l of staining buffer in round bottom plates (Becton Dickinson). 50 μ l of 2x concentration test mAb or isotype control was added at 3 dilutions and zero (120nM, 12nM, and 1.2nM and 0 nM), and the resultant solution was incubated 30 min at 4°C. 100 μ l staining buffer was added to all wells of each plate, the plates were spun at 300g for 5min, the buffer was removed, 200 μ l staining buffer was added to all wells of each plate, the plates were spun at 300g for 5min, and the buffer was removed. 50 μ l of 2 μ g/ml of Goat-anti-human Fc AF647 secondary antibody (Jackson ImmunoResearch; West Grove, PA) was added to all wells of the plates, and the plates were incubated for 30 min at 4°C. 100 μ l staining buffer was added to all wells of the plates, the plates were spun at 300g for 5min, and the buffer was removed. 200 μ l running buffer (running buffer is Staining buffer, 1mM EDTA, 0.1% Pluronic Acid) was added to all wells of the plates, the plates were spun at 300g for 5min, and the buffer was removed. 30 μ l running buffer containing Sytox Green live/dead dye

(ThermoFisher) was added to all wells with cells and the plates were read on an iQue IntelliCyt flow cytometer. Cells were gated on forward vs. side scatter to eliminate debris, then on singlets and then on live cells which excluded the Sytox stain. Antibody binding was assessed by the mean fluorescence intensity in the AF647 channel.

5 To begin assessing the biophysical binding properties of the purified mAbs an off-rate screen was performed. 76 OMNIRat anti-CD33 mAbs were tested for binding to recombinant human CD33 ECD-HSA (C33W2) and cyno CD33 ECD-HSA (C33W1) proteins (Janssen production) and the off-rate was measured by IBIS MX96 SPRi array platform (Carterra; Newton, PA). Goat anti-human Fc IgG (Jackson ImmunoResearch, Cat# 109-005-098) was
10 directly immobilized via amine coupling at 100 µg/mL in acetate buffer, pH 4.5 using a CMD50m sensor chip (Xantec, lot CMD50m0415.a) with an association time of 10 minutes in the IBIS instrument. An average GAH-Fc immobilization level of ~9000 Rus was achieved. The sensor chip was transferred to the Continuous Flow Microspotter (CFM) unit to capture each anti-CD33 mAb at 10 µg/ml for 10 minutes. Binding was measured on IBIS SPRi by single
15 cycle kinetics without regeneration. Each antigen concentration series (3 µM in 3 fold dilution series) was sequentially injected from low (0.46 nM) to high concentrations (3µM) to bind to captured mAbs with an association time of 5 minutes and dissociation time of 15 minutes using PBST (PBS with 0.005% Tween) as running buffer. The raw binding data (.trix file format) were referenced and aligned using SprintX software (Wasatch, Ver 1.9.3.2), then exported
20 (.ibmx file format) to Scrubber software (Ver. 2.0) for 1:1 binding kinetic analyses (Wasatch, version 2.0.0.33) to extract the k_{off} results.

Table 46 below summarizes the top 32 clones as assessed by binding to human and cyno CD33 expressing cell lines as well as towards recombinant antigen (off-rate of at least $>10e-3$ for one of the antigens). Of these 32, all but 4 showed appreciable binding to either human or cyno
25 expressing cells. All 32 were carried for further characterization via epitope binning and full kinetic analysis.

Table 46. Cell Binding and Off-Rate analysis of the anti-CD33 antibodies derived from OMNIRat

Prot. AA ID	%Mon	60nM CD33	6nM CD33	0.6nM CD33	0nM CD33	K_D
C33B48	91.96	400995.84	428948.75	391157.69	91.12	5.47E-05
C33B73	100.00	201493.02	33443.28	4034.64	93.98	9.12E-05
C33B125	98.48	258779.13	79728.78	9203.75	78.26	1.54E-04

C33B55	96.39	188278.42	59155.10	7625.56	105.39	2.15E-04
C33B96	98.75	476040.28	475653.41	187925.80	55.23	2.28E-04
C33B124	100.00	798.33	126.37	90.26	172.03	2.38E-04
C33B72	96.94	328194.72	105474.59	12506.85	93.32	2.84E-04
C33B79	100.00	236644.03	41925.89	4988.81	77.78	3.28E-04
C33B77	92.11	241787.16	88691.05	11484.97	69.46	3.37E-04
C33B82	96.21	188508.56	41264.92	5033.60	73.44	3.41E-04
C33B87	100.00	242185.48	79532.87	12547.05	73.65	3.52E-04
C33B80	98.33	5799.64	409.97	114.93	88.88	3.84E-04
C33B101	96.91	268805.28	204984.16	35513.63	70.07	3.98E-04
C33B83	98.07	92956.55	7856.70	1020.48	87.37	4.61E-04
C33B46	95.81	509865.97	447627.97	418017.22	134.53	4.67E-04
C33B94	98.31	200142.00	93852.22	13274.87	89.59	5.38E-04
C33B88	98.36	393148.13	481100.91	274293.53	94.81	8.25E-04
C33B66	98.71	444680.31	313288.41	56628.04	129.73	8.59E-04
C33B120	97.63	190036.14	60357.11	7054.28	92.94	1.40E-03
C33B64	98.13	200158.36	54138.77	7556.04	114.85	1.71E-03
C33B52	96.76	196557.09	46286.13	6751.01	82.46	3.13E-03
C33B56	95.59	143.73	79.73	111.95	138.04	4.02E-03
C33B75	98.68	163795.25	29603.57	4517.81	95.94	4.16E-03
C33B107	96.90	375388.25	339798.53	161369.64	86.54	4.44E-03
C33B63	98.79	247758.77	62221.71	9671.48	86.34	4.57E-03
C33B95	97.77	154556.58	44354.07	6402.00	87.38	5.99E-03
C33B61	98.87	198777.34	38699.10	5308.45	79.84	6.71E-03
C33B89	100.00	315.38	119.12	65.61	70.94	8.11E-03
C33B122	98.49	259183.69	84281.03	14291.17	65.01	8.74E-03
C33B62	99.05	157786.36	37359.44	6092.03	75.00	1.00E-02
C33B123	95.08	224078.95	88155.99	8864.39	71.05	1.03E-02
C33B54	100.00	147753.30	27461.06	3766.69	61.26	2.48E-02

Table 46, continued:

Prot. AA ID	60nM Cyno CD33	6nM Cyno CD33	0.6nM Cyno CD33	0nM Cyno CD33	Cyno CD33 binding K_D
C33B48	56491.32	47326.85	43351.12	94.01	1.20E-04
C33B73	14799.14	6987.92	795.57	72.51	4.08E-04
C33B125	15603.45	11526.47	3458.27	70.22	3.51E-04
C33B55	16020.78	9994.42	2433.94	69.38	1.16E-04
C33B96	37273.19	20087.29	11574.59	86.31	8.19E-04
C33B124	593.00	132.19	77.26	98.41	4.77E-04
C33B72	19422.07	13975.14	3894.84	90.81	7.63E-04
C33B79	15538.97	6427.73	1082.85	63.59	6.82E-03
C33B77	17516.20	11665.49	3601.76	85.23	4.18E-04
C33B82	14269.38	6622.07	1540.09	84.24	6.70E-04
C33B87	19597.18	12652.44	3266.36	103.07	2.28E-04

C33B80	4612.58	248.60	108.93	82.38	2.66E-04
C33B101	48016.75	46115.96	17989.37	79.69	1.06E-04
C33B83	5304.40	687.44	159.37	87.35	2.17E-03
C33B46	49840.14	49816.36	49729.78	92.05	1.48E-04
C33B94	16126.84	10782.54	3183.70	87.82	5.37E-04
C33B88	50388.18	43928.95	43940.23	90.13	3.89E-04
C33B66	48905.04	49076.39	42160.22	77.96	9.33E-05
C33B120	13211.32	7865.37	2726.18	75.77	8.54E-04
C33B64	21109.59	9685.04	3102.56	99.82	1.21E-03
C33B52	12582.90	8444.39	2063.44	75.24	1.20E-03
C33B56	104.27	85.94	78.56	83.31	8.46E-04
C33B75	12194.41	5577.80	1709.40	124.32	1.20E-03
C33B107	50325.07	47810.05	36786.69	55.11	1.35E-04
C33B63	18322.71	11642.38	2879.89	87.94	9.47E-04
C33B95	14774.34	9594.12	1637.99	80.81	6.98E-03
C33B61	13552.71	8211.09	1595.90	106.84	1.83E-03
C33B89	47301.14	34193.78	23334.20	112.80	4.65E-05
C33B122	19740.29	13907.32	5838.25	82.53	1.45E-03
C33B62	12737.71	5620.17	1922.97	934.44	1.32E-03
C33B123	10665.93	10404.03	3232.18	61.08	2.74E-03
C33B54	50466.68	43011.75	38091.89	28785.80	1.35E-04

The panel of mAbs was then further characterized for full affinity analysis as well as epitope binning. The binding of anti-CD33 mAbs to recombinant human CD33 ECD-HSA (C33W2) and cyno CD33 ECD-HSA (C33W1) was measured by ProteOn SPR (Bio-Rad). Goat anti-human Fc IgG (Jackson ImmunoResearch, Cat# 109-005-098) was directly immobilized via amine coupling at 30 µg/mL in acetate buffer, pH 5.0 on all 6 ligand channels in vertical orientation on a GLC Sensor Chip (Bio-Rad, catalog no. 176-5011) with a flow rate of 30 µL/min in PBS containing 0.005% Tween-20. The immobilization densities averaged about 5000 Response Units (RU) with less than 5% variation among different channels. Different mAbs were captured on the anti-human Fc IgG surface at 0.25 or 0.5 µg/ml (160~300 RU) in vertical ligand orientation, with the 6th ligand channel as no ligand surface control. Human and cyno CD33-HSA proteins at 0.3 µM concentration in 3-fold dilution series of 5 concentrations flew in as analyte to bind to captured mAbs in the horizontal orientation. A buffer sample was also injected in the 6th channel to monitor the dissociation of captured mAb and baseline stability. The dissociation phase for all concentrations of human and cyno CD33-HSA was monitored at a flow rate of 100 µL/min for 15 minutes for binding to C33B782, 60 minutes for binding to C33B912 (identical to C33B904 with hIgG4), followed by regeneration using an 18

second pulse of 0.85% phosphoric acid to remove the antigen and the bound mAb. The raw binding data were processed by double referencing after subtracting the response data from: 1) the inter-spot to correct for the non-specific interactions between the Ag and the empty chip surface; 2) the buffer channel to correct for baseline drifting due to the dissociation of captured mAb surface over time. The processed data at all antigen concentrations for each mAb were globally fit to a 1:1 simple Langmuir binding model to extract estimates of the kinetic (k_{on} , k_{off}) and affinity (K_d) constants.

To determine whether the panel of mAbs all bind 1 distinct epitope or if there was broad epitope coverage, an epitope binning experiment was performed. Competitive epitope binning of CD33 mAbs was performed on an IBIS SPRi instrument (Carterra) using a CMD-200M sensor prism chip. Each anti-CD33 antibody was directly immobilized via amine coupling on the chip at 10 μ g/ml in acetate buffer (pH 4.5) using a separate Continuous Flow Microspotter (CFM). Printed sensor chip was then transferred to the IBIS instrument for the binning analyses using a Classical or "Sandwich" binning format. Binning was performed by sequential injection of human CD33 ECD-HSA, (C33W2) at 50 nM followed by a single anti-CD33 mAb injection as competing analyte in solution at 133 nM to bind immobilized anti-CD33 mAbs with surface regeneration after each sequential injection cycle of antigen and antibody.

To monitor the activity of the immobilized mAbs before and after regeneration, a buffer injection without any competing mAb was performed at the beginning and at the end of the experiment to measure the antigen alone binding activity. The response of competing mAb binding relative to the buffer (antigen alone) binding is an indication whether the antibody in solution blocks or sandwiches the antigen binding to the immobilized mAbs. The raw binning data (.trix file format) were referenced and zeroed using SprintX software (Wasatch, Ver 1.9.3.2), then exported (.ibmx file format) to the binning software HtTools.exe (Wasatch, version 2.0.0.33) for analyses. Data were curated by removing antibodies with antigen responses below 20 RU, and antibodies that did not self-block. Competing mAb responses were normalized relative to the antigen alone binding response. Antibodies with normalized responses < 0.25 were denoted blockers, those with normalized responses ≥ 0.25 were denoted as non-blockers/Sandwichers. Different bins were predicted using a cut at height 2.5 on the combined dendrogram plot.

The table below summarizes the full kinetic analysis and epitope binning of 32 select mAbs. There are a total of 8 anti-CD33 mAbs that have sub-nanomolar affinity for both human and cyno CD33 and these mAbs correspond to 3 distinct epitope bins while the larger panel has a range of affinities and 7 distinct epitope bins.

5 Table 47. Full Kinetics Analysis and Epitope Binning of OMNIRat derived mAbs

Human CD33 ECD-HSA					
Prot. AA ID	V Region ID	k_a (1/Ms)	k_d (1/s)	K_D (M)	Epitope Bin
C33B48	C33F53	1.62E+06	1.82E-05	1.12E-11	1
C33B46	C33F51	1.45E+06	1.99E-03	1.38E-09	1
C33B66	C33F71	3.85E+04	2.03E-03	5.29E-08	1
C33B107	C33F112	binding/no fit	binding/no fit	binding/no fit	1
C33B88	C33F93	binding/no fit	binding/no fit	binding/no fit	1
C33B96	C33F101	2.26E+05	4.36E-04	1.92E-09	3
C33B101	C33F106	1.62E+05	1.08E-03	6.64E-09	3
C33B73	C33F78	5.59E+05	5.59E-05	1.00E-10	4
C33B125	C33F130	9.92E+05	1.34E-04	1.40E-10	4
C33B55	C33F60	9.85E+05	2.53E-04	2.60E-10	4
C33B82	C33F87	4.45E+05	2.70E-04	6.10E-10	4
C33B83	C33F88	2.70E+05	5.21E-04	1.93E-09	4
C33B75	C33F80	3.85E+05	4.41E-03	1.14E-08	4
C33B123	C33F128	1.02E+06	1.52E-02	1.48E-08	4
C33B52	C33F57	2.06E+05	3.96E-03	1.92E-08	4
C33B61	C33F66	4.89E+05	1.05E-02	2.14E-08	4
C33B62	C33F67	5.07E+05	1.26E-02	2.49E-08	4
C33B64	C33F69	4.33E+05	2.21E-03	5.10E-09	4
C33B63	C33F68	5.33E+05	3.74E-03	7.01E-09	4
C33B122	C33F127	7.47E+05	7.12E-03	9.53E-09	4
C33B72	C33F77	8.71E+05	2.00E-04	2.30E-10	5
C33B79	C33F84	5.15E+05	3.90E-04	7.60E-10	5
C33B77	C33F82	8.28E+05	2.62E-04	3.20E-10	6
C33B87	C33F92	7.20E+05	4.32E-04	6.00E-10	6
C33B94	C33F99	9.22E+05	5.85E-04	6.30E-10	6
C33B95	C33F100	4.82E+05	7.40E-03	1.54E-08	6
C33B120	C33F125	5.75E+05	1.68E-03	2.93E-09	6
C33B89	C33F94	low binding	low binding	low binding	8
C33B54	C33F59	low binding	low binding	low binding	9
C33B124	C33F129	3.57E+05	1.24E-04	3.50E-10	NB

C33B80	C33F85	3.23E+05	4.25E-04	1.32E-09	NB
C33B56	C33F61	low binding	low binding	low binding	NB

Table 47, continued.

Cyno CD33 ECD-HSA					
Prot. AA ID	V Region ID	k_a (1/Ms)	k_d (1/s)	K_D (M)	Epitope Bin
C33B48	C33F53	4.31E+06	1.58E-04	3.66E-11	1
C33B46	C33F51	2.97E+06	3.75E-04	1.26E-10	1
C33B66	C33F71	1.22E+06	2.66E-04	2.17E-10	1
C33B107	C33F112	3.31E+05	7.01E-05	2.12E-10	1
C33B88	C33F93	binding/no fit	binding/no fit	binding/no fit	1
C33B96	C33F101	binding/no fit	binding/no fit	binding/no fit	3
C33B101	C33F106	2.25E+05	2.69E-04	1.20E-09	3
C33B73	C33F78	6.00E+05	5.08E-04	8.46E-10	4
C33B125	C33F130	1.12E+06	3.39E-04	3.04E-10	4
C33B55	C33F60	1.16E+06	8.37E-05	7.23E-11	4
C33B82	C33F87	5.45E+05	7.51E-04	1.38E-09	4
C33B83	C33F88	2.47E+05	2.88E-03	1.17E-08	4
C33B75	C33F80	6.16E+05	1.32E-03	2.15E-09	4
C33B123	C33F128	1.26E+06	3.39E-03	2.69E-09	4
C33B52	C33F57	3.13E+05	1.48E-03	4.74E-09	4
C33B61	C33F66	7.34E+05	1.62E-03	2.21E-09	4
C33B62	C33F67	8.05E+05	1.49E-03	1.85E-09	4
C33B64	C33F69	5.90E+05	1.01E-03	1.71E-09	4
C33B63	C33F68	7.23E+05	8.80E-04	1.22E-09	4
C33B122	C33F127	binding/no fit	binding/no fit	binding/no fit	4
C33B72	C33F77	9.19E+05	5.40E-04	5.87E-10	5
C33B79	C33F84	5.48E+05	2.20E-03	4.01E-09	5
C33B77	C33F82	1.08E+06	2.66E-04	2.47E-10	6
C33B87	C33F92	1.12E+06	2.64E-04	2.36E-10	6
C33B94	C33F99	1.10E+06	5.20E-04	4.73E-10	6
C33B95	C33F100	8.44E+05	8.06E-03	9.56E-09	6
C33B120	C33F125	8.76E+05	9.02E-04	1.03E-09	6
C33B89	C33F94	2.65E+05	2.01E-04	7.60E-10	8
C33B54	C33F59	1.32E+06	6.37E-04	4.84E-10	9
C33B124	C33F129	4.67E+05	4.72E-04	1.01E-09	NB
C33B80	C33F85	4.92E+05	2.59E-04	5.27E-10	NB
C33B56	C33F61	low binding	low binding	low binding	NB

The OmniMouse panel (8 mAbs total) was generated separately and characterized further for binding to cells. Cell binding was performed as described above and summarized in the table below. Of the 8 mAbs tested 6 bound directly to CD33 expressing cells while 2 did not.

5 Table 48. Cell Binding of OMNIMouse derived mAbs to human and cyno expressing cell lines

mAb	Parental				Human CD33			
	60 nM	6 nM	0.6 nM	0 nM	60 nM	6 nM	0.6 nM	0 nM
C33B909	253.50	206.04	169.77	119.51	176.49	170.25	154.00	191.28
C33B910	193.52	176.14	108.46	190.17	213.55	183.33	151.25	155.29
C33B911	1466.02	389.41	186.22	113.30	237954.27	100333.48	13501.02	114.07
C33B912	977.91	273.07	140.62	124.53	237140.86	101295.70	15726.96	149.54
C33B913	174.49	118.08	123.26	129.07	518952.00	409071.06	204694.14	127.82
C33B914	181.37	142.74	139.10	113.48	304350.88	315129.56	153252.58	185.45
C33B915	101.28	147.65	143.51	100.00	390477.25	362902.66	138398.56	112.22
C33B916	416.08	145.16	115.70	91.75	447815.47	404033.19	192941.55	167.07

Table 48, continued:

mAb	Cyno CD33			
	60 nM	6 nM	0.6 nM	0 nM
C33B909	180.33	135.33	115.73	124.03
C33B910	202.42	135.18	116.71	175.97
C33B911	17036.56	7729.14	1935.16	97.94
C33B912	15070.88	7271.38	1726.03	124.69
C33B913	40661.90	36920.95	35224.10	106.19
C33B914	44964.85	33368.26	22086.01	86.76
C33B915	37495.34	35692.21	36165.59	113.92
C33B916	41004.43	33294.78	22790.61	104.43

The 6 mAbs that bound CD33 on cells were further characterized biophysically via full kinetic analysis to recombinant antigen using the methods described above and summarized in the table below. Of the 6 mAbs tested, 1 bound to human CD33 with a picomolar affinity (C33B912) and subnanomolar for cyno CD33, while 1 had very strong affinity for human CD33 but only nanomolar affinity towards cyno CD33 (C33B911). Two more clones were subnanomolar for both human and cyno CD33 (C33B913 and C33B916), but neither affinity was in the range of C33B912.

Table 49. Full Kinetics Analysis of OMNIMouse derived mAbs

mAb	Human CD33 ECD-HSA			Cyno CD33 ECD-HSA		
	k_a (1/Ms)	k_d (1/s)	K_D (M)	k_a (1/Ms)	k_d (1/s)	K_D (M)

C33B911	1.10E+06	4.14E-05	3.78E-11	1.15E+06	1.15E-03	1.00E-09
C33B912	1.42E+06	4.29E-05	3.02E-11	1.50E+06	6.50E-04	4.33E-10
C33B913	6.60E+05	6.40E-04	9.69E-10	2.56E+06	3.08E-04	1.20E-10
C33B914	4.44E+05	9.80E-03	2.21E-08	5.29E+05	2.33E-04	4.40E-10
C33B915	2.18E+05	9.89E-04	4.53E-09	3.81E+06	8.93E-05	2.34E-11
C33B916	6.27E+05	4.11E-04	6.55E-10	4.73E+05	4.03E-04	8.52E-10

An epitope binning experiment was performed on the 6 cell binding mAbs derived from OMNIMouse along with several control mAbs previously identified in the earlier OMNIRat campaign. The control mAbs were chosen based on their subnanomolar affinity towards human CD33 and the number of distinct epitope bins. The binning software HtTools assigns Epitope Bin numbers on a per experiment basis and therefore having several controls to already defined epitope bins was critical for cross-comparison. The two OMNIMouse derived human CD33 high affinity clones (C33B911 and C33B912) both binned with clones from bin 4 above (bin 4 in this experiment) while the subnanomolar clone (C33B916) binned into 2 here along with C33B836 (bin 1 in the above experiment).

Table 50: Epitope Bins of OMNIMouse anti-CD33 mAbs

mAb	V region ID	Epitope Bin
C33B915	C33F553	1
C33B916	C33F554	2
C33B836	C33F53	2
C33B914	C33F552	2
C33B913	C33F551	3
C33B806	C33F106	3
C33B911	C33F549	4
C33B912	C33F550	4
C33B778	C33F78	4
C33B830	C33F130	4
C33B782	C33F82	5
C33B792	C33F92	5
C33B799	C33F99	5
C33B760	C33F60	6
C33B777	C33F77	7

CD33 is comprised of 2 IgG domains, the membrane distal V domain and the membrane proximal C2 domain. The SNP rs12459419 can cause the selective alternative splicing of the CD33 pre-mRNA transcript to yield a C2 only form expressed on cells and therefore targeting this domain can provide clinical benefit. To ascertain which of the two domains, the mAbs were

5 capable of binding, an off-rate screen was performed following the protocol above on 6 mAbs with the highest binding capability that covered 4 distinct epitope bins using Human CD33 ECD-HSA, Human CD33 V-HSA and Human CD33 C2-HSA as the binding antigens. As shown in the table below, the two clones previously grouped in bin 4 both bound to the huCD33 C2 domain but not the huCD33 V domain, while the clones in bin 2 and 3 bound the V domain but

10 not the C2 domain. Two clones grouped into bin 5 did not bind either domain, and, therefore, their exact binding location could span the two domains. Three (3) commercially available mAbs were included in this experiment ((WM53 (EMD Millipore; Darmstadt, Germany), P67.7 (Biolegend, San Diego, CA), and LSBio clone 906 (LifeSpan Biosciences, Seattle, WA))) and all showed binding to the V domain, but not the C2 domain. Looking at the epitope bins in Tables

15 42 and 45 in relation to the C2 domain binding data in Table 51, there are a total of 15 mAbs that could potentially bind the C2 domain ranging in affinities from ~25 nM to ~30 pM on the human full length protein.

Table 51. Off-rate Domain Binding

	huCD33 ECD-HSA	huCD33-V-HSA	huCD33-C2-HSA	Epitope Bin
Protein ID	k_d (1/s)	k_d (1/s)	k_d (1/s)	
C33B912	1.29E-05	No/low binding response	6.68E-05	4
C33B778	4.72E-05	No/low binding response	2.57E-03	4
C33B782	2.58E-04	No/low binding response	No/low binding response	5
C33B792	4.27E-04	No/low binding response	No/low binding response	5
C33B836	5.52E-05	3.71E-05	No/low binding response	2
C33B806	1.36E-03	3.18E-03	No/low binding response	3
WM53	2.37E-03	3.78E-02	No/low binding response	

P67.7	1.05E-03	2.43E-03	No/low binding response	
LSBio clone 906	2.45E-03	4.34E-02	No/low binding response	

To support further *in vivo* and *in vitro* studies, select clones (C33B836, C33B782, C33B778, C33B904, C33B806, C33B830, C33B937, C33B792, C33B760, and C33B777) were chosen for scale-up and fab arm exchange to produce bi-specific molecules with anti-CD3 antibodies. ExpiCHO-S™ cells (ThermoFisher Scientific) were seeded at $1.25 \times 10^5 - 2.25 \times 10^5$ viable cells/mL in ExpiCHO™ Expression Medium and cultured in polycarbonate, disposable, sterile, vented, non-baffled Erlenmeyer shake flasks in a 37°C, 7% CO₂ shaker incubator (INFORS HT Multitron Pro). For routine cell growth in 125 mL – 2L shake flasks, the shake speed was set to 130 rpm for shakers with a 19mm shaking diameter. Cells were sub-

5 cultured when the density reached log phase growth at $4 \times 10^6 - 6 \times 10^6$ viable cells/mL with a 98-99% viability.

Two days before transfection, ExpiCHO-S™ cells were seeded at 1.5×10^6 viable cells/mL for the required culture volume. On the day of transfection, the viable cell density and percent viability was determined. Cells were transfected at a density of 6×10^6 viable cells/mL.

15 For optimal transfection, sterile heavy and light chain plasmid DNA at ≥ 1 mg/mL concentration in TE buffer (10mM Tris-HCl, 1mM EDTA, pH 8.0) was used.

ExpiCHO-S™ cells were transfected following manufacturer's Max Titer Transfection protocol (ThermoFisher Publication Number MAN0014337). All amounts and volumes shown below were per mL of the final transfected culture volume. Briefly, plasmid DNA was diluted

20 with 0.04mL cold OptiPRO™ medium (ThermoFisher Scientific) at the following ratio: 0.125 µg Heavy Chain DNA: 0.375 µg Light Chain DNA: 0.5 µg pAdvantage. 6.4µL of ExpiFectamine™ CHO Transfection Reagent was diluted and mixed gently with 0.04mL cold OptiPRO™ medium and incubated for 1 min. The diluted ExpiFectamine™ CHO Reagent was added to the diluted DNA, mixed gently and the ExpiFectamine™ CHO/plasmid DNA

25 complexes were incubated at room temperature for 5 minutes. Post-incubation, the complexes were added to the ExpiCHO-S™ cells in a shaker flask and incubated overnight in a 37°C, 7% CO₂ shaker incubator.

For the Max Titer protocol, on Day 1 post-transfection, 6 μ L ExpiFectamine™ CHO Enhancer and 160 μ L ExpiCHO™ Feed were added and the flask was transferred to a 32°C, 7% CO₂ shaker incubator. On Day 5 post-transfection, 160 μ L of ExpiCHO™ Feed was added for the second time to the flask and returned to the 32°C incubator with shaking. The culture was
5 harvested on Day 12 post-transfection, centrifuged at 5000 rpm for 15 mins and clarified through a 0.2 μ m Acropak 1500 filter capsule (Pall).

Expressed antibodies were purified from the clarified supernatants using MabSelect SuRe (GE Healthcare). MabSelect SuRe Protein A columns were equilibrated with 1x D-PBS, pH 7.2 prior to loading individual culture supernatants. Unbound proteins were removed by washing
10 extensively with 1x D-PBS, pH 7.2. Bound proteins were eluted with 0.1 M Na-acetate, pH 3.5. Peak fractions were neutralized with 2.5M Tris pH 7.2 and pooled. The neutralized fraction pools were either dialyzed into 1xDPBS for assays and biophysical characterization or utilized for bispecific assembly.

The protein concentration for each elution pool was determined by measuring absorbance
15 at OD280 nm and calculated using absorbance extinction coefficient based on the amino acid sequence.

6 Preparation and Functional Evaluation of CD33 $\times$ CD3 Bispecific Antibodies

6-1 Fab-arm exchange using purified parental mAbs

The formation of the CD33 $\times$ CD3 bispecific antibodies requires two parental mAbs, one
20 specific for the targeting arm (e.g. CD33) and one specific for the effector arm (e.g. CD3). CD33 mAbs were recombined with a high affinity (CD3B376: VH of SEQ ID NO: 652, and VL of SEQ IF NO: 661) or low affinity CD3 arm (CD3B450: VH of SEQ ID NO: 657, and VL of SEQ IF NO: 678) arms. These parental mAbs (CD33 and CD3 arms) are in the IgG4 PAA format (Labrijn et al, 2013) where the targeting parent (CD33) contains the 409R Genmab mutation
25 (native amino acid for IgG4), while the killing parent (CD3) contains the F405L mutation and R409K. The monospecific anti-CD3 antibody was expressed as IgG4, having Fc substitutions S228P, F234A, L235A, F405L, and R409K (CD3 arm) (numbering according to EU index) in their Fc regions. The monospecific antibodies were expressed and purified as described above. Post purification the parental CD33 antibodies were mixed with the desired parental CD3

antibody under reducing conditions in 75mM 2-MEA (2-Mercaptoethylamine) and incubated at 31°C for 5hours or at room temperature overnight. The recombination reactions were based on molar ratios, where a set amount of CD33 antibody (e.g., 10mg, or ~74.6 nanomoles) was combined with CD3 antibody (e.g., ~67.8 nanomoles), where the CD33 antibody was added in a 5 6% excess of the CD3 antibody. The concentrations of the CD33 antibody stocks varied from 0.8 to 6 mg/mL, and the volumes of the recombination reactions varied for each pairing. The recombination reactions were subsequently dialyzed overnight against PBS to remove the reductant. The CD33×CD3 bispecific antibody reactions were performed with an excess of the CD33 antibody (ratio) to minimize the amount of unreacted CD3 parental antibody remaining 10 after recombination.

The final CD33×CD3 bispecific antibodies produced, along with the parental mAbs (i.e. CD33, CD3, or Null) used in the recombination reactions are listed in Table 47.

Selected CD33 hits were also paired with a non-killing arm (Null) to create negative controls for testing purposes. For control bispecific antibodies, B2M1, an RSV antibody in the 15 IgG4 PAA format was generated, purified and, combined with either the CD3 arms CD3B219 or CD3B376 -F405L, R409K to generate CD3B288 (CD3×Null) and CD3B510 (CD3B376×Null), respectively; CD33 arms were combined with B23B49 to generate CD33×Null, as in Table 52.

Table 52: CD33×CD3 bispecific antibodies

Bispecific Ab	Parental	HC Pep ID	VH Pep SEQ ID	LC Pep ID	VL Pep SEQ ID
C3CB7	C33B836	C33H80	267	C33L73	306
	CD3B219	CD3H141	247	CD3L66	287
C3CB5	C33B830	C33H84	269	C33L66	308
	CD3B219	CD3H141	247	CD3L66	287
C3CB4	C33B806	C33H69	260	C4LL152	300
	CD3B219	CD3H141	247	CD3L66	287
C3CB16	C33B799	C33H98	275	C33L69	314
	CD3B219	CD3H141	247	CD3L66	287
C3CB14	C33B792	C33H87	270	C33L35	309
	CD3B219	CD3H141	247	CD3L66	287
C3CB12	C33B782	C33H72	262	C33L40	301
	CD3B219	CD3H141	247	CD3L66	287
C3CB11	C33B778	C33H66	258	C33L60	298
	CD3B219	CD3H141	247	CD3L66	287
C3CB10	C33B777	C33H65	257	C33L47	297
	CD3B219	CD3H141	247	CD3L66	287

C3CB8	C33B760	C33H45	250	C33L11	290
	CD3B219	CD3H141	247	CD3L66	287
C3CB97	C33B836	C33H80	267	C33L73	306
	CD3B376	CD3H219	652	CD3L150	661
C3CB98	C33B830	C33H84	269	C33L66	287
	CD3B376	CD3H219	652	CD3L150	661
C3CB99	C33B806	C33H69	260	C4LL152	300
	CD3B376	CD3H219	652	CD3L150	661
C3CB100	C33B799	C33H98	275	C33L69	314
	CD3B376	CD3H219	652	CD3L150	661
C3CB101	C33B792	C33H87	270	C33L35	309
	CD3B376	CD3H219	652	CD3L150	661
C3CB102	C33B782	C33H72	262	C33L40	301
	CD3B376	CD3H219	652	CD3L150	661
C3CB103	C33B778	C33H66	258	C33L60	298
	CD3B376	CD3H219	652	CD3L150	661
C3CB104	C33B777	C33H65	257	C33L47	297
	CD3B376	CD3H219	652	CD3L150	661
C3CB105	C33B760	C33H45	250	C33L11	290
	CD3B376	CD3H219	652	CD3L150	661
C33B941	C33B836	C33H80	267	C33L73	306
	B23B49	B23H1	246	B23L3	286
C33B942	C33B830	C33H84	269	C33L66	308
	B23B49	B23H1	246	B23L3	286
C33B943	C33B806	C33H69	260	C4LL152	300
	B23B49	B23H1	246	B23L3	286
C33B944	C33B799	C33H98	275	C33L69	314
	B23B49	B23H1	246	B23L3	286
C33B945	C33B792	C33H87	270	C33L35	309
	B23B49	B23H1	246	B23L3	286
C33B946	C33B782	C33H72	262	C33L40	301
	B23B49	B23H1	246	B23L3	286
C33B947	C33B778	C33H66	258	C33L60	298
	B23B49	B23H1	246	B23L3	286
C33B948	C33B777	C33H65	256	C33L47	297
	B23B49	B23H1	246	B23L3	286
C33B949	C33B760	C33H45	250	C33L11	290
	B23B49	B23H1	246	B23L3	286
CD3B288	B23B39	B23H1	246	B23L3	286
	CD3B219	CD3H141	247	CD3L66	287
CD3B510	B23B39	B23H1	246	B23L3	286
	CD3B376	CD3H219	652	CD3L150	661
C3CB87	C33B903	C33H251	280	C33L117	319
	CD3B219	CD3H141	247	CD3L66	287
C3CB88	C33B904	C33H252	281	C33L118	320

	CD3B219	CD3H141	247	CD3L66	287
C3CB89	C33B905	C33H253	282	C33L119	321
	CD3B219	CD3H141	247	CD3L66	287
C3CB90	C33B907	C33H255	284	C33L121	323
	CD3B219	CD3H141	247	CD3L66	287
C3CB91	C33B908	C33H256	285	C33L122	324
	CD3B219	CD3H141	247	CD3L66	287
C3CB189	C33B904	C33H252	281	C33L118	320
	CD3B376	CD3H219	652	CD3L150	661

Pep: Peptide; Nuc: Nucleotide; SEQ ID: SEQ ID NO

6-2 *Ex vivo* CD33×CD3 mediated reduction of AML blasts and T cell activation in an AML primary sample

To further assess the cytotoxicity potential of CD33×CD3 bispecific antibodies, an *ex vivo* cytotoxicity assay was performed using AML patient whole blood using the top four antibodies (**Fig. 62**). In this assay, various bispecific antibodies (CD33 antibodies paired with either CD3 arm CD3B219 and CD3B376) were added to diluted whole blood from AML patients for a period of 48 hours without providing additional T-cells, since this assay relies on the presence of autologous T-cells in the patient's blood. At 48 hours, the samples were stained with CD3 PerCPCy5.5, CD25 PE, CD33 FITC and CD38 APC (all antibodies were purchased from Biolegend; San Diego, CA). The samples were then washed at least 3 times in 1x Lyse RBC Lysis Buffer (eBioscience). The samples were then stained with the LIVE/DEAD® Fixable Near-IR Dead Cell Stain buffer (Life Technologies). The extent of tumor cytotoxicity was determined by first quantifying the live CD33⁺ cells in the fraction of AML patient cancer cells (defined as CD3⁺CD38⁺ cells) in the presence of the bispecific antibodies. Cytotoxicity was calculated as a percentage relative to PBS/untreated control using the following equation: (%CD33⁺ in PBS/untreated control - % CD33⁺ in treated sample) / (%CD33⁺ in PBS/untreated control). T cell activation was calculated as a percentage of CD25⁺ events in CD3⁺ fraction.

As shown in **Fig. 62**, all CD33 lead antibodies paired with either CD3 arm (CD3B376 and CD3B219) promoted a dose-dependent reduction of total cytotoxicity that correlated with T cell activation after 48 hours. Null arm control antibodies (NullxCD3B219 and nullxCD3B376) failed to show tumor cell cytotoxicity or T cell activation. This result also demonstrated that the CD33×CD3 bispecific antibodies work in an autologous setting. These results are representative of 4 other AML donor samples (data not shown). Table 53 summarizes the EC₅₀ values

generated with the CD33×CD3 multispecific antibodies. As seen from the EC₅₀ values, C33B904 paired with either CD3 arm (C3CB88, C3CB189) as well C33B836 paired with either CD3 arm (C3CB7, C3CB97) were the most potent and efficacious antibodies. These 4 antibodies were thus the focus of further characterization.

- 5 Table 53: CD33×CD3 T-cell mediated *ex vivo* cytotoxicity assays. Summary of the EC₅₀ values for 8 CD33×CD3 bispecific antibodies

Bispecific Ab ID	Primary AML Cell Killing EC ₅₀ (nM)
C3CB11	3.958
C3CB12	2.635
C3CB7	0.3315
C3CB88	0.6722
C3CB103	4.186
C3CB102	4.973
C3CB97	~0.2316
C3CB189	0.5782

6-3 Demonstration that the CD33×CD3 bispecific antibodies bind to the C2 domains of CD33 and induce cytotoxicity of CD33 single nucleotide polymorphism (SNP) expressing cell lines

- 10 In vitro T cell mediated cytotoxicity assays with CD33×CD3 bispecific antibodies

Recent studies showed that a single nucleotide polymorphism (SNP) rs12459419 was present in ~50% of the AML population and leads to skipping of exon 2 of CD33 which results in the deletion of the V domain of CD33. This study also showed that Mylotarg which binds to the V domain of CD33, had no efficacy in patients that express the SNP, and, therefore, reduced risk of relapse and improved survival in ~50% of the AML population (Lamba et al 2017, JCO, CD33 Splicing Polymorphism Determines Gemtuzumab Ozogamicin Response in De Novo Acute Myeloid Leukemia: Report From Randomized Phase III Children's Oncology Group Trial AAML0531). Given the data with Mylotarg in the above mentioned study, *in vitro* T cell mediated cytotoxicity assays were performed to assess whether CD33 hits (V binding C33B836 vs C2 binding C33B904) paired with CD3 arms (CD3B219 or CD3B376) mediate killing of SNP rs12459419 expressing cell lines. Briefly, effector cells (pan T cells purchased from Biological Speciality) were harvested, counted, washed, and resuspended to 1x10⁶ cells/ml in RPMI

(Invitrogen) with 10% FBS (Invitrogen) cell media. Target cells (KG1, SH2 and OCIAML3) were labeled with CFSE (Invitrogen) and resuspended to 2×10^5 cells/mL in RPMI with 10% FBS. KG1, SH2 and OCIAML3 were chosen to represent wildtype, heterozygous and homozygous for the CD33 SNP rs12459419 mutation, respectively. Effectors and CFSE-labeled target cells were mixed at effector:target ratio (E:T)=5:1 in sterile 96-well round bottom plates. 10 μ l of Fc block (ReoPro Fc fragment) along with 5 μ L aliquot of bispecific antibody was added to each well containing various concentrations. Cultures were incubated at 37°C for 48 hours under 5% CO₂. After 48 hrs, the LIVE/DEAD® Fixable Near-IR Dead Cell Stain buffer (Life Technologies) was added to samples and cultures were incubated for 20 min in the dark at RT, washed, and resuspended in 100-200 μ L FACs buffer. The drug-induced cytotoxicity was determined using CANTO II flow cytometer (BD Biosciences) and analyzed with FlowJo Software or Dive software (BD Biosciences). The population of interest is the double positive CFSE+/ live/dead+ cells. As shown in **Fig. 63**, unlike the null arm controls (null x CD3B219 and null x CD3B376), V binding and C2 binding CD33×CD3 multispecific antibodies induced T cell redirected cell cytotoxicity of CD33+ WT for SNP rs12459419 mutation cell line KG1 at 48 hrs. In contrast, unlike V binder C33B836 (C3CB97, C3CB7), only the C2 binding C33B904 paired bispecific antibodies (C3CB189, C3CB88) mediated cytotoxicity of SH2 and OCIAML3 cell lines that were heterozygous or homozygous for the rs12459419 SNP mutations, respectively. For this reason, C33B904 paired bispecific antibodies (C3CB189, C3CB88) were taken forward for further analysis and characterization. Collectively, these data suggest that CD33 C2 binding bispecific antibodies such as C33B904 paired bispecific antibodies have the potential to show efficacy in a broader group of AML patients than V binding competitor anti-CD33 antibodies.

6-4 *Ex vivo* CD33×CD3 mediated reduction of spiked in MOLM-13 and monocytes in an *ex vivo* whole blood MOLM-13 cytotoxicity assay

To assess the cytotoxicity potential of CD33×CD3 bispecific antibodies at eliminating spiked in MOLM-13 cells and normal human monocytes, an *ex vivo* cytotoxicity assay using normal healthy human whole blood with exogenously added CD33⁺ AML cell line MOLM-13 was utilized. Similar to the above experiment, various bispecific antibodies (CD33 antibodies paired with either CD3 arm CD3B219 and CD3B376) were added to diluted whole blood from 6 different normal human donors for a period of 48 hr without providing additional T-cells, since

this assay relies on the presence of autologous T-cells in the donor's blood. Prior to dilution, the concentration of T cells in the blood of each donor was enumerated. The blood was then diluted with CFSE (Invitrogen) labeled MOLM-13 cells, such that effector:target ratio (E:T) is 1:5 to mimic the effector: target ratio in AML patient samples. At 48 hs, the samples were stained with

5 CD3 PerCPCy5.5, CD25 PE, CD33 FITC and CD14 Pacific Blue (all antibodies were purchased from Biolegend). The samples were then washed at least 3 times in 1x Lyse RBC Lysis Buffer (eBioscience). The samples were then stained with the LIVE/DEAD® Fixable Near-IR Dead Cell Stain buffer (Life Technologies). The extent of tumor cytotoxicity was determined by first quantifying the live CD33⁺ cells in the fraction of CD14⁺ monocytes in the presence of the

10 bispecific antibodies. Cytotoxicity of MOLM-13 cells was determined by enumerating the percentage of dead CFSE⁺ cells. Cytotoxicity of monocytes was calculated as a percentage relative to PBS/untreated control using the following equation: (%CD33⁺ CD14⁺ in PBS/untreated control-% CD33⁺ CD14⁺ in treated sample)/(%CD33⁺ CD14⁺ in PBS/untreated control). The data in **Fig. 64** indicate that both CD33×CD3 bispecific antibodies (same CD33

15 lead C33B904 paired with either CD3 arm, CD3B376 and CD3B219) specifically induce cell cytotoxicity of MOLM-13 cells and CD33⁺ monocytes at 48 hr. The null arm controls were used as negative bispecific antibody controls. The null arm control showed little-to-no cytotoxicity activity of the MOLM-13 and CD33⁺ monocytes. These data show the average values of 6 different normal donors. The average EC₅₀ values for cytotoxicity of MOLM-13 and CD14⁺

20 monocytes are shown in Table 54.

Table 54. CD33×CD3 T-cell mediated *ex vivo* cytotoxicity assays. Summary of EC₅₀ values for 2 CD33×CD3 bispecific antibodies.

Bispecific Ab ID	MOLM13 Killing EC ₅₀ (nM)	CD33 ⁺ CD14 ⁺ Killing EC ₅₀ (nM)
C3CB189	0.1677	1.156
C3CB88	0.671	0.506

6-5 Demonstration of species cross-reactivity of CD33×CD3 bispecific antibodies to cynomologous monkey

Ex vivo CD33×CD3 mediated reduction of monocytes in an ex vivo cytotoxicity assay with cynomologous whole blood

To demonstrate functional cross-reactivity and to assess the cytotoxicity potential of CD33×CD3 bispecific antibodies at eliminating normal cynomologous monocytes, an *ex vivo* cytotoxicity assay using healthy cynomologous whole blood was utilized. Similar to the above experiment, various bispecific antibodies (CD33 antibodies paired with either CD3 arm CD3B219 and CD3B376) were added to diluted whole blood from 6 different normal cynomologous monkey donors for a period of 48 hr without providing additional T-cells, since this assay relies on the presence of autologous T-cells in the donor's blood. At 48 hrs, the samples were stained with CD3 PerCPCy5.5, CD25 PE, CD33 FITC and CD14 Pacific Blue (all antibodies were purchased from Biolegend except for the CD33 antibody which was purchased from Miltenyi, Bergisch Gladbach, Germany). The samples were then washed at least 3 times in 1x Lyse RBC Lysis Buffer (eBioscience) prior to staining with the LIVE/DEAD® Fixable Near-IR Dead Cell Stain buffer (Life Technologies). The extent of monocyte cytotoxicity was determined by first quantifying the live CD33⁺ cells in the fraction of CD14⁺ monocytes in the presence of the bispecific antibodies. Cytotoxicity was calculated as a percentage relative to PBS/untreated control using the following equation: $(\%CD33^+ CD14^+ \text{ in PBS/untreated control} - \% CD33^+ CD14^+ \text{ in treated sample}) / (\%CD33^+ CD14^+ \text{ in PBS/untreated control})$. T cell activation was calculated as a percentage of CD25⁺ events in CD3⁺ fraction. The data in **Fig. 65** indicated that both CD33×CD3 bispecific antibodies (same CD33 lead C33B904 paired with either CD3 arm, CD3B376 and CD3B219) specifically induced cell cytotoxicity of CD33⁺ monocytes as well as T cell activation at 48 hr. The null arm controls were used as negative bispecific antibody controls and showed little-to-no cytotoxicity or T cell activity. Table 55 shows the average values of 6 different cynomologous donors.

Table 55: CD33×CD3 T-cell mediated *ex vivo* cytotoxicity assays. Summary of the EC₅₀ values for 2 CD33×CD3 bispecific antibodies.

Protein AA ID	CD33 ⁺ CD14 ⁺ Killing EC ₅₀ (nM)	T cell activation EC ₅₀ (nM)
C3CB189	3.60	0.02
C3CB88	0.89	0.02

6-6 Efficacy of C3CB189 and C3CB88 in MOLM-13 human AML Xenografts in T cell humanized NSG mice

Efficacy of C3CB189 and C3CB88 was evaluated in established luciferase-transfected disseminated MOLM-13 human acute myeloid leukemia (AML) xenografts in female NOD.Cg-
5 Prkdc^{scid} Il2rg^{tm1Wjl}/SzJ (NSG) mice humanized with 20 million T cells. Animals were randomized into n=10/group by live bioluminescence imaging (BLI) on day 5 post-i.v. tumor implantation. C3CB189 and C3CB88 at 0.005, 0.05 and 0.5 mg/kg or NullxCD3 antibody control at 0.5 mg/kg were dosed i.p. every 3-4 days for 6 weeks.

On day 13 post-tumor implantation, when at least eight animals remained per group,
10 tumor growth inhibition (% TGI) as determined by bioluminescence was calculated. Statistically significant tumor growth inhibition was observed with C3CB189 (**Fig. 66**) and C3CB88 (**Fig. 68**) at all concentrations, as compared to NullxCD3 control. C3CB189 at 0.005, 0.05, and 0.5 mg/kg elicited tumor growth inhibition of 76%, 100% and 82%, respectively, and C3CB88 at 0.005, 0.05, and 0.5 mg/kg elicited tumor growth inhibition of 100%, 100% and 91%,
15 respectively, as compared to NullxCD3 treated controls.

Treatment with C3CB189 and C3CB88 resulted in reduced tumor burden and increased life span (ILS) greater than the 16-day median survival of the NullxCD3 control group. Animals treated with C3CB189 had a median survival of 19-27.5 days (**Fig. 67**) and animals treated with C3CB88 had a median survival of 26-28.5 (**Fig. 69**) days across doses. C3CB189 at 0.005, 0.05,
20 and 0.5 mg/kg resulted in an increased life span of 19%, 72% and 50%, respectively, and C3CB88 resulted in an increased life span of 63%, 78% and 72%, respectively, as compared to the control group.

7 TMEFF2 Antibodies

7-1 Antigen Generation

25 Human extracellular domain (ECD) TMEFF2 was produced based on UniProt Accession# Q9UIK5 sequence. The ECD construct was designed with a 6X His-tag (SEQ ID NO: 596) and Avi-tag sequences at the C-terminus (construct TMEW1; **SEQ ID NO: 578**). A construct containing the FS2 and EGF domains (amino acids 151-320) was designed as a human serum albumin (HSA) fusion with a 6X His-tag (SEQ ID NO: 596) and avitag sequences

(construct TMEW7; **SEQ ID NO: 579**). A construct containing the TMEFF2 membrane proximal domain (residues 230-320) was designed with a 6xHis tag (SEQ ID NO: 596) (construct TMEW19; **SEQ ID NO: 580**) or fused to a rat IgG1 Fc with a His-tag (construct TMEW20; **SEQ ID NO: 581**). Residues 230-320 of TMEFF2 contain the EGF domain which spans the residues 261-301 of TMEFF2. The human TMEFF2 ECD expression constructs were transiently transfected into HEK293 derived cells, Expi293 (Gibco/Thermo Fisher Scientific) using Expifectamine according to manufacturer protocol. Cells were incubated 5 days at 37°C with 8% CO₂ on an orbital shaker before harvesting. The expressed cells were removed by centrifugation and the soluble TMEFF2 proteins with his-tags were purified from the media using immobilized metal affinity chromatography using Ni Sepharose 6 Fast Flow resin (GE Healthcare) followed by Superdex 200 preparative size exclusion chromatography (SEC) (GE Healthcare) in Dubelcco's Phosphate Saline buffer pH 7.2 (1x DPBS). The amino acid sequences of the generated antigens are shown in **Table 58**.

Table 58.

Protein AA ID	Description	Amino Acid Sequence
TMEW1 (SEQ ID NO: 578)	TMEFF2-FL-ECD-His-Avitag	FPTSLSDCQTPTGWNCSEGYDDRENDLFLCDTNTCK FDGECLRIGDTVTCVCQFKCNNDYVPVCGSNGESY QNECYLRQAACKQQSEILVVSEGSCATDAGSGSGD GVHEGSGETSQKETSTCDICQFGAECDEDAEDVWC VCNIDCSQTNFNPLCASDGKSYDNACQIKEASCQK QEKIEVMSLGRCQDNTTTTTSKSEDGHYARTDYAEN ANKLEESAREHHIPCPEHYNGFCMHGKCEHSINMQ EPSCRC DAGYTGQHCEKKDYSVLVVPVGPVRFQY VGGGSHHHHHHLNDIFEAQKIEWHE
TMEW7 (SEQ ID NO: 579)	FS2-EGF-Tev-HSA(C34S)-His-Avitag	SGETSQKETSTCDICQFGAECDEDAEDVWCVCNID CSQTNFNPLCASDGKSYDNACQIKEASCQKQEKIEV MSLGRCQDNTTTTTSKSEDGHYARTDYAENANKLE ESAREHHIPCPEHYNGFCMHGKCEHSINMQEPSCRC DAGYTGQHCEKKDYSVLVVPVGPVRFQYVVGSGSG SENLYFQGVRRSSSDAHKSEVAHRFKDLGEENFKAL VLIAFAQYLLQSPFEDHVKL VNEVTEFAKTCVADE

		SAENCDKSLHTLFGDKLCTVATLRETYGEMADCCA KQEPERNECFLQHKDDNPPLRLVRPEVDVMCTAF HDNEETFLKKYLYEIAARRHPYFYAPELLFFAKRYKA AFTECCQAADKAAACLLPKLDEL RDEGKASSAKQRL KCASLQKFGERAFAKAWAVARLSQRFPAEFAEVSK LVTDLTKVHTECCHGDLLECADDRADLAKYICENQ DSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSL AADFVESKDVCKNYAEAKDVFLGMFLYEYARRHP DYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVF DEFKPLVEEPQNLIKQNCLEFEQLGEYKFQNALLVR YTKKVPQVSTPTLVEVSRNLGKVGSKCKKHPEAKR MPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTES LVNRRPCFSALEVDETYVPKEFNAETFTFHADICTL SEKERQIKKQTALVELVKHKPKATKEQLKAVMDDF AAFVEKCKKADDKETCFAEEGKKLVAAASQAALGL GGGSHHHHHHLNDIFEAQKIEWHE
TMEW19 (SEQ ID NO: 580)	spTMEFF2(230- 320)G3S-H6	NTTTTTKSEDGHYARTDYAENANKLEESAREHHIP CPEHYNGFCMHGKCEHSINMQEPSCRC DAGYTQQ HCEKKDYSVLYVVP GPVRFQYVGGGSHHHHHH
TMEW20 (SEQ ID NO: 581)	spTMEFF2(230-320)- G3S-ratIgG1Fc	NTTTTTKSEDGHYARTDYAENANKLEESAREHHIP CPEHYNGFCMHGKCEHSINMQEPSCRC DAGYTQQ HCEKKDYSVLYVVP GPVRFQYVGGGSPRNCGGDC KPCICTGSEVSSVFIFPPKPKDVL TITLTPKVTCVVV DISQDDPEVHFSWFVDDVEVHTAQTRPPEEQFNSTF RSVSELPILHQDWLNGRTFRCKVTSAAFPSPIEKTIS KPEGRTQVPHVYTMSPTKEEMTQNEVSITCMVKGF YPPDIYVEWQMNGQPQENYKNTPTMDTDGSYFL YSKLNVKKEKWQQGNTFTCSVLHEGLHNHHTEKS LSHSPGKGGGSHHHHHH

7-2 Generation of anti-TMEFF2 antibodies

Antibody generation using transgenic rats expressing human immunoglobulin loci

(OmniRat®) The OmniRat® contains a chimeric human/rat IgH locus (comprising 22 human

V_{HS}, all human D and J_H segments in natural configuration linked to the rat C_H locus) together with fully human IgL loci (12 V_Ks linked to J_K-C_K and 16 V_Ls linked to J_L-C_L). (see e.g., Osborn, et al. (2013) J Immunol 190(4): 1481-1490). Accordingly, the rats exhibit reduced expression of rat immunoglobulin, and in response to immunization, the introduced human heavy
 5 and light chain transgenes undergo class switching and somatic mutation to generate high affinity chimeric human/rat IgG monoclonal antibodies with fully human variable regions. The preparation and use of OmniRat®, and the genomic modifications carried by such rats, is described in WO14/093908.

OmniRats were immunized with the human TMEFF2 construct FS2-EGF-Tev-

10 HSA(C34S)-His-Avitag (TMEW7, SEQ ID NO: 579) and boosted with the construct spTMEFF2 (230-320)G3S-ratIgG1Fc (TMEW20, SEQ ID NO: 581). Following a 89 day immunization regimen, lymph nodes from the rats were harvested and used to generate hybridomas and the hybridoma supernatants were screened for binding to human TMEFF2-FL-ECD-His-Avitag (TMEW1) protein by ELISA and/or SPARCL (Spatial Proximity Analyte Reagent Capture
 15 Luminescence). Several supernatants were selected for secondary ELISA and SPARCL screening of binding to TMEFF ECD, FS2-EGF, or EGF domain only TMEFF2. Based on the screening results, several hybridoma clones were sequenced, expressed and characterized for functionality.

20 Antibody generation from phage display libraries

TMEFF2 binding Fabs were selected using standard methods from two sets of *de novo* pIX phage display libraries as described in Shi *et al.*, J Mol Biol 397:385-96, 2010 and WO2009/085462). Briefly, two sets of libraries, referred to as V3.0 and V5.0, were generated by diversifying human scaffolds where germline VH genes IGHV1-69*01, IGHV3-23*01 and
 25 IGHV5-51*01 were recombined with the human IGHJ-4 minigene *via* the H3 loop (IGHJ-6 minigene was also used in V5.0), and human germline VLkappa genes O12 (IGKV1-39*01), L6 (IGKV3-11*01), A27 (IGKV3-20*01), and B3 (IGKV4-1*01) were recombined with the IGKJ-1 minigene to assemble complete VH and VL domains. Positions in the heavy and light chain variable regions around the H1, H2, L1, L2 and L3 loops in frequent contact with protein and
 30 peptide antigens were chosen for diversification. Sequence diversity at selected positions was limited to residues occurring at each position in the IGHV or IGLV germline gene families of the

respective IGHV or IGLV genes. Diversity at the H3 loop was generated by utilizing short to mid-sized synthetic loops of lengths 7-14 amino acids for V3.0 libraries, and lengths 6-19 amino acids for V5.0 libraries. The amino acid distribution at H3 was designed to mimic the observed variation of amino acids in human antibodies. The scaffolds utilized to generate libraries were
5 named according to their human VH and VL germline gene origin. For both V3.0 and V5.0 sets, each of the three heavy chain libraries were combined with the four germline light chains or germline light chain libraries to generate 12 unique VH:VL combinations for each set of libraries which are used for selection experiments.

10 V Region Cloning

Total RNA from hybridoma cell lysates of phage were purified using RNeasy 96 kit (Qiagen) following the manufacturer's protocol. The resulting RNA was quantitated using Drop Sense and either stored at -80° C or used for cDNA synthesis using Invitrogen SuperScript III First-Strand Synthesis System by RT-PCR (Invitrogen). The first strand cDNA synthesis was
15 carried out using gene specific primers annealed to the constant regions of heavy, kappa, and lambda chains, respectively. The RT-PCR reaction mixture comprised of up to 3 µg of purified RNA, gene specific primer, dNTP mix, reaction buffer, 25 mM MgCl₂, DTT, RNaseOUT™ (40 U/µl, Invitrogen), and SuperScript™ III RT (200 U/µl, Invitrogen Cat# 18080-051) was incubated at 50°C for 50 minutes and 85°C for 5 minutes. The resulting single-stranded cDNA
20 was stored at -20°C, or used directly for PCR amplification. The PCR reaction was carried out using Platinum Pfx polymerase (Invitrogen). The v-region fragments were amplified by forward and reverse primers annealing to the leader sequences and constant regions of heavy, kappa and lambda chains, respectively, using optimized PCR conditions. The resulting PCR fragments were sequenced, the amino acid sequences of the recovered v-regions were codon optimized and
25 cloned into the pUnder-based expression vector carrying the IgG4 constant region with S228P, F234A and L235A mutations (IgG4PAA isotype).

Expi293 Small Scale Transfection and Purification

Select antibodies identified from the immunization campaigns or phage display were
30 cloned and expressed as IgG1PAA and purified via small 2 ml scale. Expi293™ cells (ThermoFisher Scientific) were seeded at 1.25×10^5 – 2.25×10^5 viable cells/mL density in

Expi293™ Expression Medium and cultured in 125 mL – 2L shake flasks at 37°C, 7% CO₂.

Cells were sub-cultured when density reached the log phase growth at $3 \times 10^6 - 5 \times 10^6$ viable cells/mL with a 98-99% viability.

On day of transfection, the viable cell density and percent viability was determined. Cells were transfected at a density of 3×10^6 viable cells/mL following manufacturer's Transfection protocol (ThermoFisher Publication Number MAN0007814). Culture were harvested on Day 6 post-transfection by centrifugation at 850xG for 15 minutes before purification. Antibodies were purified from the clarified supernatants using mAb Select Sure resin (GE Healthcare) and dialyzed into PBS. Protein concentrations were determined by A280 measurement on the filtrate using a DropSense Instrument (Trinean).

7-3 Characterization of anti-TMEFF2 antibodies

Anti-TMEFF2 antibodies bind TMEFF2 with high affinity

Binding of select IgG4PAA anti-TMEFF2 antibodies to TMEFF2 ECD (TMEW1: TMEFF2-FL ECD-His-Avitag) and/or the membrane proximal region (TMEW19: spTMEFF2(230-320)G3S-H6) was assessed using Proteon (TMEB674, TMEB675, TMEB 565 and TMEB570) or Biacore SPR (TMEB762 and TMEB757). The kinetic parameters of binding selected antibodies are shown in Table 59. The anti-TMEFF2 antibodies were found to bind both the TMEFF2 ECD and TMEFF2 membrane proximal region with picomolar affinities.

Table 59.

Antibody	Antigen	TMEFF2 domain	ka (1/Ms)	kd (1/s)	KD (nM)
TMEB674	TMEW1	ECD	2.01E+06	1.62E-04	0.10
TMEB674	TMEW19	MP*	8.37E+05	1.75E-04	0.20
TMEB675	TMEW1	ECD	2.65E+06	1.53E-04	0.10
TMEB675	TMEW19	MP	9.72E+05	1.58E-04	0.20
TMEB565	TMEW1	ECD	3.84E+05	9.13E-06	0.02
TMEB565	TMEW19	MP	7.77E+05	6.39E-06	0.01
TMEB570	TMEW1	ECD	4.64E+05	5.13E-05	0.11
TMEB570	TMEW19	MP	7.62E+05	4.67E-05	0.06
TMEB762	TMEW1	ECD	5.41E+05	1.74E-04	0.32
TMEB757	TMEW1	ECD	5.42E+05	1.67E-04	0.31
*MP: membrane proximal region					

ProteOn SPR

The binding of anti-TMEFF2 mAbs to the ECD and the membrane proximal region of human TMEFF2 was measured by ProteOn SPR (Bio-Rad). The purified mAbs (diluted to a final concentration of 1 µg/ml in PBST) were used as ligands in the assay and were immobilized through Fc capture to Goat Anti-Human (GAH) IgG Fc. For amine coupling of the GAH IgG Fc, a 1:1 mixture of EDC (40 mM) and NHS (10 mM) were mixed immediately prior to injection to activate the chip surface and injected in the vertical orientation. GAH-Fc (at 30 µg/ml) antibody in acetate buffer (pH 5.0) was then flowed over the surface for 300 seconds at 30 µl/min in the vertical orientation. Any remaining reactive carboxyl groups in the surface were subsequently deactivated by injecting 1M Ethanolamine (pH 8.5) in the same orientation. The antibodies were used at a concentration of 1 µg/ml for immobilization. The antibodies were flowed over the surface in the horizontal direction. Human TMEFF2 ECD or the membrane proximal region in 3-fold dilution series of 5 concentrations (highest concentration ranging from 100- 600 nM) was flowed in as analyte in the vertical orientation to bind to the captured molecules. A buffer sample was also injected in the 6th channel in the vertical direction to monitor any drift in the baseline signal. The association and dissociation phases for all concentrations were monitored over 3 minutes and 30 (or 15) minutes respectively, at a flow rate of 100 µL/min. The binding surface was regenerated for the next interaction cycle using an 18 second pulse of 0.8% phosphoric acid to remove the bound antigen. The raw data were processed by subtracting two sets of reference data from the response data: 1) the inter-spot signals to correct for the non-specific interactions between the antigen and the empty chip surface; 2) the empty channel signals (where only PBST was flowed over the chip) to correct for non-specific baseline drift.

Biacore 8K SPR

The binding of anti-TMEFF2 mAbs to human TMEFF2 ECD was measured by Biacore 8K SPR. The format of the assay was to capture the mAbs using a high density anti-human Fc surface, then inject human TMEFF2 concentration titration using a single cycle kinetics method. Goat anti-human Fc IgG (Jackson ImmunoResearch, Cat# 109-005-098) was directly immobilized via amine coupling at 30 µg/mL in 10mM acetate buffer, pH 4.5 on flow cells 1 and

2, on CM5 Sensor Chip (GE) with a flow rate of 30 $\mu\text{L}/\text{min}$ in HBSP (GE) buffer. The mAbs were captured on the anti-human Fc IgG surface at 0.5 $\mu\text{g}/\text{ml}$ (~200-300 RU) on flow cell 2. The running buffer was then changed to HBSP + 100 $\mu\text{g}/\text{ml}$ BSA. TMEFF2 ECD at 30nM concentration in 3-fold dilution series was injected from low to high concentration using single cycle kinetics method. The off-rate was monitored 30 minutes after the last or highest concentration injection and then the surface was regenerated using 0.8% phosphoric acid (Bio-Rad). A buffer blank run, capturing the same mAbs and using the same conditions of sample run was also completed. The raw data were processed by subtracting two sets of reference data from the response data: 1) reference flow cell 1 subtracted from sample flow cell 2 and 2) buffer blank run from experimental run. The processed data at all concentrations for each mAb were globally fit to a 1:1 simple Langmuir binding model to extract estimates of the kinetic (k_{on} , k_{off}) and affinity (KD) constants.

Thermal stability of anti-TMEFF2 antibodies

15 TMEB675 showed lower than usual thermal stability profile by DSC (Differential Scanning Calorimetry) with onset of unfolding $T_m = 52^\circ\text{C}$ and the first thermal transition (T_{m1}) at $= 60.4^\circ\text{C}$. A closer examination of the sequence of TMEB675 (see Example 4) showed the presence of Somatic HyperMutations (SHM) within the framework region of heavy and light chain. Several re-engineered variants were sub-cloned, expressed, purified and profiled by DSC. 20 The resulting mAbs TMEB762 and TMEFB757 showed desirable thermal stability profile ($T_{m1} = 69.4^\circ\text{C}$ and $T_{m1} = 69.7^\circ\text{C}$ respectively). In comparison to TMEB675, TMEB762 had the following amino acid modifications in the heavy chain: R14P, P20L and H81Q, while TMEFB757 had the following amino acid modifications in the heavy chain: R14P and P20L. In comparison to TMEB675, TMEB762 had the following amino acid modifications in the light 25 chain: A1D and A91P, while TMEFB757 had A91P modification in the light chain. Residue numbering is according to Kabat. The kinetic parameters of binding of TMEB675, TMEB762 to TMEFF2 ECD is shown in Table 59.

7-4 Structural characterization of anti-TMEFF2 antibodies

The cDNA sequences and amino acid translations of the antibodies were obtained using standard techniques. After polypeptide sequence determination, some antibody cDNAs encoding the variable regions or full-length antibodies were codon optimized using standard methods for scale-up expression.

Table 60 shows the HCDR1 and the HCDR2 amino acid sequences of select anti-TMEFF2 antibodies.

Table 61 shows the HCDR3 amino acid sequences of select anti-TMEFF2 antibodies.

Table 62 shows the LCDR1 and the LCDR2 amino acid sequences of select anti-TMEFF2 antibodies.

Table 63 shows the LCDR3 amino acid sequences of select anti-TMEFF2 antibodies.

Table 64 shows the VH and the VL amino acid sequence of select anti-TMEFF2 antibodies.

Table 65 shows the SEQ ID NOs: of heavy and light chains of select anti-TMEFF2 antibodies.

Table 66 shows the heavy chain amino acid sequences of select anti-TMEFF2 antibodies.

Table 67 shows the light chain amino acid sequences of select anti-TMEFF2 antibodies.

Table 68 shows the SEQ ID NOs: of polynucleotides encoding various anti-TMEFF2 antibody chains.

Table 60.

mAb	HCDR1 sequence	HCDR1 SEQ ID NO:	HCDR2 sequence	HCDR2 SEQ ID NO:
TMEB675	SYSMS	582	VISGSGGFTDYADSVKG	584
TMEB570	SYYSIS	583	GIIPISGRANYAQKFQG	585
TMEB674	SYSMS	582	VISGGSFTSYADSVKG	586
TMEB565	SYYSIS	583	GIIPISGRANYAQKFQG	585
TMEB762	SYSMS	582	VISGSGGFTDYADSVKG	584
TMEB757	SYSMS	582	VISGSGGFTDYADSVKG	584

Table 61.

mAb	HCDR3 sequence	HCDR3 SEQ ID
TMEB675	MPLNSPHDY	587
TMEB570	DGYSSGRSTTYAFDY	16
TMEB674	MPLNSPHDC	17

TMEB565	DGYSSGRSTTYAFDY	16
TMEB762	MPLNSPHDY	587
TMEB757	MPLNSPHDY	587

Table 62.

mAb	LCDR1 amino acid	LCDR1 SEQ ID NO.	LCDR2 amino acid	LCDR2 SEQ ID NO:
TMEB675	RASQGIRNDLG	18	AASSLQS	588
TMEB570	RASQSVSTYYLA	19	GASYRAT	21
TMEB674	RASQGIRNDLG	18	AASSLQS	588
TMEB565	RASQGIRNDLG	18	AASSLQS	588
TMEB762	RASQGIRNDLG	18	AASSLQS	588
TMEB757	RASQGIRNDLG	18	AASSLQS	588

Table 63.

mAb	LCDR3 amino acid	LCDR3 SEQ ID NO:
TMEB675	LQDYNYALT	22
TMEB570	QQYGHSPIT	23
TMEB674	LQDYNYSLT	24
TMEB565	LQDYNYALT	22
TMEB762	LQDYNYPLT	603
TMEB757	LQDYNYPLT	603

5

Table 64.

Antibody	VH name	VH amino acid sequence	VH SEQ ID NO:	VL name	VL amino acid sequence	VL SEQ ID NO:
TMEB675	TMEH41 1	EVQLLESG GGLVQRG GSLRPSCA ASGFTFSS YSMSWVR QAPGKGLE WVSVISGS GGFTDYA DSVKGRFT ISRDN SKN TLYLHMNS	25	TMEL127	AIQMTQSPSS LSASVGDRV TITCRASQGI RNDLGWYQ QKPGKAPKL LIYAASSLQS GVPSRFSGS GSGTDFTLTI SSLQPEDFAT YYCLQDYN	28

		LRAEDTAV YYCARMF LNSPHDY WGQGTLV TVSS			YALTFGGGT KVEIK	
TMEB570	TMEH39 6	QVQLVQS GAEVKKP GSSVKVSC KASGGTFS SYYISWVR QAPGQGLE WMGGIIPIS GRANYAQ KFQGRVTI TADESTST AYMELSSL RSEDNAVY YCARDGY SSGRSTTY AFDYWGQ GTLVTVSS	589	TMEL112	EIVLTQSPGT LSLSPGERAT LSCRASQSV STYYLAWY QQKPGQAPR LLIYGASYR ATGIPDRFSG SGSGTDFTL TISRLEPEDF AVYYCQQY GHSPITFGQG TKVEIK	29
TMEB674	TMEH41 0	EVQLLESG GGLVQPPG GSLRLSCA ASGFTFSS YSMSWVR QAPGKGLE WVSVISGG GSFTSYAD SVKGRFTIS RDNSNNTL	27	TMEL126	AIQMTQSPSS LSASVGDVR TITCRASQGI RNDLGWYQ QKPGKAPKL LIYAASSLQS GVPSRFSGS GSGTDFTLTI SSLQPEDFAT YYCLQDYN	30

		YLQMSSLR AEDTAFYY CARMPLNS PHDCWGQ GTLVTVSS			YSLTFGGGT KVEIR	
TMEB565	TMEH39 6	QVQLVQS GAEVKKP GSSVKVSC KASGGTFS SYYISWVR QAPGQGLE WMGGIIPIS GRANYAQ KFQGRVTI TADESTST AYMELSSL RSEDNAVY YCARDGY SSGRSTTY AFDYWGQ GTLVTVSS	589	TMEL111	EIVLTQSPGT LSLSPGERAT LSCRASQSV ATYYLAWY QQKPGQAPR LLIYGASSRA TGIPDRFSGS GSGTDFTLTI SRLEPEDFA VYYCQQYG YNPITFGQG TKVEIK	31
TMEB762	TMEH45 9	EVQLLESG GGLVQPG GSLRLSCA ASGFTFSS YSMSWVR QAPGKGLE WVSVISGS GGFTDYA DSVKGRFT ISRDN SKN	604	DL3L129	DIQMTQSPSS LSASVGDRV TITCRASQGI RNDLGWYQ QKPGKAPKL LIYAASSLQS GVPSRFSGS GSGTDFTLTI SSLQPEDFAT YYCLQDYN	607

		TLYLQMNS LRAEDTAV YYCARMF LNSPHDY WGQGTLV TVSS			YPLTFGGGT KVEIK	
TMEB757	TMEH460	EVQLLESG GGLVQPG GSLRLSCA ASGFTFSS YMSWVR QAPGKGLE WVSVISGS GGFTDYA DSVKGRFT ISRDNSKN TLYLHMNS LRAEDTAV YYCARMF LNSPHDY WGQGTLV TVSS	612	B76L85	AIQMTQSPSS LSASVGDRV TITCRASQGI RNDLGWYQ QKPGKAPKL LIYAASSLQS GVPSRFSGS GSGTDFTLTI SSLQPEDFAT YYCLQDYN YPLTFGGGT KVEIK	613

Table 65.

Antibody	VH name	VL name	HC protein SEQ ID NO:	LC protein SEQ ID NO:
TMEB675	TMEH411	TMEL127	32	35
TMEB570	TMEH396	TMEL112	33	36
TMEB674	TMEH410	TMEL126	34	37
TMEB565	TMEH396	TMEL111	33	38
TMEB762	TMEH459	DL3L129	614	615
TMEB757	TMEH460	B76L85	616	617

Table 66.

HC protein SEQ ID NO:	HC amino acid sequence
32 (TMEB675 HC)	evqllesggglvqrggslrpscaasgftfssysmswvrqapgkglewvsvisgggftdyads vkgrftisrdnsntlylhmnsraedtavyycarmplnsphdywgqgtltvtssastkgpsvf plapcsrstsastaalgclvkdyfpepvtvswngaltsgvhtfpavlqssglyslssvvtvpsssl gtktytcnvdhkpsntkvdkrveskygppcpcpapeaaggpsvflfppkpkdtlmisrtp vtcvvdvsqedpevqfnwyvdgvevhnaktkpreeqfnstyrvvsvltvlhqdwlngkey kckvsnkglpssiectiskakgqprepvytlppsqeemtknqvslclvkgfypsdiavewe sngqpennykttppvldsdgsfflysrltvdksrwqegnvfscsvmhealhnhytqkslsisl gk
33 (TMEB570, TMEB565 HC)	qvqlvqsgaevkkpgssvkvscasggftssyyiswvrqapgqglewmggiipisgranya qkfqrvtitadeststaymelsslrsestavyycardgyssgrsttyafdywgqgtltvtssast kgpsvfplapcsrstsastaalgclvkdyfpepvtvswngaltsgvhtfpavlqssglyslssv tvpssslgtktytcnvdhkpsntkvdkrveskygppcpcpapeaaggpsvflfppkpkdtl misrtpvtcvvdvsqedpevqfnwyvdgvevhnaktkpreeqfnstyrvvsvltvlhqdw lngkeykckvsnkglpssiectiskakgqprepvytlppsqeemtknqvslclvkgfyp sdiavewesngqpennykttppvldsdgsfflysrltvdksrwqegnvfscsvmhealhnhy tqkslsisl gk
34 (TMEB674 HC)	evqllesggglvqppggslrpscaasgftfssysmswvrqapgkglewvsvisgggsftsya svkgrftisrdnsntlylqmsslrsestavyycarmplnsphdcwgqgtltvtssastkgpsvf plapcsrstsastaalgclvkdyfpepvtvswngaltsgvhtfpavlqssglyslssvvtvpsssl gtktytcnvdhkpsntkvdkrveskygppcpcpapeaaggpsvflfppkpkdtlmisrtp vtcvvdvsqedpevqfnwyvdgvevhnaktkpreeqfnstyrvvsvltvlhqdwlngkey kckvsnkglpssiectiskakgqprepvytlppsqeemtknqvslclvkgfypsdiavewe sngqpennykttppvldsdgsfflysrltvdksrwqegnvfscsvmhealhnhytqkslsisl gk

614 (TMEB762 HC)	evqllesggglvqpggsrlscaasgftfssysmswvrqapgkglewvsvisgsggftdyads vkgrftisrdnsntlylqmnsiraedtavyycarmplnsphdywgqgtltvssastkgpsvf plapcsrstsestaalgclvkdyfpepvtvswngaltsgvhtfpavlqssglyslssvvtvpsssl gtktytcnvdhkpsntkvdkrveskygppcpcpapeaaggpsvflfppkpkdtlmsrtpe vtcvvvdvsqedpevqfnwyvdgvevhnaktkpreeqfnstyrvvsvltvlhqdwlngkey kckvsnkglpssiectiskakgqprepvytlppsqeemtknqvslclvkgfypsdiavewe sngqpennykttppvldsdgsfflysrltdksrwqegnvfscsvmhleahnhytqkslsisl k
616 (TMEB757 HC)	evqllesggglvqpggsrlscaasgftfssysmswvrqapgkglewvsvisgsggftdyads vkgrftisrdnsntlylhmnsiraedtavyycarmplnsphdywgqgtltvssastkgpsvf plapcsrstsestaalgclvkdyfpepvtvswngaltsgvhtfpavlqssglyslssvvtvpsssl gtktytcnvdhkpsntkvdkrveskygppcpcpapeaaggpsvflfppkpkdtlmsrtpe vtcvvvdvsqedpevqfnwyvdgvevhnaktkpreeqfnstyrvvsvltvlhqdwlngkey kckvsnkglpssiectiskakgqprepvytlppsqeemtknqvslclvkgfypsdiavewe sngqpennykttppvldsdgsfflysrltdksrwqegnvfscsvmhleahnhytqkslsisl k

Table 67.

LC protien SEQ ID NO:	LC amino acid sequence
35 (TMEB67 5 LC)	aiqmtqspsslsasvgdrvtitcrasqgirndlgwyqqkpgkapklliyaasslqsgvpsrfsqsgs gtdftltisslqpedfatyyclqdynaltfgggtkveikrtvaapsvfifppsdeqlksgtasvvcll nnfybreakvqwkvdnalqsgnsqesvteqdsdstyslstltskadyekhkvyacevthqgl sspvtksfnrgec
36 (TMEB57 0 LC)	eivltqspgtlslsperatlscrasqsvstyylawyqqkpgqaprlliygasyratgipdrfsgsgsg tdftltisrlpedfavyycqyghspitfgqgtkveikrtvaapsvfifppsdeqlksgtasvvclln nnfybreakvqwkvdnalqsgnsqesvteqdsdstyslstltskadyekhkvyacevthqgl spvtksfnrgec

37 (TMEB67 4 LC)	aiqmtqspsslsasvgdrvtitcrasqgirndlgwyqqkpgkapklliyaasslqsgvpsrfsqsgs gtdftltisslqpedfatyyclqdynsltfgggkveirrtvaapsvfifppsdeqlksgtasvvclln nfypreakvqwkvdnalqsgnsqesvteqdsdstyslstltlskadyekhkvyacevthqgls spvtksfnrgec
38 (TMEB56 5 LC)	eivltqspgtlslspgeratlscrasqsvatyylawyqqkpgqaprlliygassratgipdrfsqsgsg tdftltisrlepedfavyycqygynpitfgggkveikrtvaapsvfifppsdeqlksgtasvvclln nfypreakvqwkvdnalqsgnsqesvteqdsdstyslstltlskadyekhkvyacevthqgls spvtksfnrgec
615 (TMEB76 2 LC)	diqmtqspsslsasvgdrvtitcrasqgirndlgwyqqkpgkapklliyaasslqsgvpsrfsqsgs gtdftltisslqpedfatyyclqdynpltfgggkveikrtvaapsvfifppsdeqlksgtasvvcll nnfypreakvqwkvdnalqsgnsqesvteqdsdstyslstltlskadyekhkvyacevthqgl sspvtksfnrgec
617 (TMEB75 7 LC)	aiqmtqspsslsasvgdrvtitcrasqgirndlgwyqqkpgkapklliyaasslqsgvpsrfsqsgs gtdftltisslqpedfatyyclqdynpltfgggkveikrtvaapsvfifppsdeqlksgtasvvcll nnfypreakvqwkvdnalqsgnsqesvteqdsdstyslstltlskadyekhkvyacevthqgl sspvtksfnrgec

Table 68.

Antibody	VH cDNA SEQ ID NO:	VL cDNA SEQ ID NO:	HC cDNA SEQ ID NO:	LC cDNA SEQ ID NO:
TMEB675	39	42	46	49
TMEB570	40	43	47	50
TMEB674	41	44	48	51
TMEB565	40	45	47	590
TMEB762	618	619	620	621
TMEB757	622	623	624	625

SEQ ID NO: 39 (TMEB675 VH cDNA)

Gaggtgcagctgctggaaagcggcgaggcctggtgcagagaggaggaagcctgagaccagctgtgccgccagcggcttcaccttc
agcagctacagcatgagctgggtcaggcaggccccctggcaaaaggactggagtgggtgagcgtgattagcggcagcggcggttcaccg
attacccgacagcgtgaagggcaggttcacatcagcagggacaatagcaagaacaccctgtacctgcacatgaacagcctgagggcc
gaggacaccgctgtactactgcgccaggatgccctgaacagccctcacgactactggggccagggaaccctggtgaccgtgtccag

5 c

SEQ ID NO: 40 (TMEB570, TMEB565 VH cDNA)

Caggtgcagctggtgcagagcggcgagggaagtgaaaaaacgggcagcagcgtgaaagtgagctgcaaagcagcggcgccacctt
cagctcctattacattagctgggtgcgccaggcgccgggcccaggcctggaatggatgggtggcattatcccaatcagtggcgctgcta
10 tatgcgcagaaatttcagggccgctgaccattaccgctgatgaaagcaccagcaccgctatatggaactgagcagcctgcgcagcgaa
gataccgcggtgtattattgcgcgcgcgacggctacagtagtgacgtagcacaacatacgcatttgactattggggccagggcaccctgg
tgaccgtgtcgagt

SEQ ID NO: 41 (TMEB674 VH cDNA)

15 Gaagtgcagctgctggagagcgggaggaggactggtgcagcctcctggcggaagcctgagactgagctgcgccgctagcggcttcac
tcagcagctacagcatgagctgggtgagacaggctcctggcaaggcctggagtgggtgagcgtgatcagcggcgaggcagccttacc
agctacgccgacagcgtgaagggcaggttcacatcagcagggacaacagcaacaacaccctgtacctgcagatgagcagcctgaggg
ccgaggacaccgcttctactactgcgccaggatgccctgaacagcccccactgactgctggggacagggcaccctggtgaccgtgagc
agc

20

SEQ ID NO: 42 (TMEB675 VL cDNA)

Gccatccagatgaccagagccctagcagcctgagcgtgagcgtggcgacagggtgaccatcacctgcagggccagccagggcac
agaaacgacctgggctggtaccagcagaagcccggcaaggcccccaagctgctgatctacgccgacagcctgcagagcggagt
cctagcaggttcagcggaagcggcagcggcaccgacttcacctgaccatcagcagcctgcagcccgaggacttcgccacctactactg
25 cctgcaggactacaactacgccctgacattcggcgggcgccaccaagggtggagatcaag

SEQ ID NO: 43 (TMEB570 VL cDNA)

Gaaattgtctgacctagagcccgggacccctgagcctgagcccggggaacgcgcgaccctgagctgccgcgcgagccagagcgtt
tccacatactacctggcgtggtatcagcagaaaccgggcccaggcgccgcgcctgctgattacggtgcctctatcgcgcgaccggcattc
30 cggatcgctttagcggcagcgggtccggcaccgattttacctgaccattagccgcctggaaccggaagattttgcggtgtattattgccagc
agtacggtcacagcccgattacttttggccagggcaccaaagtggaaatcaaa

SEQ ID NO: 44 (TMEB674 VL cDNA)

Gccatccagatgaccagagccctagcagcctgagcgtggtggcgacagggtagcatcacctgcagggccagggcatc
aggaacgacctgggtgtaccagcagaagcccggaaggcccccaagctgctgatctacgccgccagcagcctgcagagcggagtg
5 cctagcaggttcagcggcagcgggaagcggcaccgacttcacctgacctctccagcctgcagcccaggagacttcgccacctactactgc
ctgcaggactacaactacagcctgaccttcggcggcgccaccaaggtggagatcagg

SEQ ID NO: 45 (TMEB565 VL cDNA)

Gaaattgtgctgaccagagcccgggacccctgagcctgagcccggggaacgcgcgaccctgagctgccgcgcgagccagagcgtt
10 gccacctattatcttgcgtggtatcagcagaaacccggccaggcgcgcgcctgctgatttacggtgcatctccctgcgaccggcattcc
ggatcgcttttagcggcagcgggtccggcaccgattttacctgaccttagccgcctggaaccggaagattttgcgggtgtattattgccagca
gtacggctataaccaattacctttggccagggcaccaaagtggaaatcaaa

SEQ ID NO: 46 (TMEB675 HC cDNA)

15 gaggtgcagctgctggaaagcggcgaggcctggtgcagagaggaggaagcctgagaccagctgtgccgccagcggcttcacctca
gcagctacagcatgagctgggtcaggcaggcccctggcaaaggactggagtgggtgagcgtgattagcggcagcggcggttcaccga
ttacgccgacagcgtgaaggcgaggttcacctacgacaggggacaatagcaagaacacctgtacctgcacatgaacagcctgagggccg
aggacaccgccgtgtactactgcgccaggatgccctgaacagccctcacgactactggggccagggaacctggtgacctgtccagc
gcttcaccaaggggcccatccgtcttccccctggcgccctgctccaggagcacctccgagagcacagccgcccctgggtgctcctggtcaag
20 gactacttccccgaaccggtgacgggtgctggaactcaggcgccctgaccagcggcgtgcacaccttcccggtgctcctacagtcctcag
gactctactccctcagcagcgtggtgacctgcccctcagcagcttgggcacgaaaacctacacctgcaacgtagatcacaagcccagca
acaccaagggtggacaagagagttgagtc aaatatgggtccccatgccaccatgccagcacctgagggccgcccgggggaccatcagtc
ttcctgttcccccaaaaccaaaggacactctcatgatctccggacccctgaggtcacgtgcgtggtggtggacgtgagccaggaagacc
ccgaggtccagttcaactggtacgtggatggcgtggaggtgcataatgccaaagacaaagccgcgggaggagcagttcaacagcacgtac
25 cgtgtggtcagcgtcctcacctcctgcaccaggactggctgaacggcaaggagtacaagtgaaggtctcaacaaaggcctcccgctcc
tccatcgagaaaacctctccaaaggcaaaggcgagccccgagagccacaggtgtacacctgcccccatccaggaggagatgacca
agaaccaggtcagcctgacctgcctggtcaaaggcttctacccagcgcacatcgccgtggagtgggagagcaatgggcagccggagaa
caactacaagaccacgcctcccgctgctggactccgacggctccttctcctctacagcaggctaacctggacaagagcaggtggcagga
ggggaatgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacacagaagagcctctccctgtctctgggtaaa

30

SEQ ID NO: 47 (TMEB570, TMEB565 HC cDNA)

cagggtgcagctggtgcagagcggcgcggaagtgaacccgggcagcagcgtgaaagtgcagctgcaaagcagcggcgccacctt
cagctcctattacattagctgggtgcgccaggcgccggccaggccctggaatggatgggtggcattatcccaatcagtggcgctgcta
tatgcgcagaaatttcagggccgcgtgaccattaccgctgatgaaagcaccagcaccgcgtatatggaactgagcagcctgcgcagcgaa
gataccgcggtgtattattgcgcgcgcgacggctacagtagtgagcagcacaacatacgcatcttgactattggggccaggccacccctgg
5 tgaccgtgtcagtgcttccaccaaggggcccatccgtcttccccctggcgccctgctccaggagcacctccgagagcacagccgcccctgg
gctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcggcgtgcacaccttcccggctg
tctacagtctcaggactctactccctcagcagcgtggtgacggtgcctccagcagcttgggcacgaaaacctacacctgcaacgtagat
cacaagcccagcaacaccaagggtggacaagagagttgagtcctcaaatatgggtcccccatgccaccatgccagcacctgaggccgccc
ggggaccatcagtcttctgttcccccaaaacccaaggacactctcatgatctcccgaccctgaggtcacgtgcgtggtggtgacgt
10 gagccaggaagaccccgagggtccagttcaactggtacgtggatggcggtggaggtgcataatgccaagacaaagccgcccggaggagca
gttcaacagcacgtaccgtgtggtcagcgtctcaccgtcctgcaccaggactggctgaacggcaaggagtaacaagtgaagggtctccaa
caaaggcctcccgtcctcatcgagaaaacctctcaaagccaaaggcgagccccgagagccacaggtgtacacctgccccatccc
aggaggagatgaccaagaaccaggtcagcctgacctgctgtaaaaggcttctacccagcgacatcgccgtggagtgggagagcaat
ggcgacccggagaacaactacaagaccacgctccgtgctggactccgacggctccttcttctctacagcaggctaaccgtggacaag
15 agcaggtggcaggagggaatgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacagaagagcctctccctgtctct
gggtaaa

SEQ ID NO: 48 (TMEB674 HC cDNA)

gaagtgcagctgctggagagcggaggaggactggtgcagcctcctggcggaagcctgagactgagctgcgccgctagcggcttcacctt
20 cagcagctacagcatgagctgggtgagacaggctcctggcaagggcctggagtggtgagcgtgatcagcggcgaggagcagctttacc
agctacgccgacagcgtgaaggcgaggttcaccatcagcagggacaacagcaacaacacctgtacctgcagatgagcagcctgaggg
ccgaggacaccgccttctactactgcgccaggatgcccctgaacagccccatgactgctggggacagggcaccctggtgaccgtgagc
agcgttccaccaagggcccatccgtcttccccctggcgccctgctccaggagcacctccgagagcacagccgcccctgggctgcctggtc
aaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcggcgtgcacaccttcccggctgtcctacagtct
25 caggactctactccctcagcagcgtggtgacggtgcctccagcagcttgggcacgaaaacctacacctgcaacgtagatcacaagccca
gcaacaccaagggtggacaagagagttgagtcctcaaatatgggtcccccatgccaccatgccagcacctgaggccgcccggggaccatc
agtcttctgttcccccaaaacccaaggacactctcatgatctccggaccctgaggtcacgtgcgtggtggtgacgtgagccaaggaa
gaccccgaggtccagttcaactggtacgtggatggcgtggaggtgcataatgccaagacaaagccgcccggaggagcagttcaacagca
cgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaacggcaaggagtacaagtgaaggtctcaacaaggcctcc
30 cgtctccatcgagaaaacctctccaaagccaaaggcgagccccgagagccacaggtgtacacctgccccatcccaggaggagat
gaccaagaaccaggtcagcctgacctgcctggtaaaaggcttctacccagcgacatcgccgtggagtgggagagcaatgggcagccc

gagaacaactacaagaccacgcctcccgtgctggactccgacggctccttcttctctacagcaggctaaccgtggacaagagcagggtgg
caggagggggaatgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacacagaagagcctctccctgtctctgggtaaa

SEQ ID NO: 49 (TMEB675 LC cDNA)

5 Gccatccagatgaccagagccctagcagcctgagcgctagcgtgggcgacagggtgaccatcacctgcagggccagccaggggcatc
agaaacgacctgggctggtaccagcagaagcccggcaaggcccccaagctgctgatctacgccgccagcagcctgcagagcggagtg
cctagcagggttcagcgggaagcggcagcggcaccgacttcacctgaccatcagcagcctgcagcccaggacttcgccactactactg
cctgcaggactacaactacgccctgacattcggcggcgccaccaaggtggagatcaagcgtacgggtggctgcaccatctgtcttcatcttc
ccgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagaggccaaagtacagtgggaag
10 gtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagcaaggacagcacctacagcctcagcagcacct
gacgtgagcaaaagcagactacgagaaacacaaagtctacgcctgcgaagtcacccatcagggcctgagctcgcccgtcacaaagagct
tcaacaggggagagtgt

SEQ ID NO: 50 (TMEB570 LC cDNA)

15 Gaaattgtctgaccagagcccgggcaccctgagcctgagcccggggaacgcgcgaccctgagctgccgcgcgagccagagcgtt
tccacatactacctggcgtggtatcagcagaaacggggccaggcgccgcgcctgctgattacgggtgcctcctatcgcgcgaccggcattc
cggatcgctttagcggcagcgggtccggcaccgatttaccctgaccattagccgcctggaaccggaagattttgcggtgtattattgccagc
agtacgggtcacagcccattacttttgccagggcaccaaagtggaaatcaaacgtacgggtggctgcaccatctgtcttcatcttccgccat
ctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagaggccaaagtacagtgggaaggtggata
20 acgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagcaaggacagcacctacagcctcagcagcacctgacgct
gagcaaagcagactacgagaaacacaaagtctacgcctgcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaaca
ggggagagtgt

SEQ ID NO: 51 (TMEB674 LC cDNA)

25 Gccatccagatgaccagagccctagcagcctgagcgctagcgtgggcgacagggtgaccatcacctgcagggccagccaggggcatc
aggaacgacctgggctggtaccagcagaagcccggcaaggcccccaagctgctgatctacgccgccagcagcctgcagagcggagtg
cctagcagggttcagcggcagcgggaagcggcaccgacttcacctgaccatctccagcctgcagcccaggacttcgccactactactgc
ctgcaggactacaactacagcctgaccttcggcggcgccaccaaggtggagatcaggcgtacgggtggctgcaccatctgtcttcatcttcc
cgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagaggccaaagtacagtgggaagg
30 tggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagcaaggacagcacctacagcctcagcagcacctg

acgctgagcaaaagcagactacgagaaacacaaagtctacgcctgcgaagtcacccatcagggcctgagctcgcccgtcacaagagctt
caacaggggagagtg

SEQ ID NO: 590 (TMEB565 LC cDNA)

5 Gaaattgtgctgaccagagccccgggcacccctgagcctgagccccgggcgaacgcgcgaccctgagctgccgcgcgagccagagcgtt
gccacctattatcttgcgtggatcagcagaaacggggccaggcgcgcgcctgctgattacgggtgcatcctcccgtgcgaccggcattcc
ggatcgcttttagcggcagcgggtccggcaccgattttaccctgaccattagccgcctggaaccggaagattttgcgggtgtattattgccagca
gtacggctataaccaattacctttggccagggcaccaaagtggaaatcaaactgacgggtggctgcaccatctgtcttcatcttcccgccatct
gatgagcagttgaaatctggaactgcctctgttgtgtgcctgtgaataacttctatcccagagaggccaaagtacagtggaggtggataac
10 gccctccaatcgggtaactcccaggagagtggtcacagagcaggacagcaaggacagcacctacagcctcagcagcacccctgacgctga
gcaaagcagactacgagaaacacaaagtctacgcctgcgaagtcacccatcagggcctgagctcgcccgtcacaagagcttcaacagg
ggagagtg

SEQ ID NO: 618 (TMEB762 VH cDNA)

15 gaggtgcagctgctggaaaagcggcgaggcctggtgcagccccggagggaagcctgagactcagctgtccgccagcggcttcacctca
gcagctacagcatgagctgggtcaggcaggccccctggcaaaggactggagtgggtgagcgtgattagcggcagcggcggttcaccga
ttacgccgacagcgtgaagggcaggttcaccatcagcagggacaatagcaagaacacccctgtacctgcagatgaacagcctgagggccg
aggacaccgccgtgtactactgcgccaggatgccctgaacagccctcacgactactggggccagggaacccctggtgaccgtgtccagc

20 SEQ ID NO: 619 (TMEB762 VL cDNA)

gacatccagatgaccagagccctagcagcctgagcgtagcgtggcgacagggtgacctcacctgcagggccagccaggggcatca
gaaacgacctgggctggtaaccagcagaagccccggcaaggcccccaagctgctgatctacgccgccagcagcctgcagagcggagtg
ctagcaggttcagcgggaagcggcagcggcaccgacttcacctgacctcagcagcctgcagcccaggacttcgccactactactgc
ctgcaggactacaactacccctgacattcggcgggcgccaccaagggtggagatcaag

25

SEQ ID NO: 620 (TMEB762 HC cDNA)

gaggtgcagctgctggaaaagcggcgaggcctggtgcagccccggagggaagcctgagactcagctgtccgccagcggcttcacctca
gcagctacagcatgagctgggtcaggcaggccccctggcaaaggactggagtgggtgagcgtgattagcggcagcggcggttcaccga
ttacgccgacagcgtgaagggcaggttcaccatcagcagggacaatagcaagaacacccctgtacctgcagatgaacagcctgagggccg
30 aggacaccgccgtgtactactgcgccaggatgccctgaacagccctcacgactactggggccagggaacccctggtgaccgtgtccagc
gcttcaccaaggggcccatccgtcttccccctggcgccctgctccaggagcacctccgagagcacagccgccctgggtgctgctggtcaag

gactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcggcgtgcacaccttcccggctgtcctacagtccctcag
gactctactccctcagcagcgtggtgaccgtgccctccagcagcttgggcacgaaaacctacacttgcaacgtagatcacaagcccagca
acaccaagggtggacaagagagttgagtc aaatatggtcccccattgccaccatgccagcacctgaggccgcccgggggaccatcagtc
ttcctgttcccccaaaacccaaggacactctcatgatctcccgaccctgaggtcacgtgcgtggtggtggacgtgagccaggaagacc
5 ccgaggtccagttcaactggtacgtggatggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagttcaacagcacgtac
cgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaacggcaaggagtacaagtgcagggtctcaacaaaggcctcccgtcc
tccatcgagaaaaccatctcaaaaggcgaagggcagccccgagagccacaggtgtacacctgcccccatcccaggaggagatgacca
agaaccaggtcagcctgacctgctgtcaaaggcttctacccagcgcacatcgccgtggagtgggagagcaatgggcagccggagaa
caactacaagaccacgcctcccgtgctggactccgacggctccttctcctctacagcaggctaaccgtggacaagagcagatggcagga
10 ggggaatgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacacagaagagcctctccctgtctctgggtaaa

SEQ ID NO: 621 (TMEB762 LC cDNA)

gacatccagatgacccagagccctagcagcctgagcgttagcgtggcgacagggtgacctcacctgcagggccagccagggcatca
gaaacgacctgggctggtaccagcagaagcccggcaaggcccccaagctgctgatctacgccgccagcagcctgcagagcggagtgcc
15 ctgacaggttcagcgggaagcggcagcggcaccgacttcacctgacctcagcagcctgcagcccaggacttcgccactactactgc
ctgcaggactacaactacccctgacattcggcggcgccaccaaagggtggagatcaagcgtacgggtggctgcaccatctgtcttcatcttccc
gccatctgatgagcagttgaaatctggaactgcctctgtgtgtgcctgctgaataacttctatcccagagaggccaaagtagcagtggaaggt
ggataacgccctccaatcgggtaactcccaggagagtggtcacagagcaggacagcaaggacagcacctacagcctcagcagcacctg
acgctgagcaaaagcagactacgagaaacacaaagtctacgcctgcgaagtcacccatcagggcctgagctcgcccgtcacaagagctt
20 caacaggggagagtgttag

SEQ ID NO: 622 (TMEB757 VH cDNA)

gagggtcagctgctggaagcggcgaggcctggtgcagcccggagggaagcctgagactcagctgtccgccagcggcttcaccttca
gcagctacagcatgagctgggtcaggcaggccccctggcaaaggactggagtgggtgagcgtgattagcggcagcggcggttcaccga
25 ttacgccgacagcgtgaagggcaggttcacctcagcagggacaatagcaagaacacctgtacctgcacatgaacagcctgagggccg
aggacaccgccgtgtactactgcgccaggatgccctgaacagccctcacgactactggggccagggaacctggtgaccgtgtccagc

SEQ ID NO: 623 (TMEB757 VL cDNA)

gccatccagatgacccagagccctagcagcctgagcgttagcgtggcgacagggtgacctcacctgcagggccagccagggcatca
30 gaaacgacctgggctggtaccagcagaagcccggcaaggcccccaagctgctgatctacgccgccagcagcctgcagagcggagtgcc

ctagcagggtcagcggaagcggcagcggcaccgacttcaccctgaccatcagcagcctgcagcccaggacttcgccactactactgc
ctgcaggactacaactacccctgacattcggcggcgccaccaaggtggagatcaag

SEQ ID NO: 624 (TMEB757 HC cDNA)

5 gaggtgcagctgctgaaaagcggcggaggcctggtgcagcccggagggaagcctgagactcagctgtccgccagcggcttcacctca
gcagctacagcatgagctgggtcaggcaggcccctggcaaaggactggagtggtgagcgtgattagcggcagcggcggcttcaccga
ttacgccgacagcgtgaaggcaggttcaccatcagcagggacaatagaagaacaccctgtacctgcacatgaacagcctgagggccg
aggacaccgccgtgtactactgcgccaggatgccctgaacagccctcacgactactggggccagggaaccctggtgaccgtgtccagc
gcttcaccaagggcccatccgtcttccccctggcgccctgtccaggagcacctccgagagcacagccgccctgggtgcctggtcaag
10 gactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcggcgtgcacaccttccggctgtcctacagtcctcag
gactctactccctcagcagcgtggtgaccgtgccctccagcagcttgggcacgaaaacctacacttgcaacgtagatcacaagcccagca
acaccaaggtggacaagagagttgagtcctaatatggtccccatgccaccatgccagcacctgaggccgcccgggggaccatcagtc
ttcctgttcccccaaaaccaaaggacactctcatgatctccggacccctgaggtcacgtgcgtggtggtggacgtgagccaggaagacc
ccgaggtccagttcaactggtacgtggatggcgtggaggtgcataatgccaaagacaaagccgcgggaggagcagttcaacagcacgtac
15 cgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaacggcaaggagtacaagtgaaggtctccaacaaaggcctccgtcc
tccatcgagaaaaccatctccaaagccaaaggcagccccgagagccacaggtgtacacctgcccccatcccaggaggagatgacca
agaaccaggtcagcctgacctgctgcaaggcttctacccagcgacatcgccgtggagtgggagagcaatgggcagccggagaa
caactacaagaccacgcctccgtgctggactccgacggctccttctctctacagcaggctaaccgtggacaagagcagatggcagga
ggggaaatgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacacagaagagcctctccctgtctctgggtaaa

20

SEQ ID NO: 625 (TMEB757 LC cDNA)

gccatccagatgacccagagccctagcagcctgagcgttagcgtgggcgacagggtgacctcacctgcagggccagccaggggcatca
gaaacgacctgggctggtaccagcagaagcccggcaaggcccccaagctgctgatctacgccgccagcagcctgcagagcggagtgc
ctagcagggtcagcggaagcggcagcggcaccgacttcaccctgaccatcagcagcctgcagcccaggacttcgccactactactgc
25 ctgcaggactacaactacccctgacattcggcggcgccaccaaggtggagatcaagcgtacggtggctgcaccatctgtcttcatcttccc
gccatctgatgagcagttgaaatctggaactgcctctgtgtgtgcctgctgaataacttctatccagagaggccaaagtacagtggaaagg
ggataacgccctccaatcgggtaactcccaggagagtggtcagagcaggacagcaaggacagcacctacagcctcagcagcaccctg
acgctgagcaaaagcagactacgagaaacacaaagtctacgcctgcgaagtcacccatcagggcctgagctcgcccgctcacaagagctt
caacagggggagagtgttag

30

The frameworks for the select anti-TMEFF2 antibodies are shown in **Table 69**.

Table 69.

Antibody	VH framework	VH framework SEQ ID NO:	VL framework	VL framework SEQ ID NO:
TMEB675	VH3_3-23	53	VKI_L11	55
TMEB570	VH1_1-69	54	VKIII_A27	591
TMEB674	VH3_3-23	53	VKI_L11	55
TMEB565	VH1_1-69	54	VKI_L11	55
TMEB762	VH3_3-23	53	VKI_L11	55
TMEB757	VH3_3-23	53	VKI_L11	55

SEQ ID NO: 53 (VH3_3-23 framework)

5 EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGGSTY
YADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKWGQGTLTVSS

SEQ ID NO: 54 (VH1_1-69 framework)

QVQLVQSGAEVKKPGSSVKVSCKASGGTFS SYAIS WVRQAPGQGLEWMG
10 GIPIFGTANYAQKFQG RVTITADESTSTAYMELSSLRSEDVAVYYCAR

SEQ ID NO: 55 (VKI_L11 framework)

aiqmtqspsslsasvgrvtitcrasqgirndlgwyqqkpgkapklliyaasslqsgvpsrfsqsgsg tdftltisslqpedfatyyc
lqdynyp
15

SEQ ID NO: 591 (VKIII_A27 framework)

EIVLTQSPGTLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIY
GASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSP

20 7-5 Epitope mapping of anti-TMEFF2 antibodies

Epitope mapping of TMEB570 and TMEB675 was done using H/D exchange. TMEW1 (SEQ ID NO: 578) was used as source of TMEFF2 in these assays.

10 µg of TMEW1 in 130 µL of control buffer (50 mM phosphate, 100 mM sodium chloride at pH 7.4) was denatured by adding 130 µL of 4 M guanidine hydrochloride, 0.85 M TCEP buffer (final pH was 2.5) and incubating the mixture for 3 min at 10°C. The mixture was then subjected to on-column pepsin/protease XIII digestion using an in-house packed
5 pepsin/protease XIII (w/w, 1:1) column (2.1 x 30 mm). The resultant peptides were analyzed using an UPLC-MS system comprised of a Waters Acquity UPLC coupled to a Q Exactive™ Hybrid Quadrupole-Orbitrap Mass Spectrometer (Thermo). The peptides were separated on a 50 x 1 mm C8 column with a 16.5 min gradient from 2-34% solvent B (0.2% formic acid in acetonitrile). Solvent A was 0.2% formic acid in water. The injection valve and pepsin/protease
10 XIII column and their related connecting tubings were kept inside a cooling box maintained at 10 °C. The second switching valve, C8 column and their related connecting stainless steel tubings were inside another chilled circulating box maintained at -6 °C. Peptide identification was done through searching MS/MS data against the TMEW1 sequence with Mascot. The mass tolerance for the precursor and product ions were 7 ppm and 0.02 Da, respectively.

15 10 µL of TMEW1 (5 µg) or 10 µL of TMEW1 & TMEB570 or TMEB675 mixture (5 µg:15 µg) was incubated with 120 µL deuterium oxide labeling buffer (50mM sodium phosphate, 100mM sodium chloride at pH 7.4) for 0 s, 30 s, 360 s, 3600 s, or 14400 s at 10°C. Hydrogen/deuterium (H/D) exchange at each time point was performed in duplicate. Hydrogen/deuterium exchange was quenched by adding 130 µL of 4 M guanidine hydrochloride,
20 0.85 M TCEP buffer (final pH was 2.5). Subsequently, the quenched samples were subjected to on column pepsin/protease XIII digestion and LC-MS analysis as described above. The mass spectra were recorded in MS only mode.

Raw MS data was processed using HDX WorkBench, software for the analysis of H/D exchange MS data (Pascal et al., J. Am. Soc. Mass Spectrom. 2012, 23 (9), 1512-1521). The
25 deuterium levels were calculated using the average mass difference between the deuteriated peptide and its native form (t0). About 97-99% of the protein could be mapped to specific peptides. The deuterium buildup curves showed significant difference in slopes, over exchange time for the peptides.

TMEB570 epitope: TMEW1 showed a modest reduction in deuterium uptake at residues
30 235-249 (residue numbering according to SEQ ID NO: 575), e.g. residues HGKCEHSINMQEPSC (SEQ ID NO: 592) within the membrane proximal region were

protected from H/D exchange upon binding to TMEB570.

TMEB675 epitope: TMEW1 showed a modest reduction in deuterium uptake at residues 252-268 (residue numbering according to SEQ ID NO: 575), e.g. residues

DAGYTGQHCEKKDYSVL (**SEQ ID NO: 600**) within the membrane proximal region were
5 protected from H/D/ exchange upon binding to TMEB675.

TMEB570 TMEFF2 epitope residues thus encompassed HGKCEHSINMQEPSC (**SEQ ID NO: 592**) and TMEB675 epitope residues encompassed DAGYTGQHCEKKDYSVL (**SEQ ID NO: 600**). Both antibodies bound TMEFF2 within the membrane proximal region.

10 7-6 **Generation of bispecific TMEFF2xCD3 antibodies**

Select monospecific anti-TMEFF2 and anti-CD3 antibodies (see Example 1-7) were expressed as IgG4/κ. F405L and R409K substitutions (EU numbering) were made into the anti-CD3 antibodies while the anti-TMEFF2 antibodies had wild-type IgG4. In addition to position 405 and 409 substitutions, the IgG4 mAbs were engineered to have S228P, F234A and L235A
15 substitution.

The monospecific antibodies were expressed and purified using standard methods using a Protein A column (HiTrap MabSelect SuRe column). After elution, the pools were dialyzed into D-PBS, pH 7.2.

Bispecific TMEFF2xCD3 antibodies were generated by combining a monospecific
20 TMEFF2 mAb and a monospecific CD3 mAb in *in vitro* Fab arm exchange as described in Int. Patent Publ. No. WO2011/131746. Briefly, at about 1-20 mg/ml at a molar ratio of 1:1 of each antibody in PBS, pH 7-7.4 and 75 mM 2-mercaptoethanolamine (2-MEA) was mixed together and incubated at 25-37°C for 2-6 h, followed by removal of the 2-MEA via dialysis, diafiltration, tangential flow filtration and/or spun cell filtration using standard methods.

25 The bispecific antibodies were further purified after the *in vitro* Fab-arm exchange using hydrophobic interaction chromatography to minimize residual parental anti-TMEFF2 and anti-CD3 antibodies using standard methods.

Table 73 and Table 74 show the generated bispecific antibodies.

30 **Table 73.**

Bispecific antibody	Parental (TMEFF2 arm/CD3 arm)	HCDR1	HCDR2	HCDR3	LCDR1	LCDR2	LCDR3
TMCB13 2	TMEB675	582	584	587	18	588	22
	CD3B376	662	663	664	671	673	690
TMCB13 1	TMEB570	583	585	16	19	21	23
	CD3B376	662	663	664	671	673	690
TMCB15 0	TMEB762	582	584	587	18	588	603
	CD3B376	662	663	664	671	673	690

Table 74.

Bispecific antibody	Parental (TMEFF2 arm/CD3 arm)	VH	VL	HC	LC
TMCB13 2	TMEB675	25	28	32	35
	CD3B376	652	661	640	676
TMCB13 1	TMEB570	589	29	33	36
	CD3B376	652	661	640	676
TMCB15 0	TMEB762	604	607	614	615
	CD3B376	652	661	640	676

5

7-7 Characterization of bispecific TMEFF2 x CD3 antibodies**Purity analysis by Analytical Ultra Centrifugation (AUC)**

Analytical ultracentrifugation (AUC) allows for the determination of the size, shape, state of aggregation, and reversible interaction of macromolecules in solution. Sedimentation velocity (SV) is an AUC technique that allows for a concentration gradient of a macromolecule to move to the outer radius of the sample holder (cell) as the centrifuge spins. This enables the determination of the sedimentation coefficient which is a factor of the size and shape of a molecule, and it unique to each molecule. Beckman Optima AUC instrument was used for this purpose. The samples were loaded into centrifuge cells equipped with 1.2 cm Beckman centerpieces (rated to 50K rpm) and quartz windows. The cells are assembled and torqued to 130 lbs. The centrifuge cells were placed into an An-50 (8 hole) or An-60 (4 hole) rotor and placed within the AUC chamber. The temperature of the AUC was equilibrated to 20.5°C for at least one hour with the rotor in the

chamber before initiating the run. Runs were performed at 40K rpm for mAb sample with scan count (250 scans), frequency of scan collection (90 seconds), data resolution (10 μ M), wavelength at 280nm. The data were analyzed using the direct boundary fitting software SEDANAL. Purity of the bispecific antibody TMCB150 and its parental mAbs were measured. TMCB150 showed 5 97.1% monomer, 2.8 % dimer monomer and no aggregation, as determined by AUC meeting acceptable criteria for transiently expressed research material for further biophysical characterization. TMEB762 showed 95.5% monomer, 4.5 % dimer and no aggregation while CD3B376 showed 97.7% monomer and 2.2 % dimer with no aggregation. Aggregate levels of >5% of a minimum two-step purified molecule could have a significant impact on biological 10 activity, solubility, stability and shelf-life.

Conformational stability of anti-TMEFF2/CD3 bispecific by DSC

TMCB150 thermal unfolding was determined by DSC (Differential Scanning Calorimetry) that showed an onset of unfolding $T_m = 52.6^\circ\text{C}$, the first thermal transition (T_{m1}) at 61.8°C , 15 second thermal transition (T_{m2}) at 67.6°C and third thermal transition (T_{m3}) at 75.5°C . Based on parental antibodies (anti-TMEFF2, TMEB762 and anti-CD3, CD3B376) thermal transition profile as assessed by DSC before, T_{m1} of TMCB150 corresponds to CD3B376 FAB unfolding and T_{m3} of TMCB150 corresponds to TMEB762 Fab unfolding transitions.

20 Serum Stability

Serum stability assay is developed to evaluate properties of lead candidates for non-specific or off-target binding to human serum components. This may be predictive of poor pharmacokinetics and bio distribution properties. Binding and stability of TMCB150 is evaluated in both buffer and human serum using a fluorescence-based chromatography method. Bispecific 25 antibody is labeled with Alexa Fluor 488 conjugate (Invitrogen kit according to manufacturer's instructions), incubated in Hepes buffer and human serum (Sigma, cat # H4522) at 4°C and 37°C for 2 days and then analysed by SEC-HPLC using Agilent HPLC system equipped with fluorescence detector. Percent aggregate is calculated from the integration of area under the curve of each peak. TMCB150 showed 2.4% aggregation in Hepes buffer at time zero and 2.0% and 30 1.3% aggregation after two days at 4° and 37° Celcius, respectively. In human serum, TMCB150

showed 1,7% aggregation at time zero and 1.1% aggregation after two days at both 4° and 37° Celcius.

Non-Specific Binding

5 Non-specific binding of the lead molecule to unrelated surfaces is determined by biosensor technology (Biacore 8K). Antibody is passed over SPR surfaces coated with unrelated proteins. If the antibody displays significant binding to these irrelevant surfaces, its predicted to have poor in-vivo properties and exhibit manufacturing challenges. Lead molecule is tested at the final concentration of 1μM. Irrelevant surfaces include negatively charged protein (Soy Trypsin
10 Inhibitor), positively charged protein (Lysozyme and β-defensin), hydrophobic (Rh-integrin a4b7), human IgG, sticky protein (Rh-CD19). Proper controls are used in this experiment. Lead is flown over two surfaces, one is a blank and the other has a molecule directly immobilized. The response unit (RU) level is determined by subtracting the blank RU from the test surface RU. The RU of TMCB150 and the parental mAbs are given below in the table. A response unit ≥ 100 predicts
15 high risks for non-specific binding to charged/hydrophobic/IgG surfaces which would create challenges during manufacturing and translate to poor PK properties. None of the antibodies show non-specific binding to irrelevant surfaces predicting low to no risks for manufacturing and in-vivo behavior.

20 **Table 75.**

	STI	B-Defensin-3	Human IgG	Lysozyme	rh-Integrin a4b7	rh-CD19
TMCB150	1.6	6.4	7.5	4.2	0	3.4
TMEB762	0	4.1	8.4	4.6	0	3.3
CD3B376	19.5	3.1	0.4	0.2	0	0

High concentration stability

Many monoclonal antibodies are formulated at high concentration (≥100 mg/ml) to reduce
25 injection volume to facilitate subcutaneous administration. In addition, all monoclonal antibodies are exposed to transiently high concentrations (≥50 mg/ml) during the purification process. High concentration stability is therefore a critical quality attribute for these molecules. Concentration is

performed using centrifugal ultrafiltration devices with 30kDa MWCO membranes. 5.1 to 5.3 mg of each protein were initially diluted to the same starting concentration and centrifuged at 4000xg in 15-minute intervals. At the end of each 15-minute centrifugation step, the concentrators are removed from the centrifuge and a visual estimate of the remaining sample volume is recorded.

- 5 Concentration is measured by SoloVPE instrument. Concentrated samples were incubated at 4C and 40C for 2 weeks and aliquots were drawn at timed intervals to check for the integrity by analytical SEC. TMCB150 and the parental mAbs (CD3B376 and TMEB762) concentrated normally. Final concentration of TMCB150 was 99.4 mg/mL and that of the parental mAbs were 52.2 mg/mL (TMEB762) and 52.6 mg/mL (CD3B376). Concentration remained the same for 2
- 10 weeks at 4C and 40C suggesting that molecules have good intrinsic properties with no potential for aggregation or adsorption to the eppendorf tubes. % species (A: Aggregate; M: Monomer; F: Fragment) as measured from SEC peak integration is provided below in the table. At high concentration, molecules are intact with 4-5% aggregates and $\leq 0.3\%$ fragments after storing for 2 weeks at 40C predicting good shelf life.

15

Table 76.

	Time Zero			2 weeks, 4°C			2 weeks, 40°C		
	A	M	F	A	M	F	A	M	F
TMCB150	0.8	99.2	0	1.4	98.6	0	3.6	96.1	0.3
TMEB762	2.5	97.5	0	2.7	97.3	0	3.1	96.9	0
CD3B376	1.1	98.9	0	2.5	97.5	0	5.1	94.7	0.2

Affinity determination of anti-TMEFF2/CD3 bispecific antibody by kinetic exclusion assay (KinExA)

- 20 A KinExA 3200 instrument (Sapidyne Instruments, Inc.) was used to measure solution equilibrium affinity, K_D , of the bispecific mAb TMCB150 and its bivalent TMEFF2 parent TMEB762 mAb to human TMEFF2 extracellular domain (ECD). Serial dilutions of human TMEFF2 extracellular domain (ECD) were prepared with a constant concentration of anti-TMEFF2 mAb in 10 mM HEPES, 150 mM NaCl, 0.05% surfactant P20, pH 7.4, 0.1% BSA,
- 25 and 0.02% NaN₃. The reaction mixtures were incubated at RT until the binding interactions reached equilibrium. The duration of the incubation was determined using KinExA software simulation. Beads were prepared by direct covalent immobilization of TMEFF2-ECD by amine-

coupling on pre-activated beads composed of bis-acrylamide/azlactone copolymer (Pierce Biotechnology, Inc.). After incubation the samples were run on the KinExA instrument to assess free antibody in the mixture by passing the mixture through the TMEFF2-modified beads, and detecting the captured antibody using a fluorescently labeled secondary antibody. The data was fit with a 1:1 binding model using the KinExA Pro software.

Table 77.

mAb sample	K _D pM	95% CI, K _D pM
TMCB150	63.6	55.8 - 71.9
TMEB762	46.1	38.0 - 55.1

10

Measurement of binding affinity of anti-TMEFF2/CD3 bispecific antibody to N-terminal CD3ε peptide

Kinetic rate constants were measured by SPR performed using Biacore 8K (GE Healthcare) and anti-human Fc biosensor surfaces. Anti-human immunoglobulin antibodies were covalently coupled to the surface of a CM4 sensor chip (GE Healthcare). Antibodies of interest were captured on the anti-human immunoglobulin sensor chip, followed by injection of N-terminal CD3ε peptide at various concentrations in HEPES Buffered Saline containing 0.05% surfactant P20 (Tween™ 20) and 100 ug/mL BSA. The surface was regenerated with 2 pulses injections of 30 µL of 0.8% phosphoric acid at 100 µL/min. Data reported is the difference in SPR signal between the flow cell containing the captured antibody and a reference cell without captured antibody. Additional instrumental contributions to the signal were removed by subtraction of the data from the blank injection from the reference-subtracted signal. The data were analyzed by fitting association and dissociation phases at all concentrations (global fit) with a 1:1 binding model using the Biaevaluation software (Biacore, Inc.). Data is reported as average + 95% CI (Confidence Interval) which is calculated by t value for 95% CI * stdev/square root of the number of replicates.

Table 78.

mAb sample	Average k _{on} (1/Ms)	Average k _{off} (1/s)	Average K _D , nM	95% CI, K _D pM

TMCB150	3.57E+04	1.03E-03	28.7	24.4-34.3
CD3B376	4.33E+04	1.17E-03	26.9	21.1-34.4

7-8 Bispecific TMEFF2xCD3 antibodies are effective in T-cell mediated killing of prostate cancer cells

5 T-cell mediated killing of prostate cancer cells

Select bispecific TMEFF2xCD3 antibodies were assessed for their ability to mediate T-cell mediated killing of prostate cancer cells.

T-cell mediated killing of the TMEFF2xCD3 bispecific antibodies was measured using a caspase cytotoxicity assay that indirectly measures cell killing via cleavage of a fluorescent substrate by active caspase 3/7. Cleavage of the substrate results in a fluorescent DNA dye, with fluorescence restricted to the cell nucleus. Repeated fluorescence measurements are taken in each well throughout the course of the assay, using a motorized 10X objective, capable of precisely imaging well(s) at the same coordinates. Target cell populations are identified based on defined size restrictions and/or through the use of a secondary label.

Frozen Pan CD3⁺ T-cells (Biological Specialty Corporation, Colmar, PA) were isolated by negative selection from normal healthy donors. Prostate cancer cells expressing TMEFF2 (LNCaP-AR) were cultured in RPMI 1640 with 10% HI FBS + supplements (Life Technologies). T-cells and target cells were combined at an effector to target ratio (E:T) of 3:1 in Phenol Red free RPMI + 10% FBS and supplements (Life Technologies), without selection reagents, and 0.6uL of NucView caspase reagent (Essen Bioscience) was added to each mL of cells, per manufacturer guidelines. A total volume of 0.1mL cells were added to appropriate wells of a clear, 96-well flat-bottom plate (BD Falcon). TMEFF2xCD3 bispecific antibodies were prepared at 2X final concentration in Phenol Red free RPMI, prepared as indicated above, and 0.1mL of compounds were added to each well. After 30 minute incubation at room temperature to minimize cell aggregation at the edge of wells, plates were transferred to the Zoom Incucyte instrument (Essen Bioscience) held at 37°C, 5% CO₂.

Processing definitions on the Incucyte were designed for each cell line tested, per manufacture guidelines. Measurements were taken every six hours, until a plateau in the caspase

signal was observed, and followed by three or more successive decreases from the maximum signal in the well(s) containing the highest concentration of the test compound(s).

After the assay was complete, each plate was analyzed using the appropriate processing definition. Raw fluorescent data was exported from the Incucyte Zoom software, and pasted into
 5 GraphPad Prism (GraphPad Software, Inc., La Jolla, CA). Caspase 3/7 activity was determined by calculating the area under the curve (AUC) for each well in GraphPad. AUC values were plotted as a function of Log₁₀ nM compound. The EC₅₀ for each dose curve, in nanomolar (nM), was reported following non-linear regression analysis (4 parameter fit, least ordinary squares). Each assay contained a minimum of three biologic replicates, and each cell line was
 10 tested using T-cells from five healthy donors. Data were further analyzed by non-clinical statistics using a non-linear regression model.

Bispecific TMEFF2xCD3 antibodies are effective in *in vivo* prostate cancer tumor models

15 Select bispecific antibodies were tested in *ex vivo* LnCaP prostate cancer model in male NSG mice. For the study, 10⁶LnCaP cells in 50% Cultrex in 0.2 mL/animal were administered by subcutaneous injection into right flank on Day 0. The animals were randomized when tumors reached a volume of about ~100-150 mm³ and injected 20⁶ T-cells intraperitoneally/mouse at day 15. Ten animals were in each group. Treatment with the antibodies began 1-3 days post T-
 20 cell injections. Antibodies were administered intraperitoneally twice a week. Prior to dosing, all animals received IVIG + Fc Block. Tumor volume and body weight was assessed twice a week until tumors reached ~1200 mm³. Treatment groups are shown in **Table 79**. CD3xNull antibody was used as a negative control in these assays, having a CD3 binding arm and a null arm binding HIV gp120.

Table 79.

Group	Treatment	Dose
1	CD3xNull	5 mg/kg
6	TMCB131 (TMEB570 x	5 mg/kg
7	TMCB131 (TMEB570 x	0.5 mg/kg
8	TMCB132 (TMEB675 x	5 mg/kg
9	TMCB132 (TMEB675 x	0.5 mg/kg

Table 80 shows the percent tumor growth inhibition on day 38 per each group post tumor implant.

Figure 72 shows the reduction in mean tumor volume over time post tumor implant. **Figure 73** shows the reduction in mean tumor volume of each mouse treated with 0.05, 0.1 or 0.5 mg/kg

5 TMEB762xCD3B376.

Table 80.

Treatment	%TGI on day 38
CNTO7008 (Null x CD3)	
TMCB132 (TMEB675 x CD3B376) 5mg/kg	48
TMCB132 (TMEB675 x CD3B376) 0.5mg/kg	47.7
TMCB131 (TMEB570 x CD3B376) 5mg/kg	23.3
TMCB131 (TMEB570 x CD3B376) 0.5mg/kg	35

Efficacy of TMEB762xCD3B376 (TMCB150) was also evaluated in established LNCaP
 10 xenografts in male NOD.Cg-Prkdc^{scid} Il2rg^{tm1Wjl}/SzJ (NSG) mice humanized with 20e6 T cells. Animals were randomized into groups of 10 animals each by mean tumor volume on day 13 post tumor implantation. TMEB762xCD3B376 at 0.5, 0.1 and 0.05 mg/kg or nullxCD3B376 antibody control at 0.5 mg/kg were dosed IP twice weekly for 5 weeks. On day 35 post-tumor implantation, when at least eight animals remained per group, tumor growth inhibition (% TGI) as determined
 15 by tumor volume was calculated. Statistically significant tumor growth inhibition was observed with TMEB762xCD3B376 at 0.5 and 0.1 mg/kg, but not at 0.05 mg/kg, as compared to nullxCD3 control (Figure 73, $p \leq 0.0001$). TMEB762xCDB376 at 0.5, 0.1, and 0.05 mg/kg elicited tumor growth inhibition of 110%, 88% and 25%, respectively, as compared to nullxCD3 treated controls. TMEB762xCDB376 treatment resulted in seven and three complete responses at 0.5 and 0.1
 20 mg/kg, respectively. Subcutaneous LNCaP tumors were measured by caliper twice weekly and the results presented as mean tumor volume (mm^3) $\pm$ SEM (≥ 8 mice remaining per group).

T cell activation in response to administration of TMCB132

T cell activation in LNCaP prostate cancer cells was measured by flow cytometry, specifically by assessing CD25 positivity of CD3+/CD8+ T cells in 6 separate normal healthy

donors (9642, 9672, 9762, 9772, 9832, 9852) 72 hours after treatment with TMCB132 (FIG. 74). Activation of CD3⁺ pan-T cells added at a 3:1 effector:target ratio was observed in response to administration of TMCB132 on LnCaP prostate cancer cells.

5 **T-cell mediated cytotoxicity of TMCB132 *in vitro*.**

T-cell-mediated cytotoxicity assay was used to evaluate the cytotoxicity potential of TMCB132 *in vitro*, using live-time lapse imaging on the Incucyte platform. TMCB132 was tested in TMEFF2 positive cell line LnCaP, in presence of isolated pan human CD3⁺ T cells from healthy donors at a (Effector:Target) effector:target ratio (E:T ratio) of 3:1. Cell death by apoptosis was
10 monitored by measuring the fluorescence signal for active caspase-3/7 over a time period of 96 hours. TMCB132 promoted a dose-dependent reduction of viable LnCaP cells with increasing time. Dose-dependent increase in caspase-3/7 activity or fluorescence signal indicated cell death in LnCaP cells in presence of the T cells (FIG. 75). The data suggests that TMCB132 is effective in inducing T cell-mediated death in the LnCaP tumor cells.

15

Efficacy of TMCB132 in established SC human prostate xenograph in T-cell humanized mice.

The antitumor efficacy of TMCB132 was evaluated in established subcutaneous (SC) human prostate LNCaP xenografts in male NOD.Cg-Prkdc^{scid} Il2rg^{tm1Wjl}/SzJ (NSG, The Jackson
20 Laboratory, Bar Harbor, ME) mice humanized with 20e⁶ T cells. Animals were randomized into groups of 10 animals each by mean tumor volume on day 13 post tumor implantation. TMCB132 at 0.5, 0.1 and 0.05 mg/kg or nullxCD3B219 antibody control at 0.5 mg/kg were dosed IP twice weekly for 4 weeks. On day 45 post-tumor implantation, when at least seven animals remained per group, tumor growth inhibition (% TGI) as determined by tumor volume was calculated.
25 Statistically significant tumor growth inhibition was observed with TMCB132 at 0.5 and 0.1 mg/kg and 0.05 mg/kg, as compared to nullxCD3 control (FIG. 76, p≤ 0.0001). TMCB132 at 0.5, 0.1, and 0.05 mg/kg elicited tumor growth inhibition of 102%, 109% and 47%, respectively, as compared to nullxCD3 treated controls. TMCB132 treatment resulted in three, two and one complete responses at 0.5, 0.1 and 0.05 mg/kg, respectively

30

WHAT IS CLAIMED:

1. An isolated recombinant anti-CD3 antibody, or antigen-binding fragment thereof, comprising:
 - 5 a) a heavy chain comprising a heavy chain complementarity determining region (HCDR) 1 comprising SEQ ID NO: 662; a HCDR2 comprising SEQ ID NO: 663; and a HCDR3 comprising SEQ ID NO: 664 and a light chain comprising a light chain complementarity determining region (LCDR) 1 comprising SEQ ID NO: 671, a LCDR2 comprising SEQ ID NO: 673, and a LCDR3 comprising SEQ ID NO: 690;
 - 10 b) a heavy chain variable region comprising SEQ ID NO: 652 and a light chain variable region comprising SEQ ID NO: 661;
 - c) a heavy chain comprising SEQ ID NO: 640 and a light chain comprising SEQ ID NO: 676;
 - d) a heavy chain variable region comprising SEQ ID NO: 657 and a light chain variable
15 region comprising SEQ ID NO: 678; or
 - e) a heavy chain comprising SEQ ID NO: 675 and a light chain comprising SEQ ID NO: 677.
2. An isolated recombinant anti-CD3 antibody or antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment specifically binds *Macaca fascicularis* or human
20 CD3d, or CD3e, or CD3e and CD3d with a binding affinity of about 300 nM or less.
3. The isolated recombinant anti-CD3 antibody or antigen-binding fragment thereof of claim 2, wherein the binding affinity is about 100 nM or less.
4. The isolated recombinant anti-CD3 antibody or antigen-binding fragment thereof of claim 2 or 3, wherein the binding affinity is measured by flow cytometry or by Proteon surface
25 plasmon resonance assay ProteOn XPR36 system at +25°C.
5. The isolated recombinant anti-CD3 antibody or antigen-binding fragment thereof of any one of the previous claims, wherein the antibody or antigen-binding fragment has one, two, three, or four of the following properties:
 - a) binds human and *Macaca fascicularis* CD3+ T lymphocytes with a calculated EC50 of
30 300 nM or less and binds *Macaca fascicularis* CD3-expressing HEK cells with a calculated EC50 of 300 nM or less, wherein the difference in calculated EC50 between binding CD3+ T lymphocytes and binding *Macaca fascicularis* CD3-expressing HEK

cells is less than 5-fold, and wherein the calculated EC₅₀ is measured in a whole cell binding assay at 0 °C using flow cytometry;

- b) binds recombinant CD3d from human (SEQ ID NO:691), or binds recombinant CD3e from human (SEQ ID NO:636), or binds recombinant CD3d from *Macaca fascicularis* (SEQ ID NO:692), or binds recombinant CD3e from *Macaca fascicularis* (SEQ ID NO:693) with an equilibrium dissociation constant (K_D) of 300 nM or less, wherein the K_D is measured using Proteon surface plasmon resonance assay ProteOn XPR36 system at +25°C;
 - c) binds residues 1-6 of CD3e as determined by X-ray crystallography; or
 - d) activates T cells or induces CD69 expression to a similar degree as cOKT3 or SP34-2 as determined by fluorescence-activated cell sorting assay.
6. The antibody or antigen-binding fragment thereof of any one of the previous claims comprising at least one substitution in an antibody constant domain, the at least one substitution comprising:
- a) heavy chain substitutions K409R, F405L, or F405L and R409K;
 - b) heavy chain substitutions S228P, F234A, and L235A;
 - c) heavy chain substitutions L234A, G237A, P238S, H268A, A330S and P331S, wherein the antibody is an IgG1 isotype; or
 - d) heavy chain substitution S228P, wherein the antibody is an IgG4 isotype;
- wherein residue numbering is according to the EU Index.
7. The antibody or antigen-binding fragment thereof of any one of the previous claims, comprising the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2, and the LCDR3 of SEQ ID NOs:662, 663, 664, 671, 673, and 690, respectively.
8. The antibody or antigen-binding fragment thereof of any one of the previous claims, comprising a heavy chain variable region (VH) and a light chain variable region (VL) of SEQ ID NOs:652 and 661, respectively.

9. The antibody or antigen-binding fragment thereof of any one of the previous claims, comprising a heavy chain sequence (HC) and a light chain sequence (LC) of SEQ ID NOs:640 and 676, respectively.
10. The antibody or antigen-binding fragment thereof of any one of claims 1-5, comprising a VH
5 and a VL of SEQ ID NOs:657 and 678, respectively.
11. The antibody or antigen-binding fragment thereof of any one of claims 1-5, comprising a HC and a LC of SEQ ID NOs:675 and 677, respectively.
12. An antibody or antigen-binding fragment thereof, comprising the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2, and the LCDR3 of SEQ ID NOs: 662, 663, 664, 671, 673,
10 and 690, respectively.
13. An antibody or antigen-binding fragment thereof, comprising a VH and a VL of SEQ ID NOs:652 and 661, respectively.
14. An antibody or antigen-binding fragment thereof, comprising a HC and a LC of SEQ ID NOs:640 and 676, respectively.
- 15 15. An antibody or antigen-binding fragment thereof, comprising a VH and a VL of SEQ ID NOs:657 and 678, respectively.
16. An antibody or antigen-binding fragment thereof, comprising a HC and a LC of SEQ ID NOs:675 and 677, respectively.
17. The antibody or antigen-binding fragment thereof of any one of the previous claims, wherein
20 the antibody is human or humanized.
18. The antibody of claim 17, wherein the antibody is an IgG4 or IgG1 isotype.
19. The antibody of claim 18, comprising one, two, three, four, five, six, seven, eight, nine or ten substitutions in the antibody Fc.
20. An antibody or antigen-binding fragment thereof, comprising a HC of SEQ ID NO:639 and
25 a LC of SEQ ID NOs:646, comprising at least one substitution comprising:
 - a) D43G, L49M, L50I, S62N, Q85E light chain substitutions;
 - b) D43G, V48L, L49M, L50I, S62N, Q85E, H89Y light chain substitutions;

- c) R10G, R13K, V73I, R70K, T83S, L96V heavy chain substitutions;
 - d) any one of light chain substitutions D43G, V48L, L49M, L50I, S62N, Q85E, or H89Y; or
 - e) any one of heavy chain substitutions R10G, R13K, V73I, R79K, T83S, or L96V,
- wherein residue numbering is according to the EU Index.

5

- 21. The antibody of any one of the previous claims, wherein the antibody is bispecific or multispecific.
- 22. A bispecific antibody comprising a first domain that specifically binds CD3 and a second domain that specifically binds a second antigen, wherein the first domain comprises the
10 HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2, and the LCDR3 of SEQ ID NOs:662, 663, 664, 671, 673, and 690, respectively.
- 23. The bispecific antibody of claim 22 wherein the first domain and second domain are an IgG4 isotype, and wherein the first or the second domain comprises S228P, F234A, L235A, F405L and R409K heavy chain substitutions and the other domain of the first or the second domain
15 comprises S228P, F234A and L235A heavy chain substitution, wherein residue numbering is according to the EU Index.
- 24. The bispecific antibody of claim 22, wherein the first and/or the second domain comprises at least one substitution in a CH3 constant domain comprising a F405L, or F405L and R409K substitution, wherein residue numbering is according to the EU Index.
- 20 25. The bispecific antibody of claim 22, wherein one of the first or the second domains comprises a F405L heavy chain substitution and the other of the first or second domains comprises a K409R heavy chain substitution, wherein residue numbering is according to the EU Index.
- 26. The bispecific antibody of claim 22, wherein the first domain and the second domain are an
25 IgG4 isotype, wherein one of the first or the second domains comprises a S228P heavy chain substitution and the other of the first or the second domains comprises S228P, F405L and R409K heavy chain substitutions, wherein residue numbering is according to the EU Index.

27. The bispecific antibody of claim 22, wherein the first domain comprises the VH and the VL of SEQ ID NOs: 652 and 661, respectively.
28. The bispecific antibody of claim 22, wherein the first domain comprises the HC and the LC of SEQ ID NOs: 640 and 676, respectively.
- 5 29. The bispecific antibody of claim 22, wherein the first domain comprises the VH and the VL of SEQ ID NOs: 657 and 678, respectively.
30. The bispecific antibody of claim 22, wherein the first domain comprises the HC and the LC of SEQ ID NOs: 675 and 677, respectively.
31. The bispecific antibody of claim 22, wherein the second antigen is a cell surface antigen that
10 is expressed on a target cell other than an immune effector cell.
32. The bispecific antibody of claim 31, wherein the cell surface antigen is a tumor associated antigen.
33. The bispecific antibody of any one of claims 24-34, wherein the second antigen is CD33, IL1RAP, PSMA or TMEFF2.
- 15 34. A pharmaceutical composition comprising the antibody of any one of the previous claims and a pharmaceutically acceptable carrier.
35. A polynucleotide encoding the antibody of any one of the claims 1-34.
36. A vector comprising the polynucleotide of claim 35.
37. A host cell comprising the vector of claim 36.
- 20 38. A method of producing the antibody of any one of claims 1-34, comprising culturing the host cell of claim 37 in conditions that the antibody is expressed, and recovering the antibody produced by the host cell.
39. A method of treating a cancer in a subject, comprising administering a therapeutically effective amount of the isolated antibody of any one of claims 1-34 to the subject in need
25 thereof for a time sufficient to treat the cancer.
40. The method of claim 39, wherein the cancer is a solid tumor or a hematological malignancy.

41. The method of claim 40, wherein the solid tumor is a prostate cancer, a colorectal cancer, a gastric cancer, a clear cell renal carcinoma, a bladder cancer, a lung cancer, a squamous cell carcinoma, a glioma, a breast cancer, a kidney cancer, a neovascular disorder, a clear cell renal carcinoma (CCRCC), a pancreatic cancer, a renal cancer, a urothelial cancer or an
5 adenocarcinoma to the liver.
42. The method of claim 41, wherein the prostate cancer is a refractory prostate cancer, a prostatic intraepithelial neoplasia, an androgen independent prostate cancer, or a malignant prostate cancer.
43. The method of claim 40, wherein the hematological malignancy is acute myeloid leukemia
10 (AML), myelodysplastic syndrome (MDS), acute lymphocytic leukemia (ALL), diffuse large B-cell lymphoma (DLBCL), chronic myeloid leukemia (CML) or blastic plasmacytoid dendritic cell neoplasm (DPDCN).
44. The method of any one of claims 38-43, wherein the antibody is administered in combination with a second therapeutic agent.
- 15 45. The antibody of any one of claims 1-34 for use in therapy.
46. An anti-idiotypic antibody binding to the antibody of any one of claims 1-34.

Fig. 1A

VH		1	50
BLW-2B4-gamma	(1)	QVQLQQSGPGLVKPSQTLSLTCAISGDSVFNNNAAWSWIRQSPSRGLEWL	
BLW-3B4-gamma	(1)	QVQLQQSGPGLVKPSQTLSLTCAISGDSVFNNNAAWSWIRQSPSRGLEWL	
BLX-1F8-gamma	(1)	QVQLQQSGPGLVKPSQTLSLTCAISGDSVFNNNAAWSWIRQSPSRGLEWL	
BLX-3G8-gamma	(1)	QVQLQQSGPGLVKPSQTLSLTCAISGDSVFNNNAAWSWIRQSPSRGLEWL	
BLX-3F4-gamma	(1)	QVQLQQSGPGLVKPSQTLSLTCAISGDSVFNNNAAWSWIRQSPSRGLEWL	
BLW-2E6-gamma	(1)	QVQLQQSGPGLVKPSQTLSLTCAISGDSVFNNNAAWSWIRQSPSRGLEWL	
BLX-2E9-gamma	(1)	QVQLQQSGPGLVKPSQTLSLTCAISGDSVFNNNAAWSWIRQSPSRGLEWL	
IGHV6-1*01_Homo	(1)	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWNWIRQSPSRGLEWL	
		CDR1	
		51	100
BLW-2B4-gamma	(51)	GRTYYRSKWLYDYAVSVKSRLITVNPDTSRNQFTLQLNSVTPEDTALYYCV	
BLW-3B4-gamma	(51)	GRTYYRSKWLYDYAVSVKSRLITVNPDTSRNQFTLQLNSVTPEDTALYYCV	
BLX-1F8-gamma	(51)	GRTYYRSKWLYDYAVSVKSRLITVNPDTSRNQFTLQLKSVTPEDTALYYCS	
BLX-3G8-gamma	(51)	GRTYYRSKWLYDYAVSVKSRLITVNPDTSRNQFTLQLKSVTPEDTALYYCS	
BLX-3F4-gamma	(51)	GRTYYRSKWLYDYAVTVKSRLITVNPDTSRNQFTLQLTSVTPEDTALYYCA	
BLW-2E6-gamma	(51)	GRTYYRSKWLYDYAVSVKSRLITVNPDTSRNQFTLQLNSVTPEDTALYYCA	
BLX-2E9-gamma	(51)	GRTYYRSKWLYDYAVSVKSRLITVNPDTSRNQFTLQLNSVTPEDTALYYCA	
IGHV6-1*01_Homo	(51)	GRTYYRSKWYNDYAVSVKSRLITINPDTSKNQFTLQLNSVTPEDTAVYYCA	
		CDR2	
		101	120
BLW-2B4-gamma	(101)	RGYSSSFQYWGQGTLLTVSS	
BLW-3B4-gamma	(101)	RGYSSSFQYWGQGTLLTVSS	
BLX-1F8-gamma	(101)	RGYSSSFQYWGQGTLLTVSS	
BLX-3G8-gamma	(101)	RGYSSSFQYWGQGTLLTVSS	
BLX-3F4-gamma	(101)	RGYSSSFQYWGQGTLLTVSS	
BLW-2E6-gamma	(101)	RGYSSSFQYWGQGTLLTVSS	
BLX-2E9-gamma	(101)	RGYSSSFQYWGQGTLLTVSS	
IGHV6-1*01_Homo	(101)	R-----	
		CDR3	

Fig. 1B

VL		1	50
BLW-2B4-lambda	(1)	QSALTQPASVSGSPGQSITISCTGTSS RD IGTYKFVSWYQQHPDKAPKVLL	
BLW-3B4-lambda	(1)	QSALTQPASVSGSPGQSITISCTGTSS RD IGTYKFVSWYQQHPDKAPKVLL	
BLX-1F8-lambda	(1)	QSALTQPASVSGSPGQSITISCTGTSS D IGTYKFVSWYQQHPDKAPKVLL	
BLW-2E6-lambda	(1)	QSALTQPASVSGSPGQSITISCTGTSSNIGTYKFVSWYQQHPDKAPKVLL	
BLX-2E9-lambda	(1)	QSALTQPASVSGSPGQSITISCTGTSSNIGTYKFVSWYQQHPDKAPKVLL	
BLX-3F4-lambda	(1)	QSALTQPASVSGSPGQSITISCTGTSSNIGTYKFVSWYQQHPDKAPKVLL	
BLX-3G8-lambda	(1)	QSALTQPASVSGSPGQSITISCTGTSSNIGTYKFVSWYQQHPDKAPKVLL	
IGLV2-23*02_Homo	(1)	QSALTQPASVSGSPGQSITISCTGTSS DVGSYNL VSWYQQHP GKAPKLMI	
		CDR1	
		51	100
BLW-2B4-lambda	(51)	YEV N KRPSGVSSRFSGSKSGNTASLTISGLQAEDQADYHCCSYAGSGTLL	
BLW-3B4-lambda	(51)	YEVSKRPSGVSSRFSGSKSGNTASLTISGLQAEDQADYHCCSYAGSGTLL	
BLX-1F8-lambda	(51)	YEVSKRPSGVSSRFSGSKS D NTASLTISGLQAEDQADYHCCSYAGSGTLL	
BLW-2E6-lambda	(51)	YEVSKRPSGVSSRFSGSKSGNTASLTISGLQAEDQADYHCCSYAGSGTLL	
BLX-2E9-lambda	(51)	YEVSKRPSGVSSRFSGSKSGNTASLTISGLQAEDQADYHCCSYAGSGTLL	
BLX-3F4-lambda	(51)	YEVSKRPSGVSSRFSGSKSGNTASLTISGLQAEDQADYHCCSYAGSGTLL	
BLX-3G8-lambda	(51)	YEVSKRPSGVSSRFSGSKSGNTASLTISGLQAEDQADYHCCSYAGSGTLL	
IGLV2-23*02_Homo	(51)	YEVSKRPSGVSS NR FSGSKSGNTASLTISGLQAED EADY YCCSYAGSSTF -	
		CDR2	CDR3
		101	
BLW-2B4-lambda	(101)	FGGGTKLTVL	
BLW-3B4-lambda	(101)	FGGGTKLTVL	
BLX-1F8-lambda	(101)	FGGGTKLTVL	
BLW-2E6-lambda	(101)	FGGGTKLTVL	
BLX-2E9-lambda	(101)	FGGGTKLTVL	
BLX-3F4-lambda	(101)	FGGGTKLTVL	
BLX-3G8-lambda	(101)	FGGGTKLTVL	
IGLV2-23*02_Homo	(100)	-----	

Fig. 2

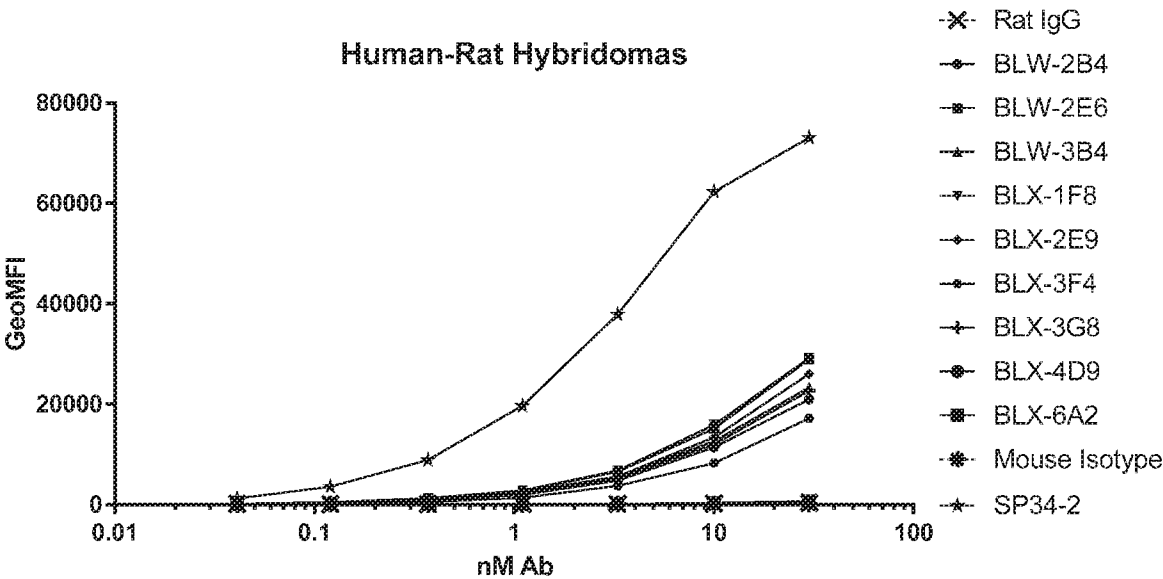


Fig. 3

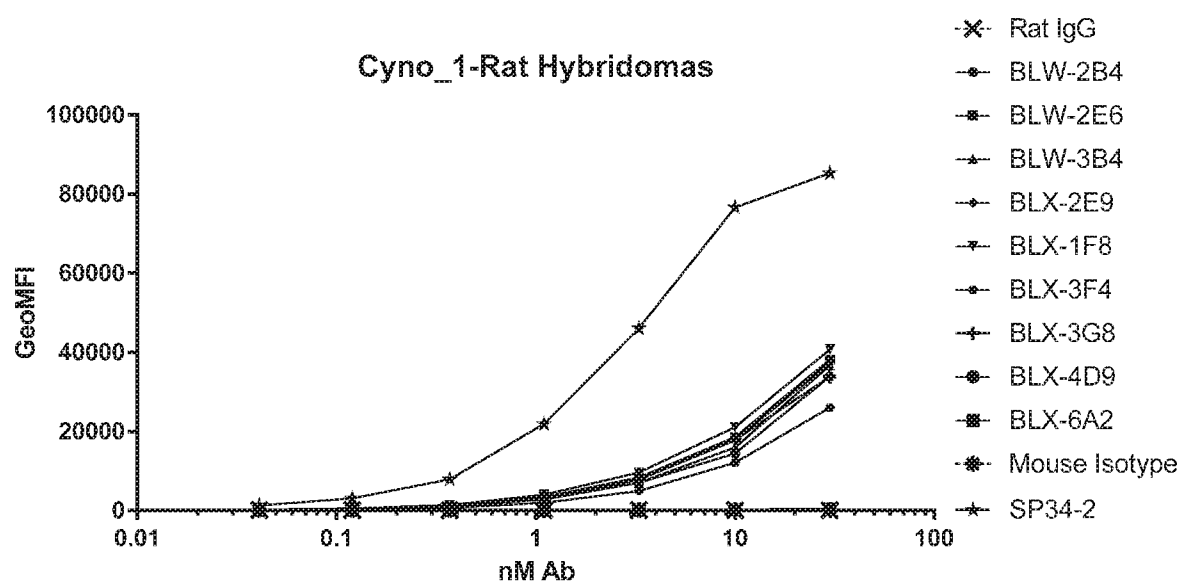


Fig. 4

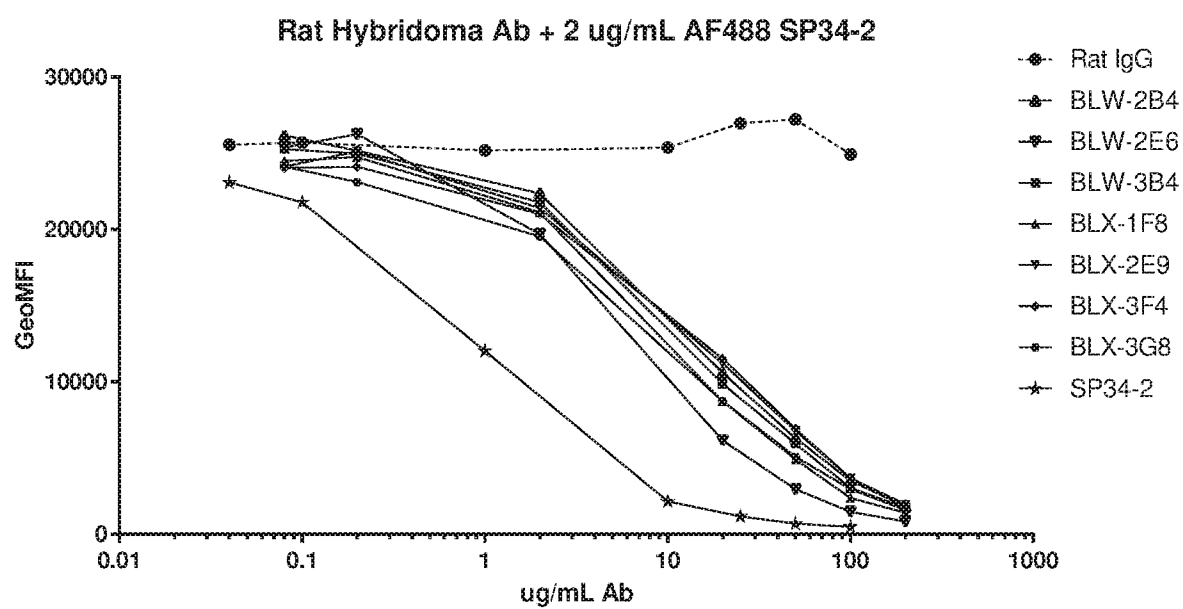


Fig. 5

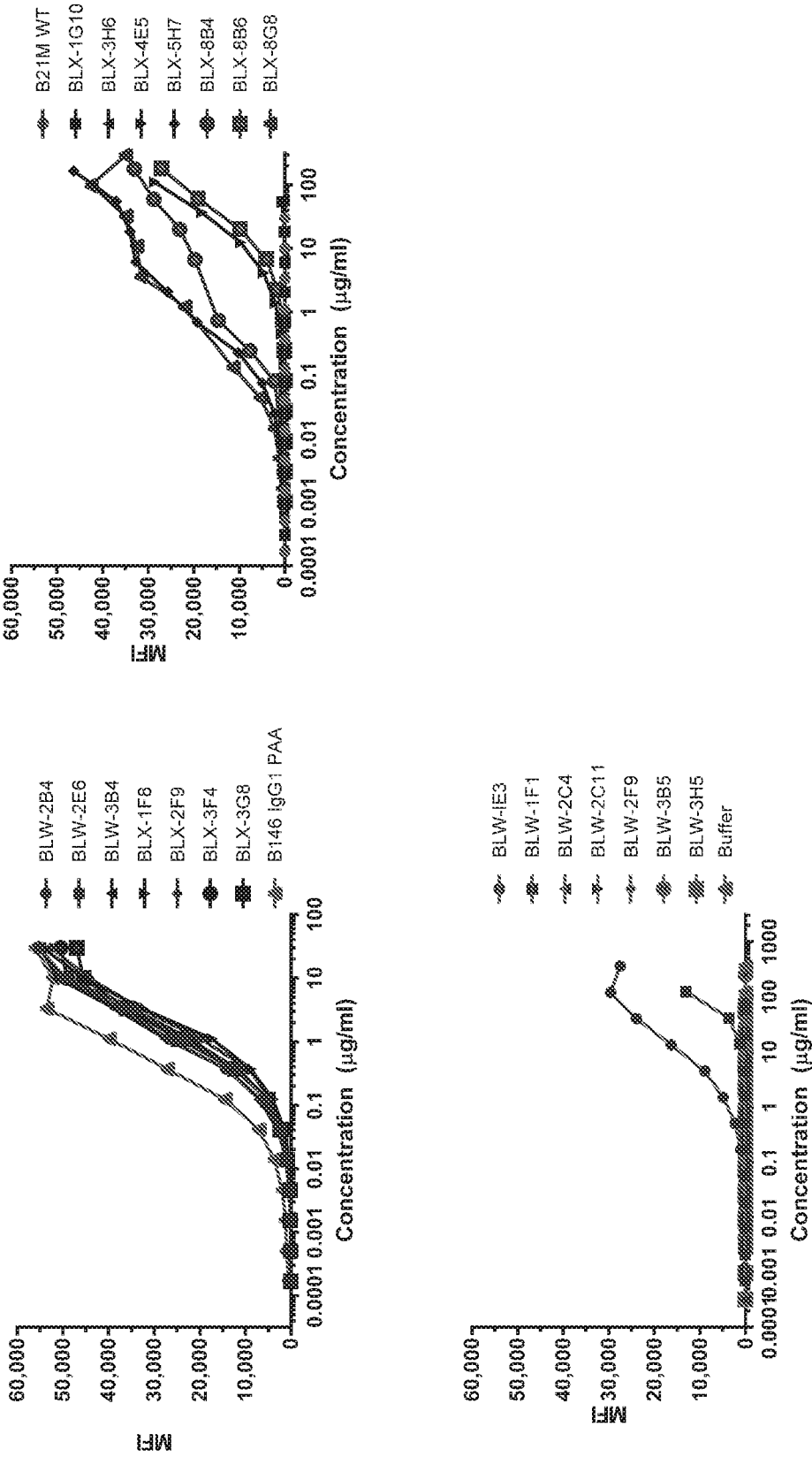


Fig. 6

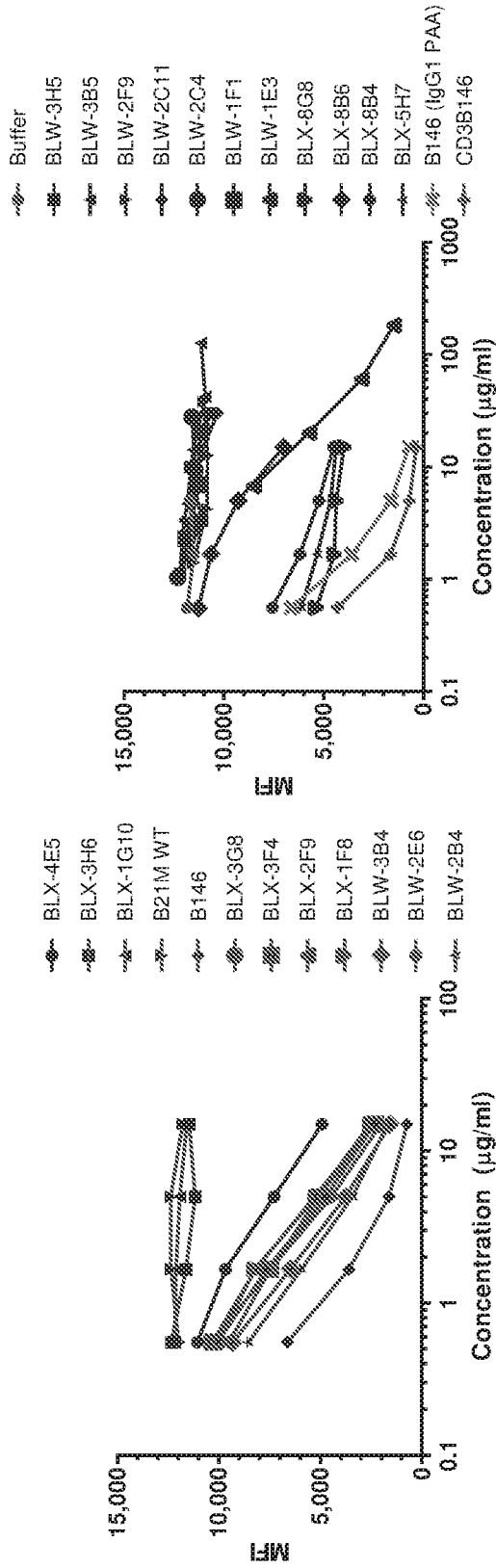


Fig. 7

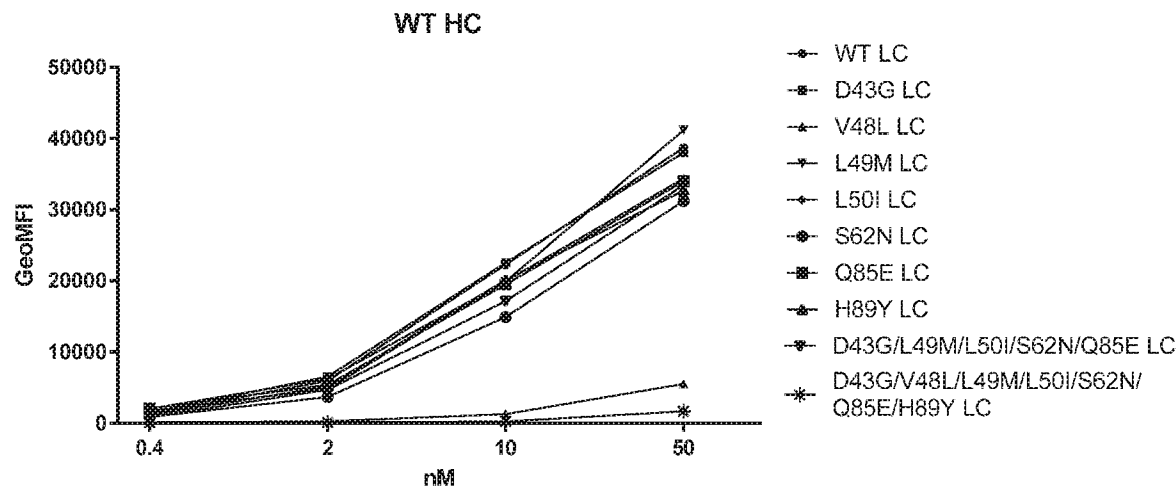


Fig. 9

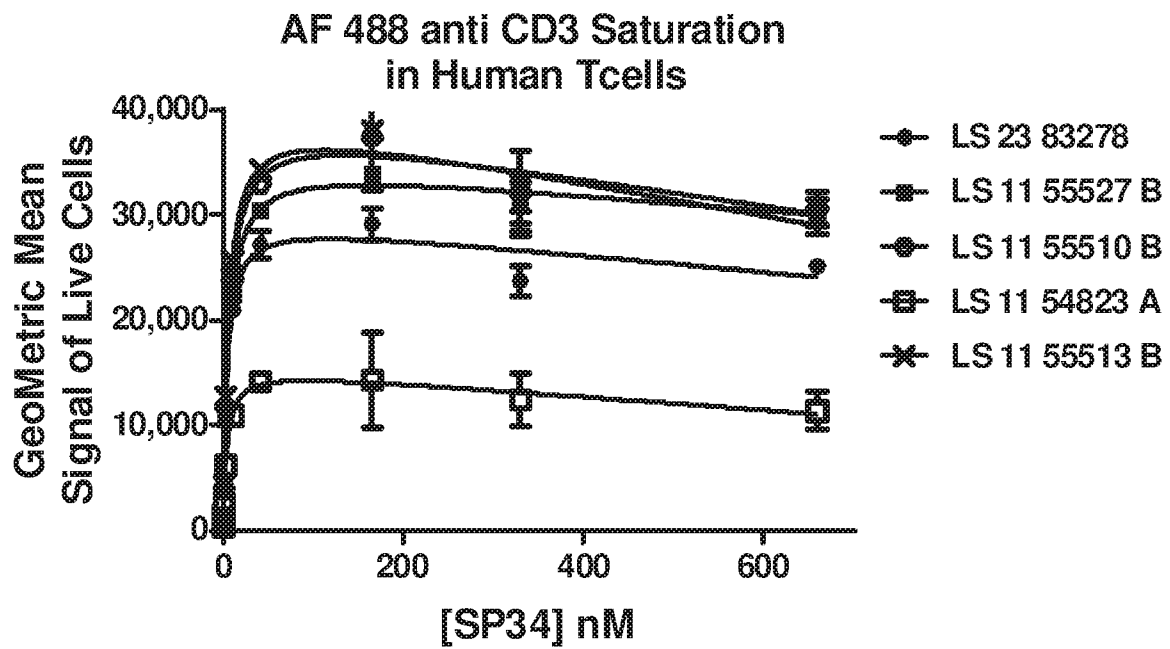


Fig. 10

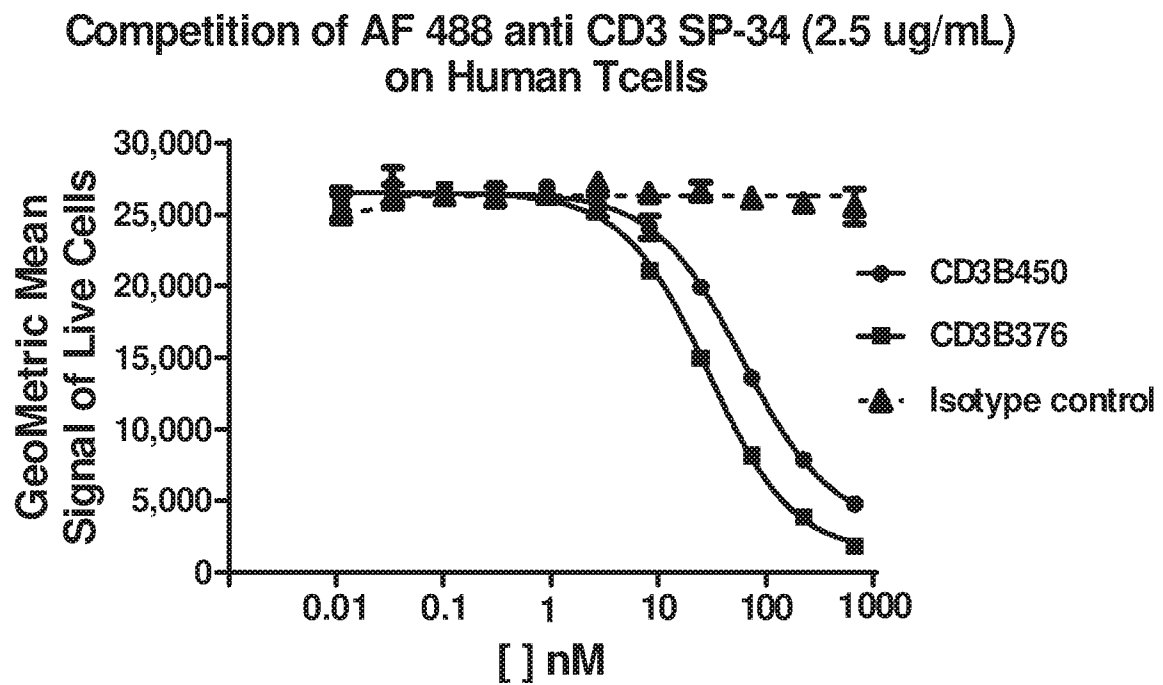


Fig. 11

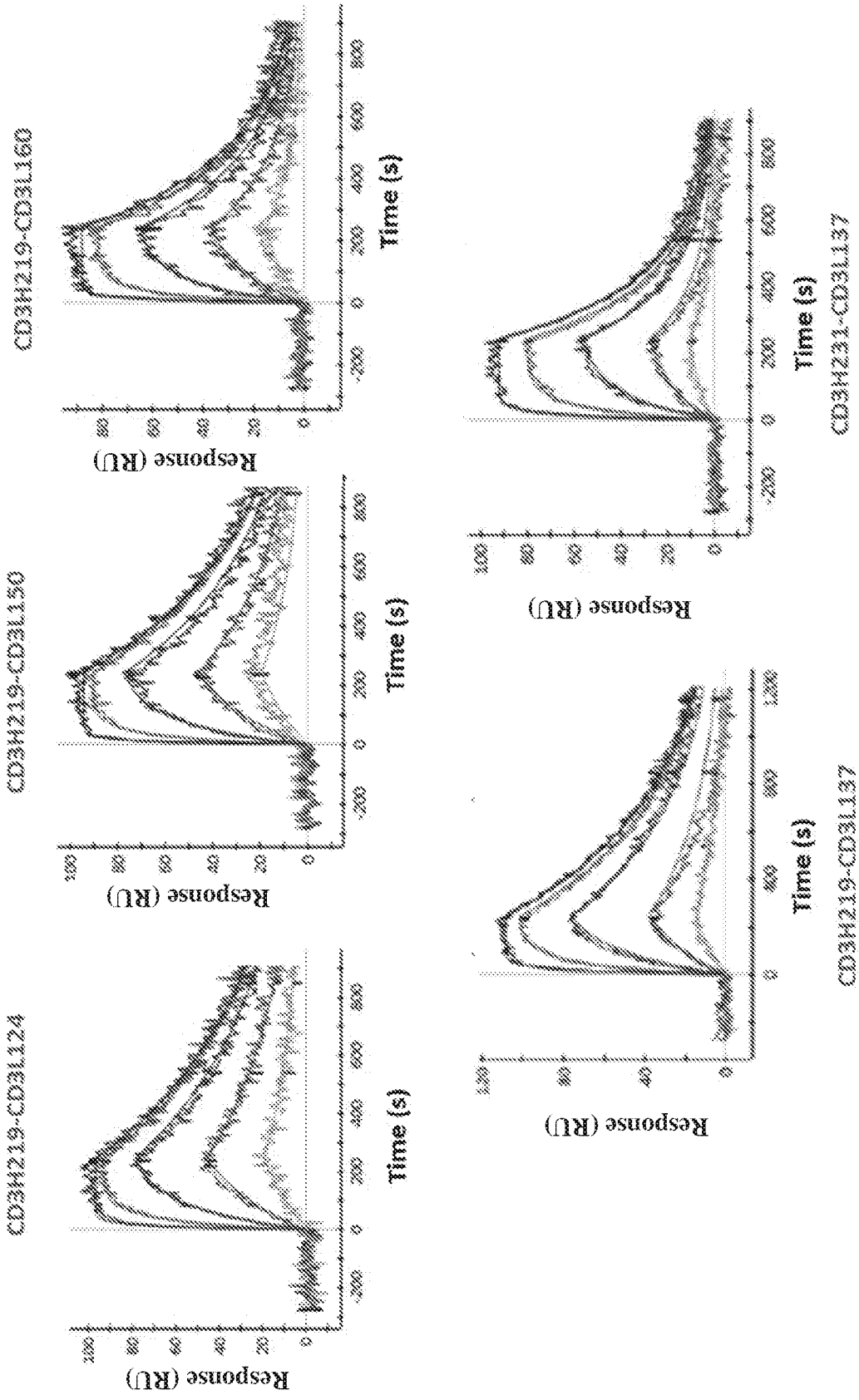


Fig. 12A

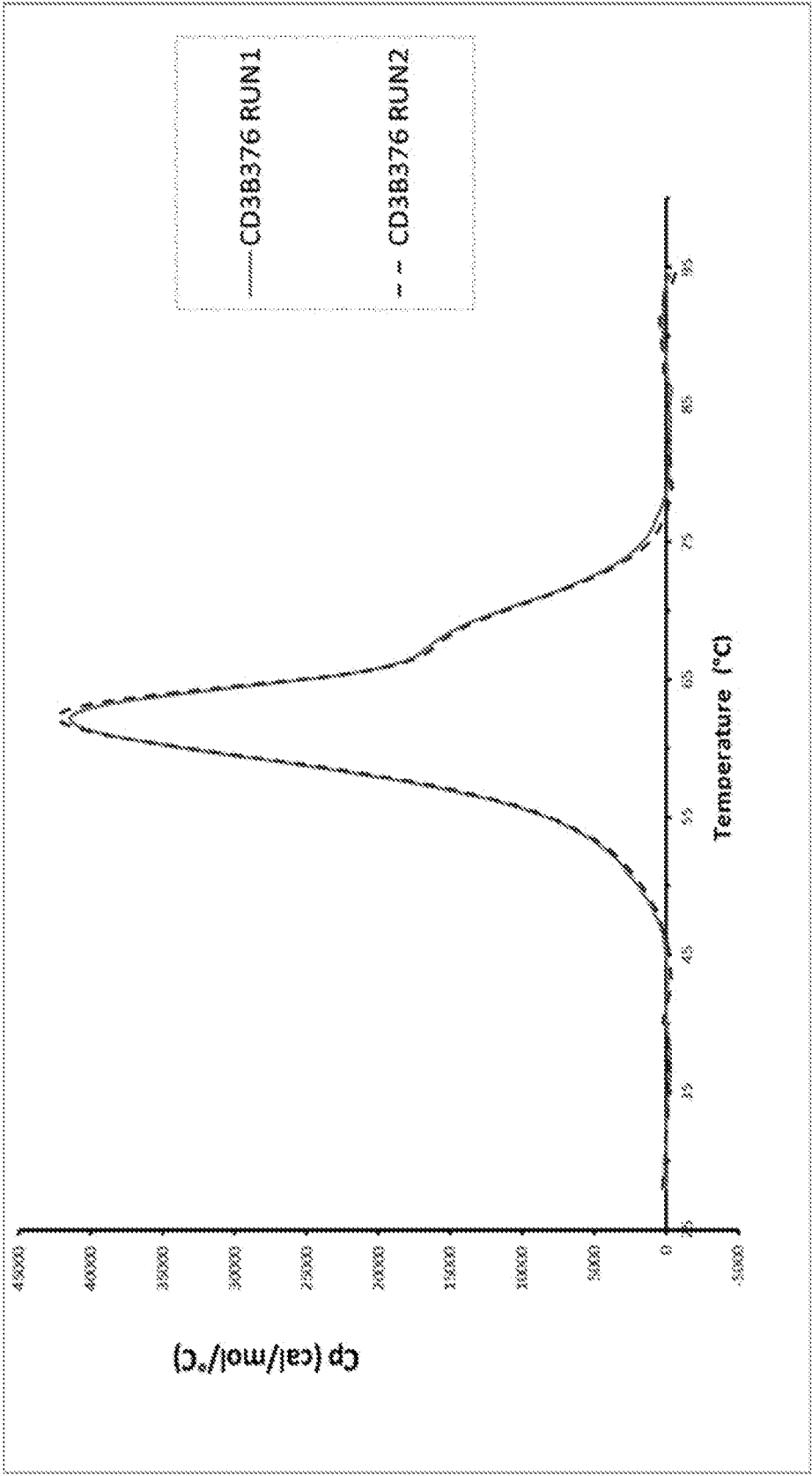


Fig. 12B

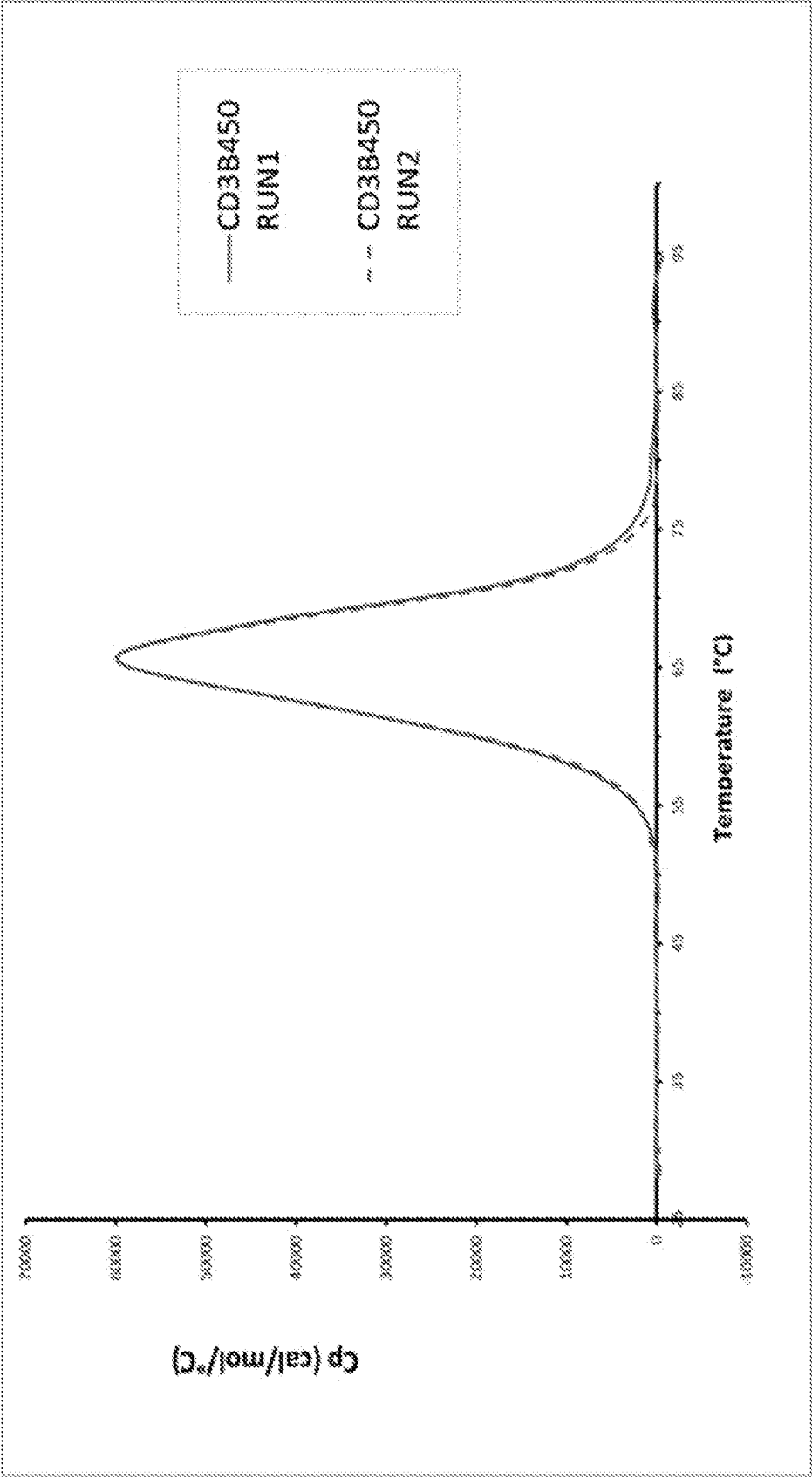


Fig. 12C

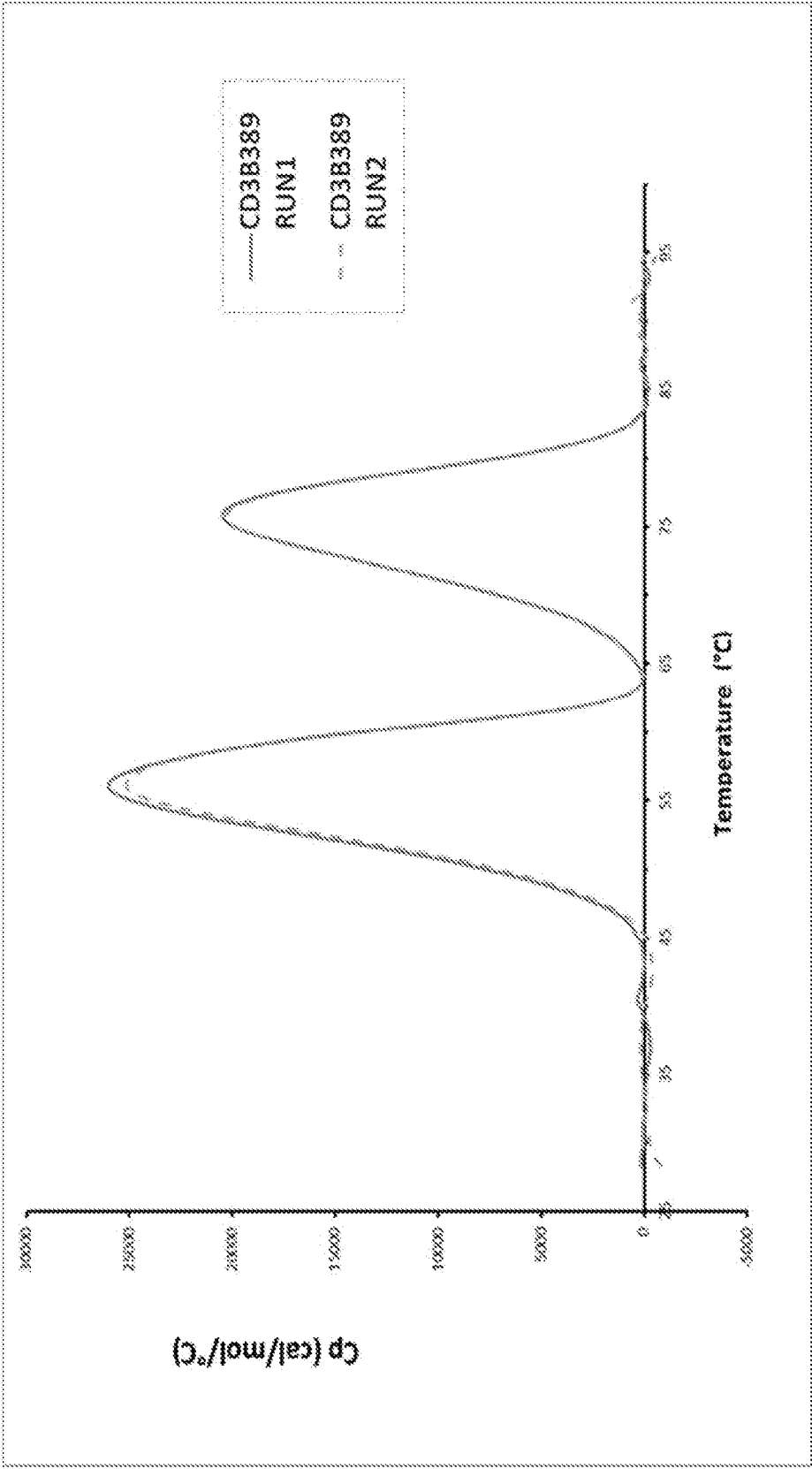


Fig. 12D

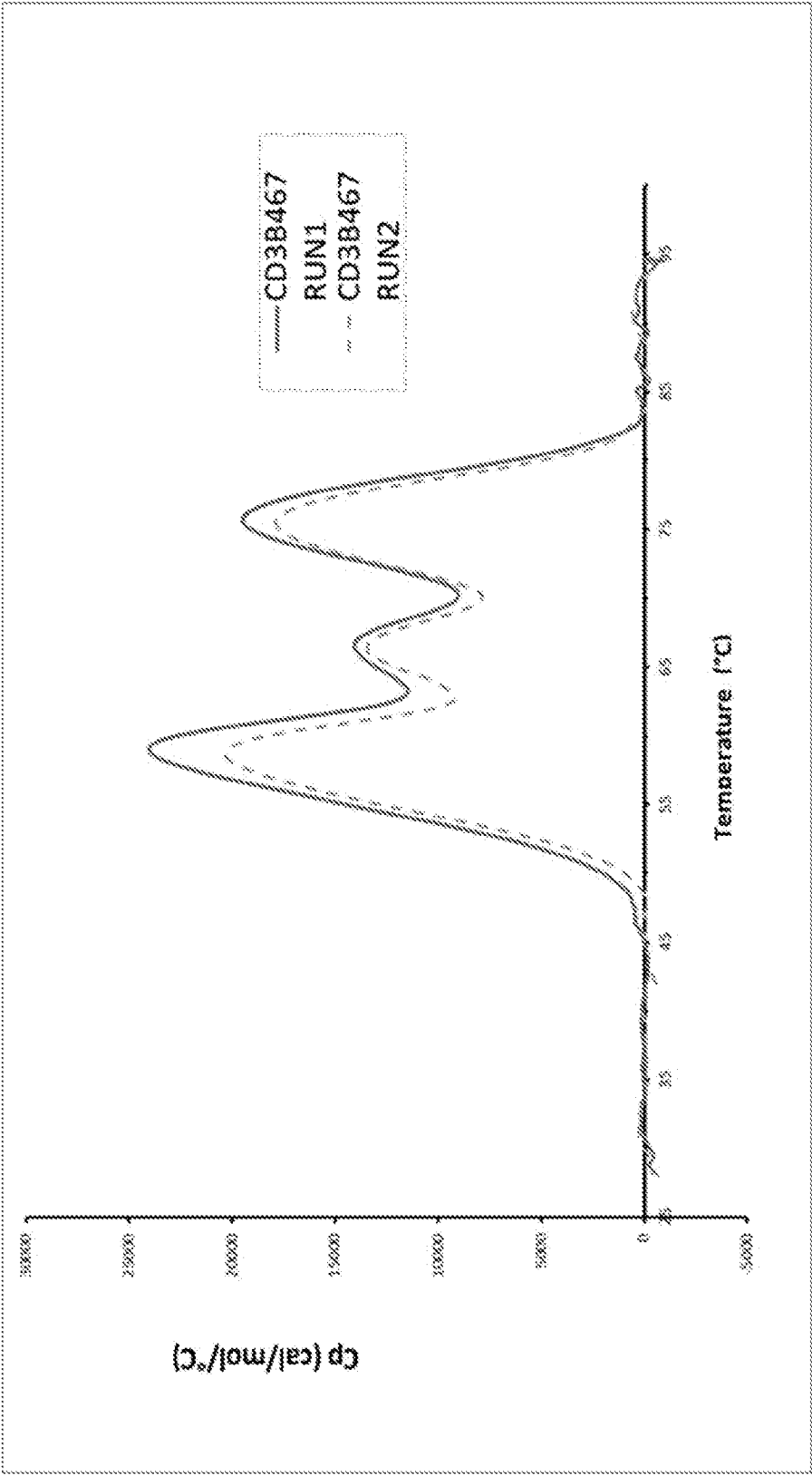
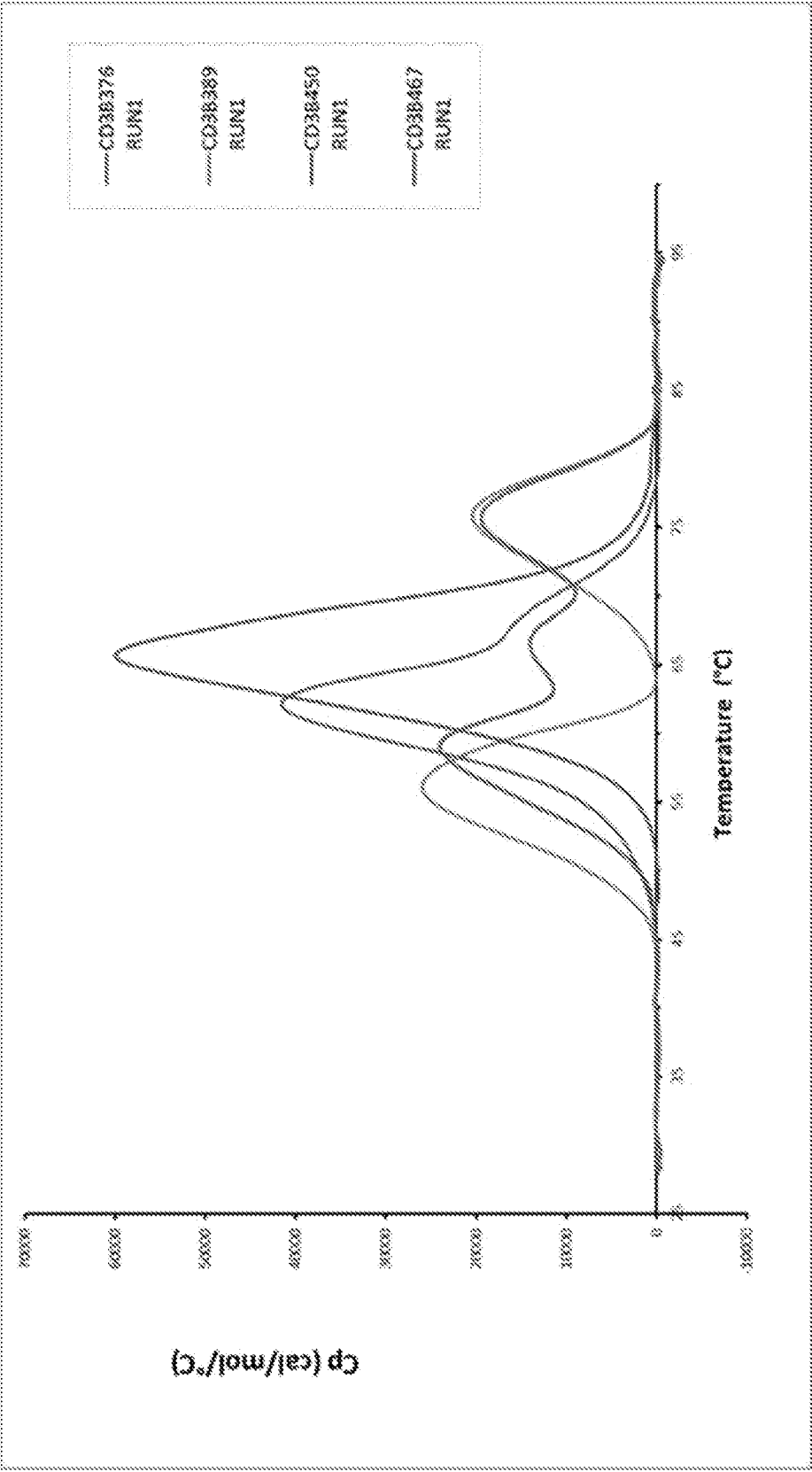


Fig. 12E



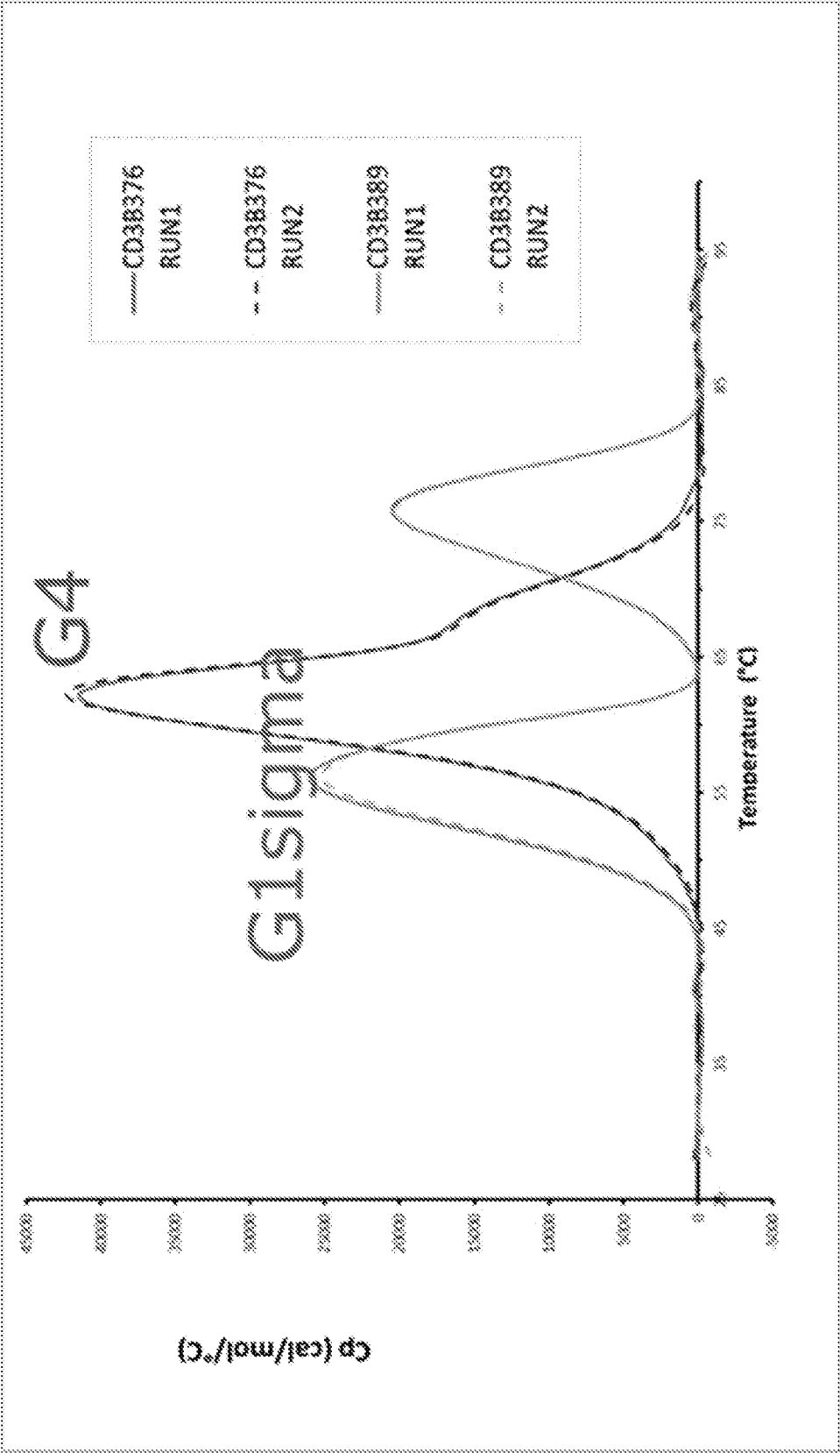


Fig. 13A

Fig. 13B

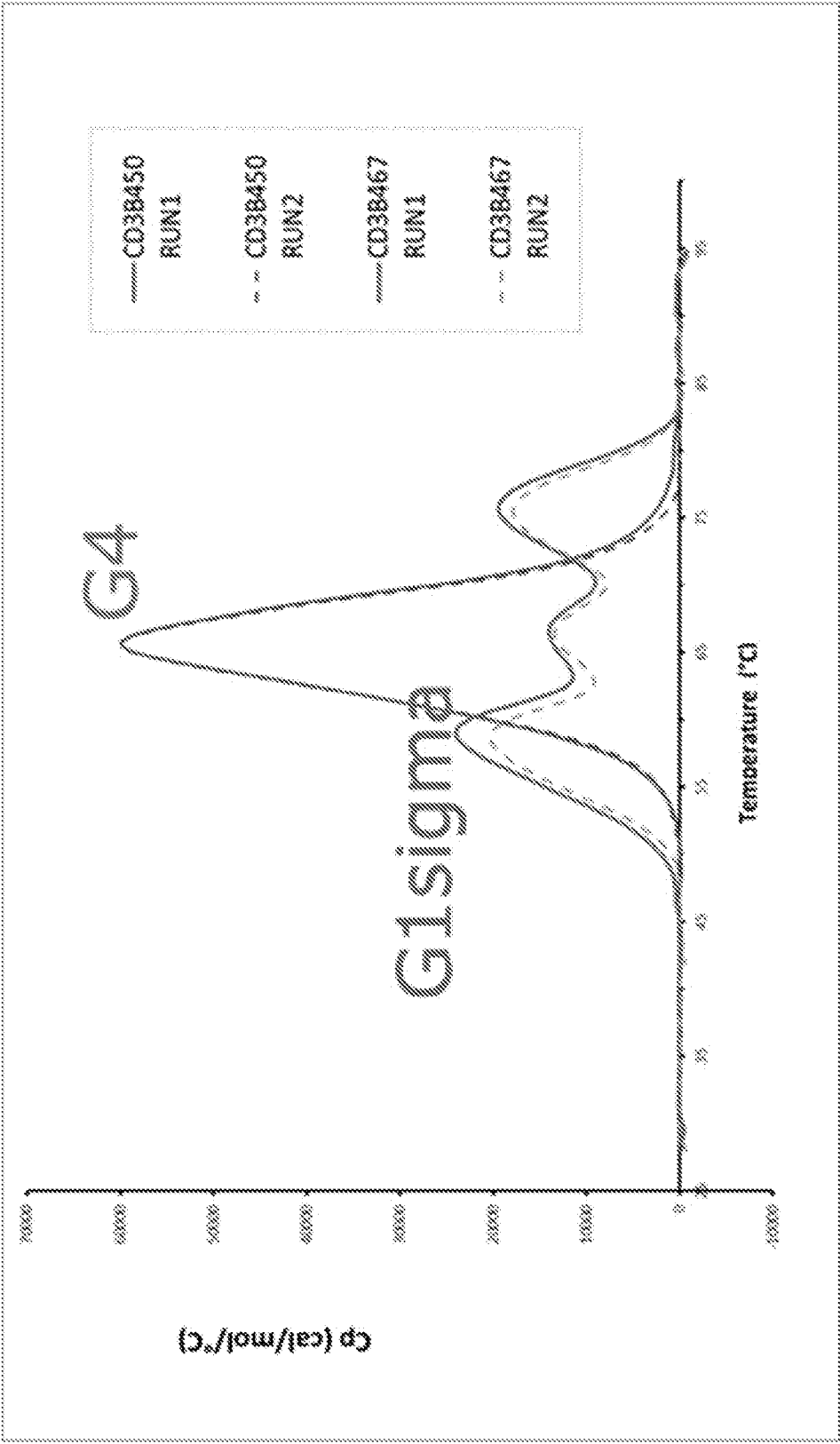


Fig. 14

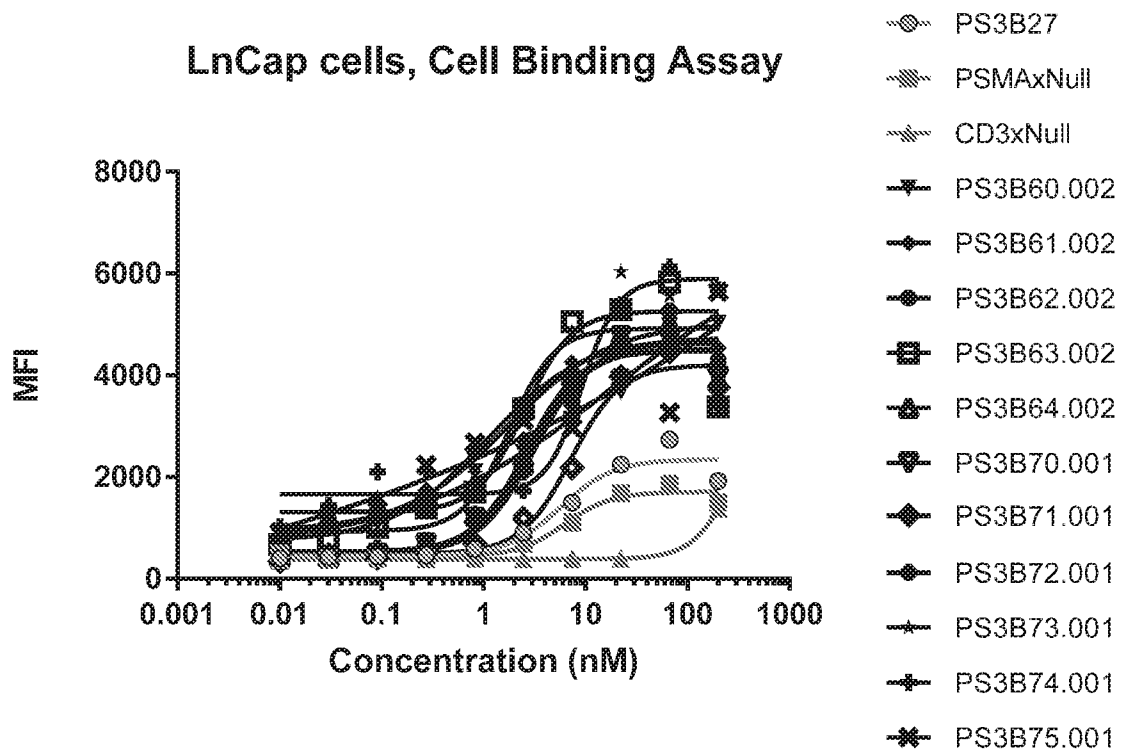


Fig. 15

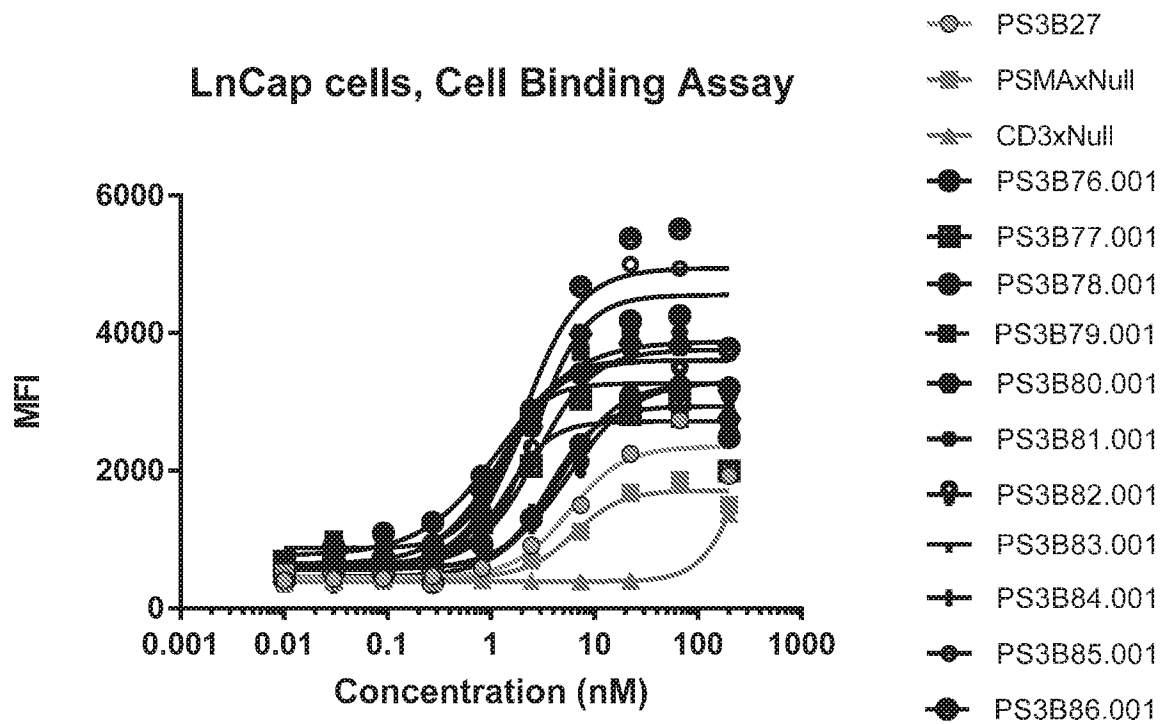


Fig. 16

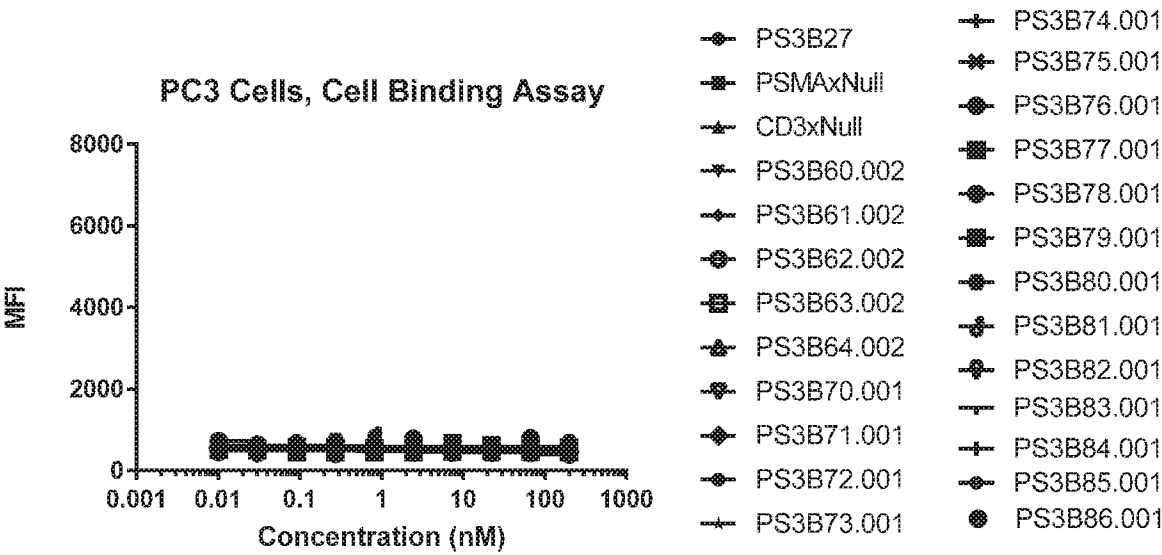


Fig. 17

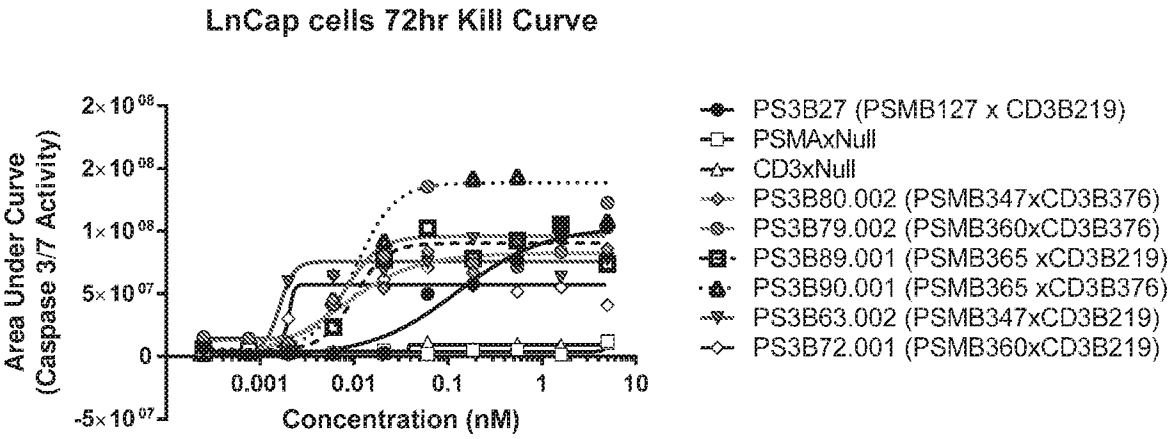


Fig. 19

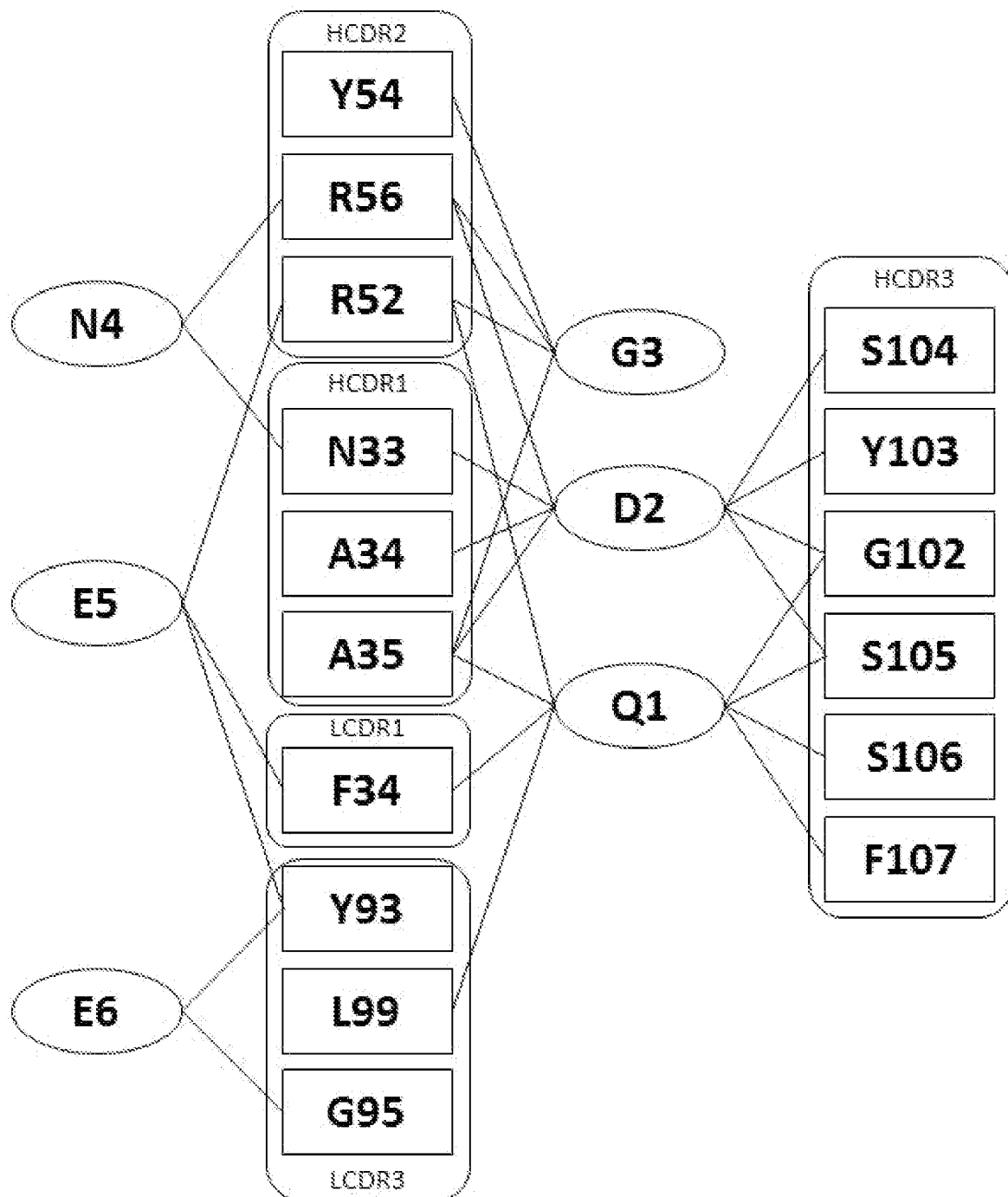


Fig. 20

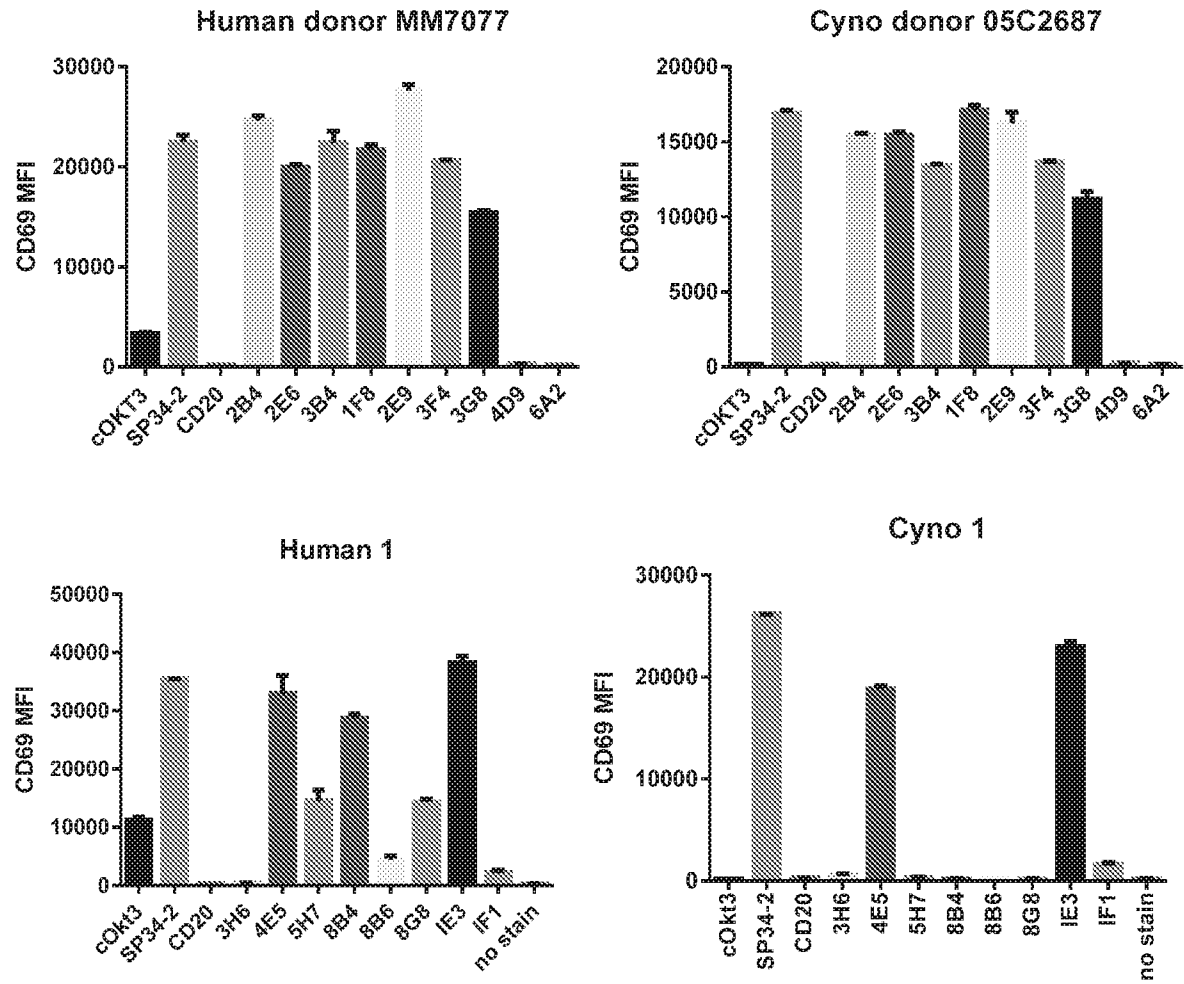


Fig. 21

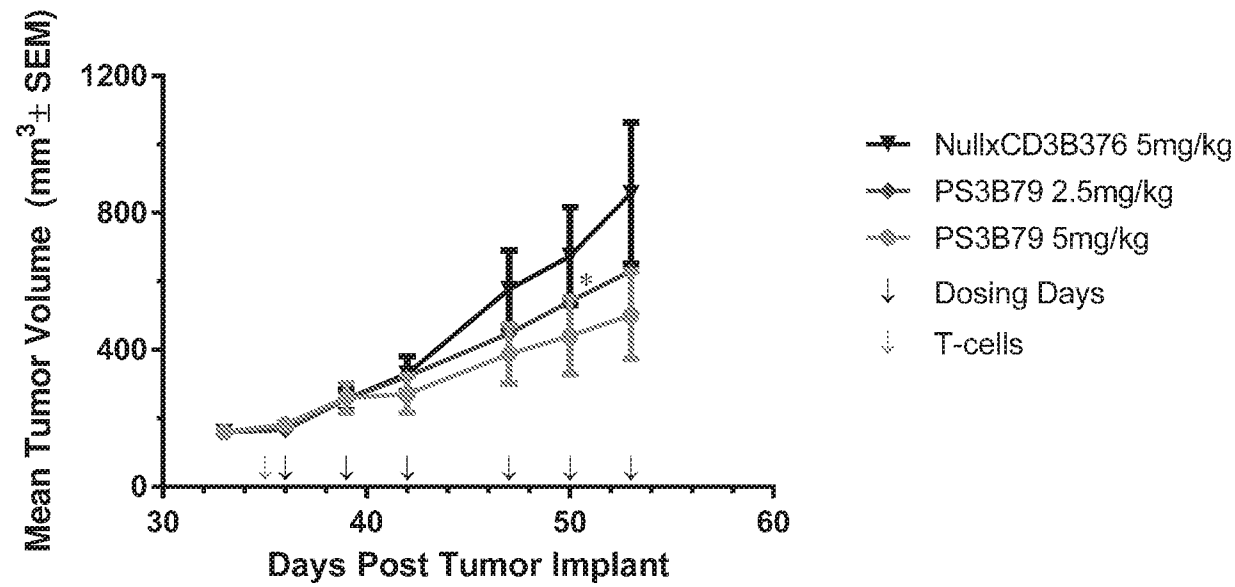


Fig. 22

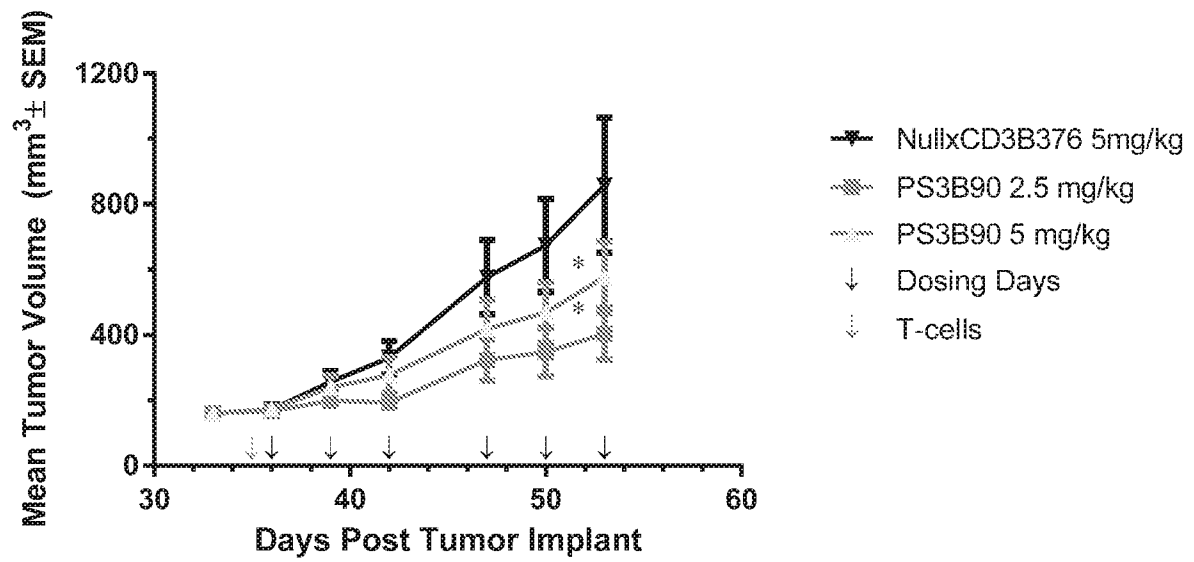


Fig. 23A

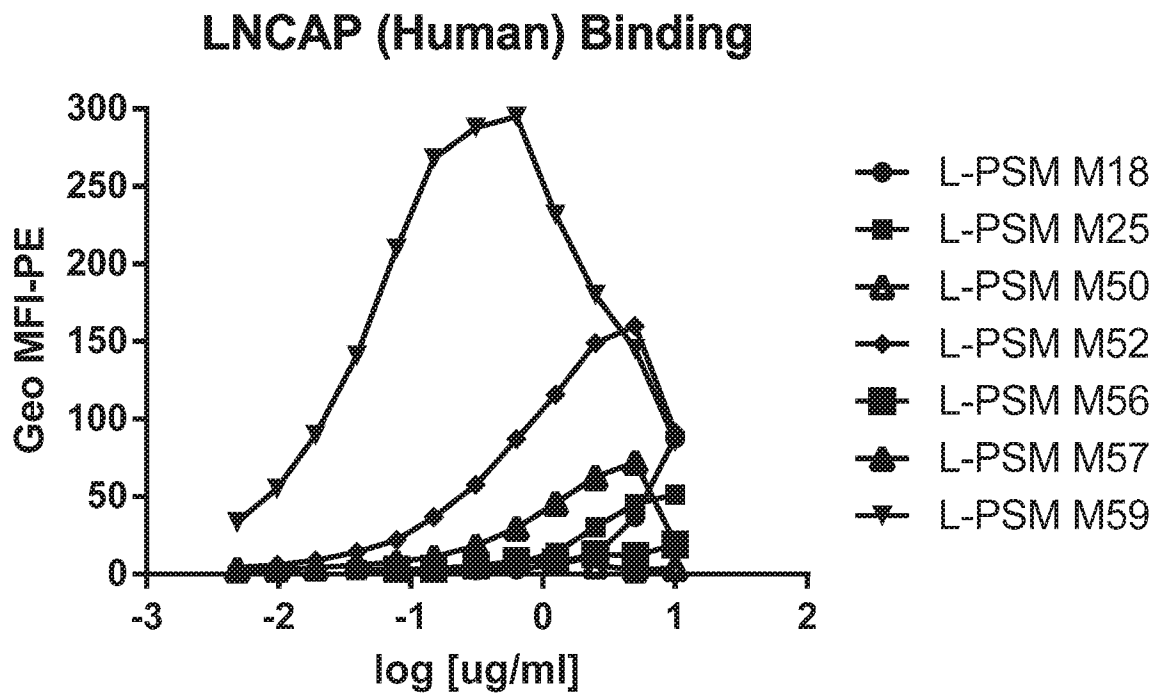


Fig. 23B

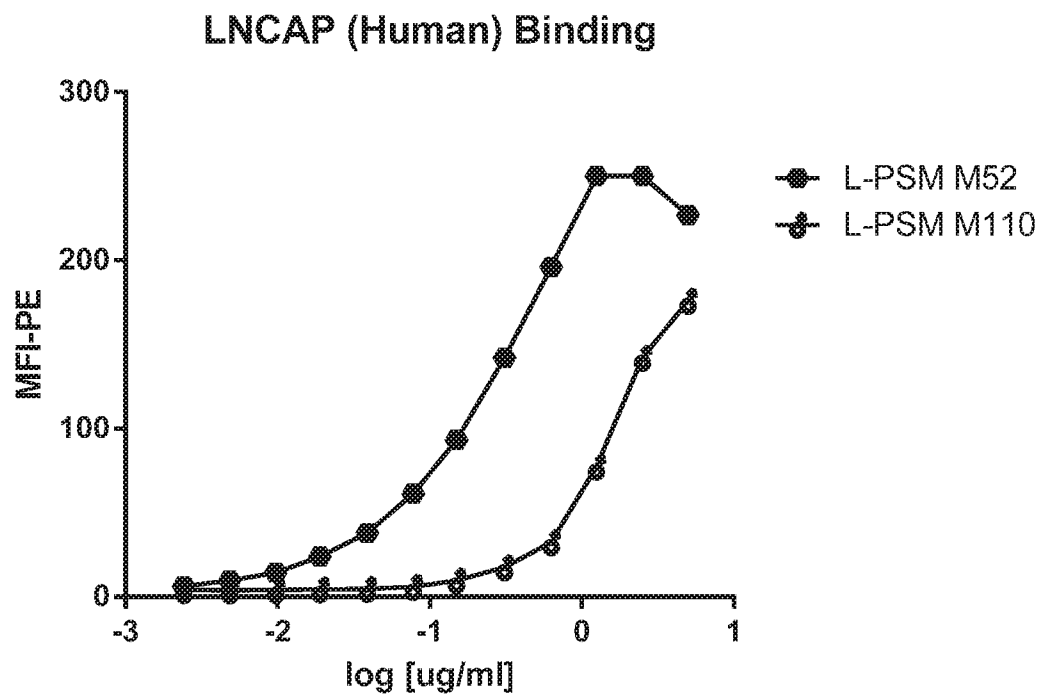


Fig. 23C

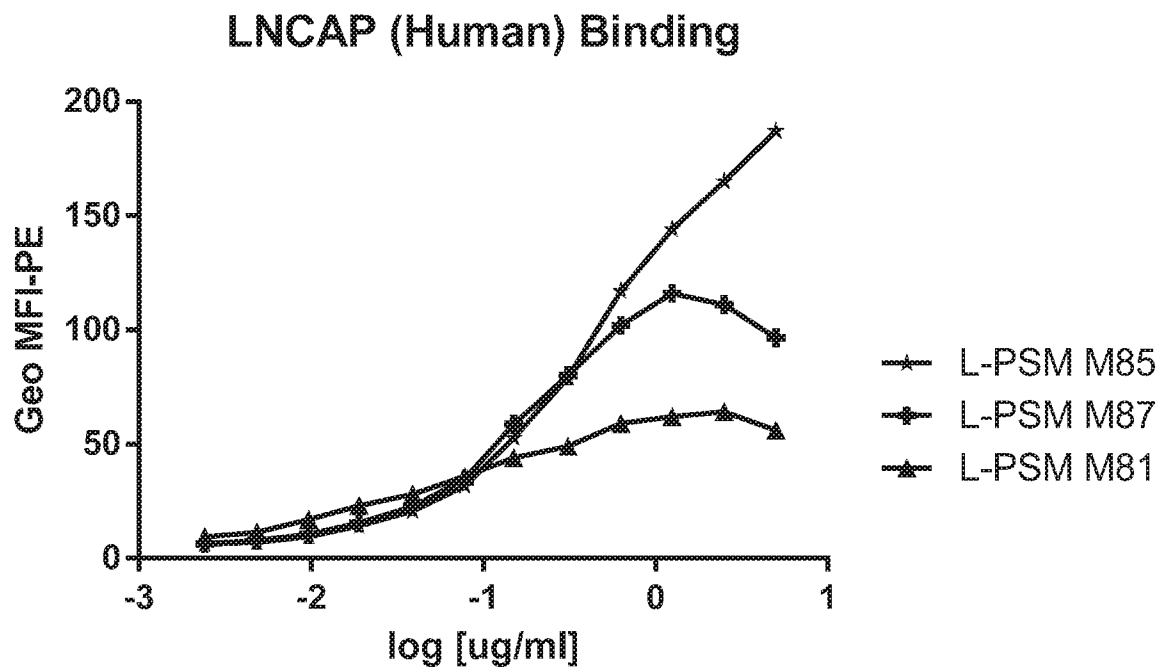


Fig. 23D

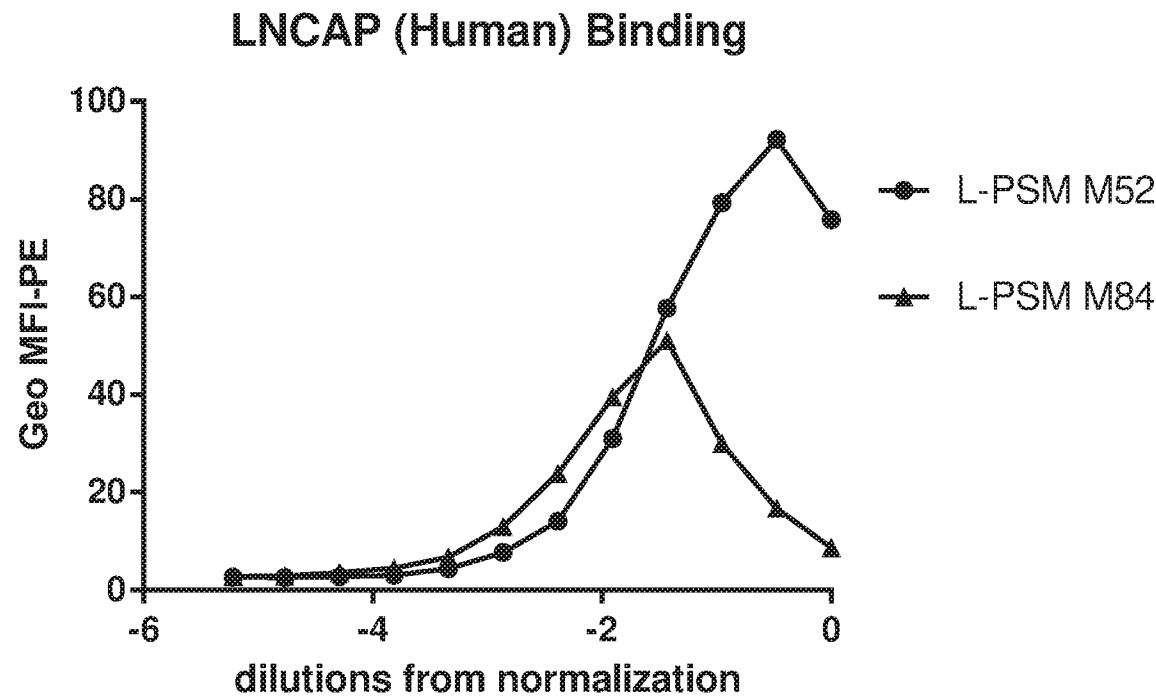


Fig. 24A

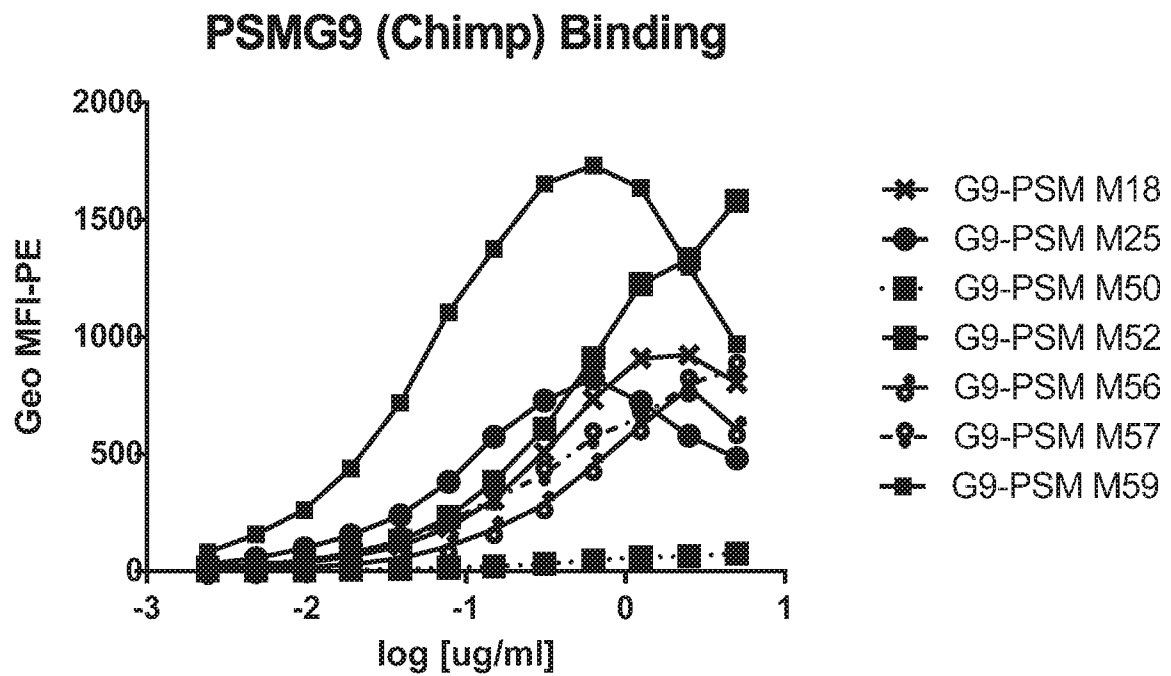


Fig. 24B

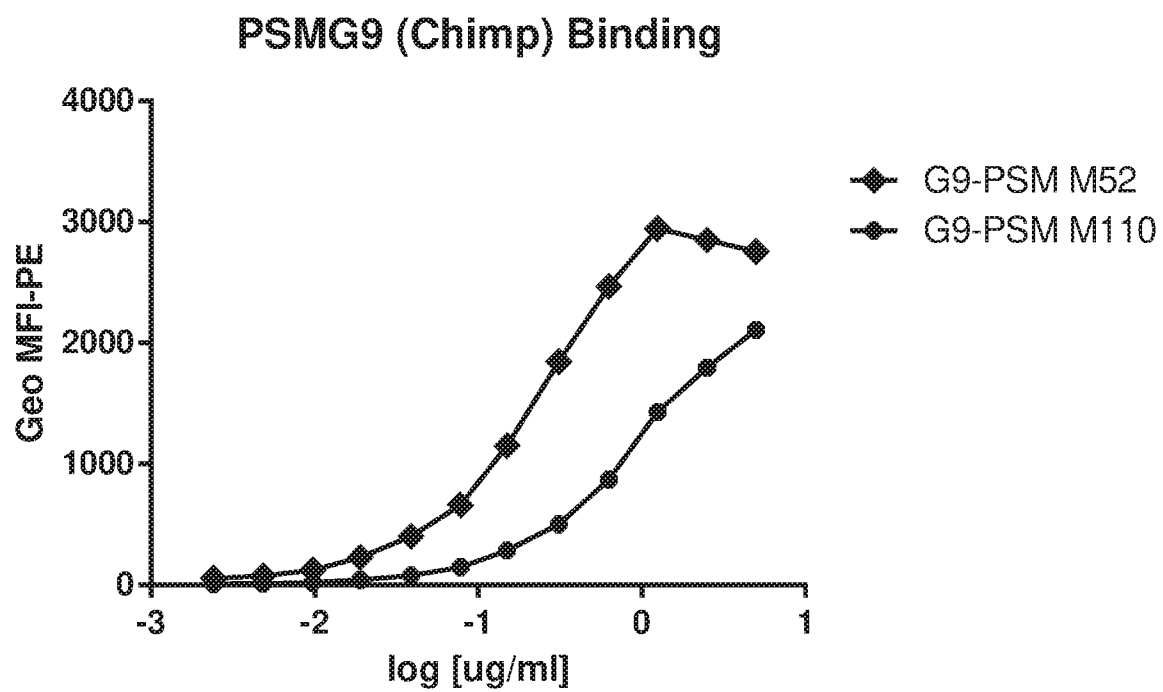


Fig. 24C

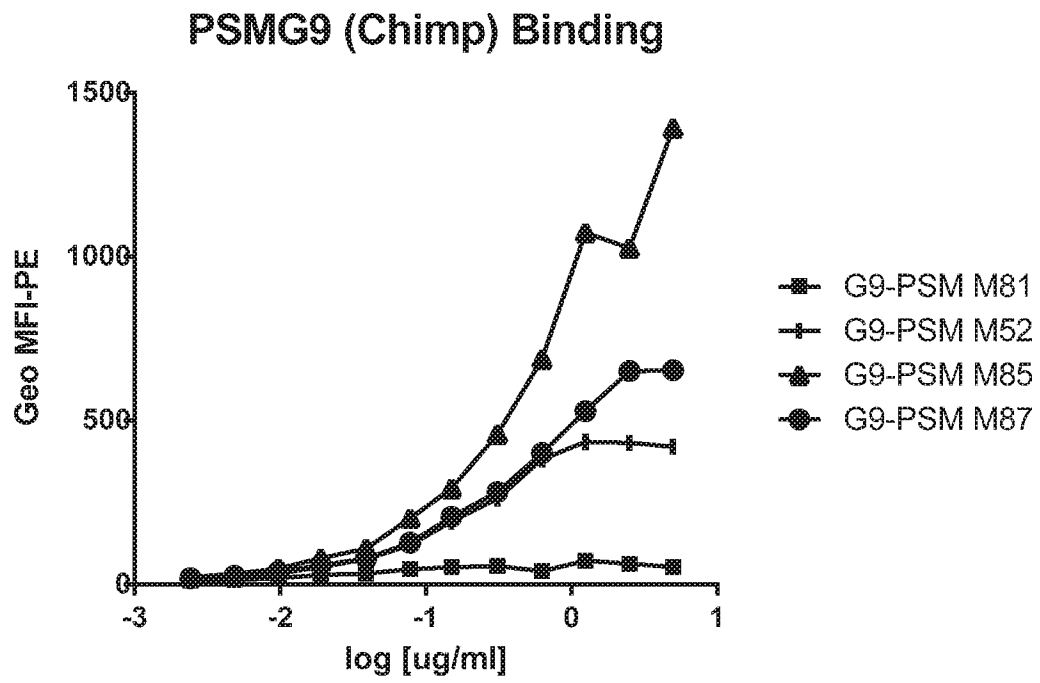


Fig. 24D

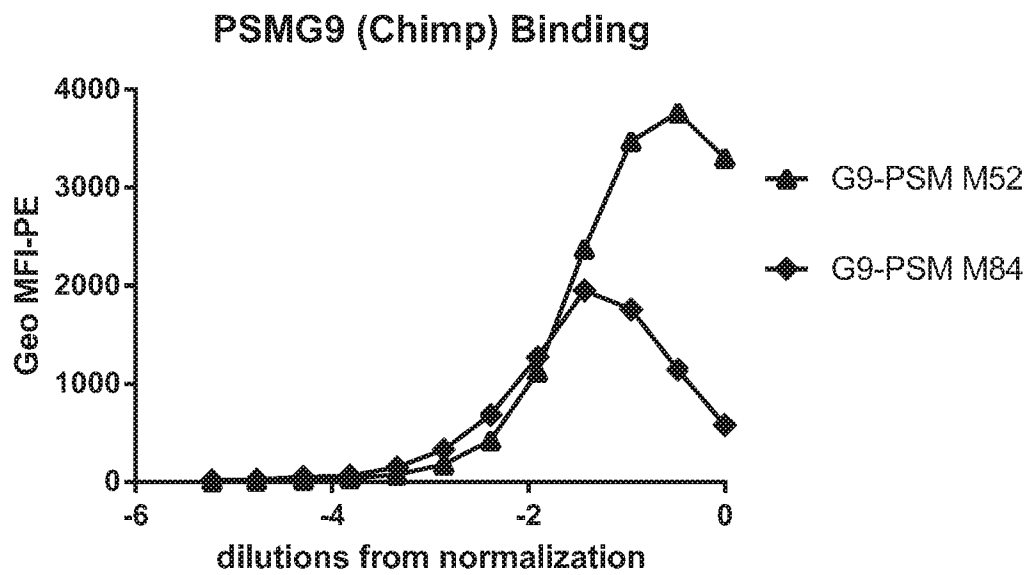


Fig. 25A

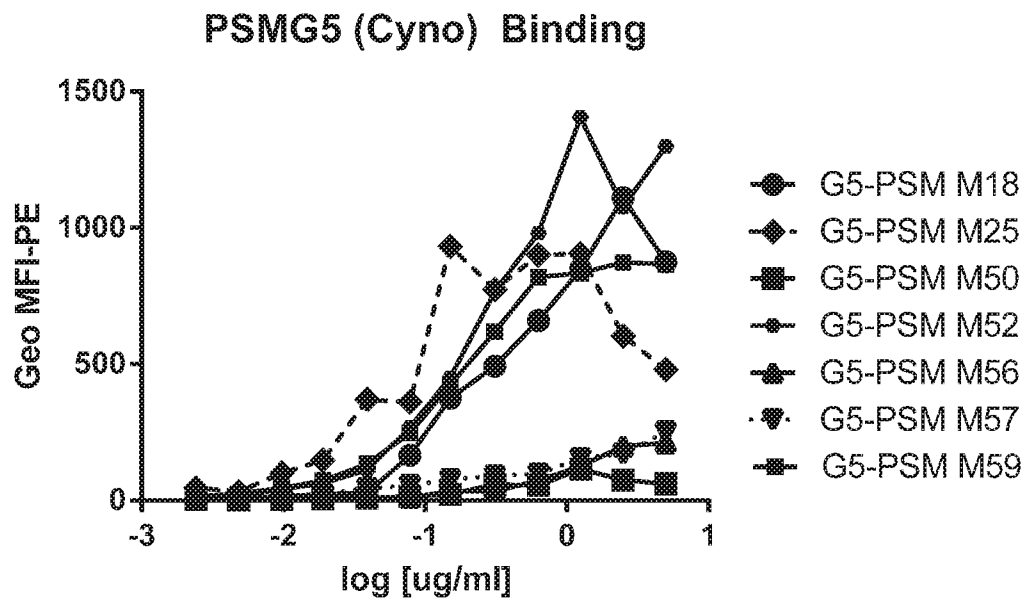


Fig. 25B

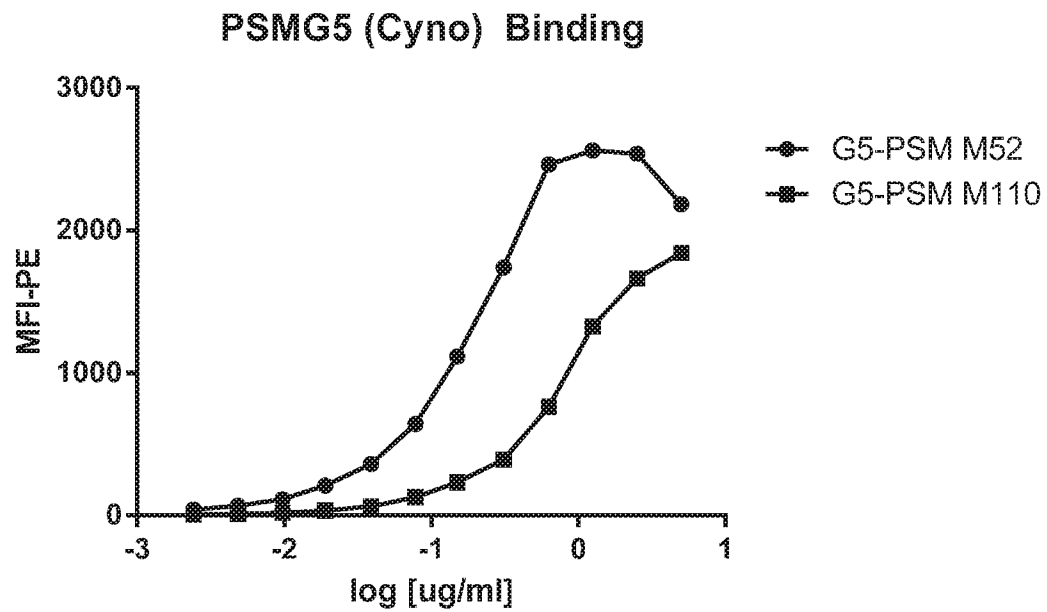


Fig. 25C

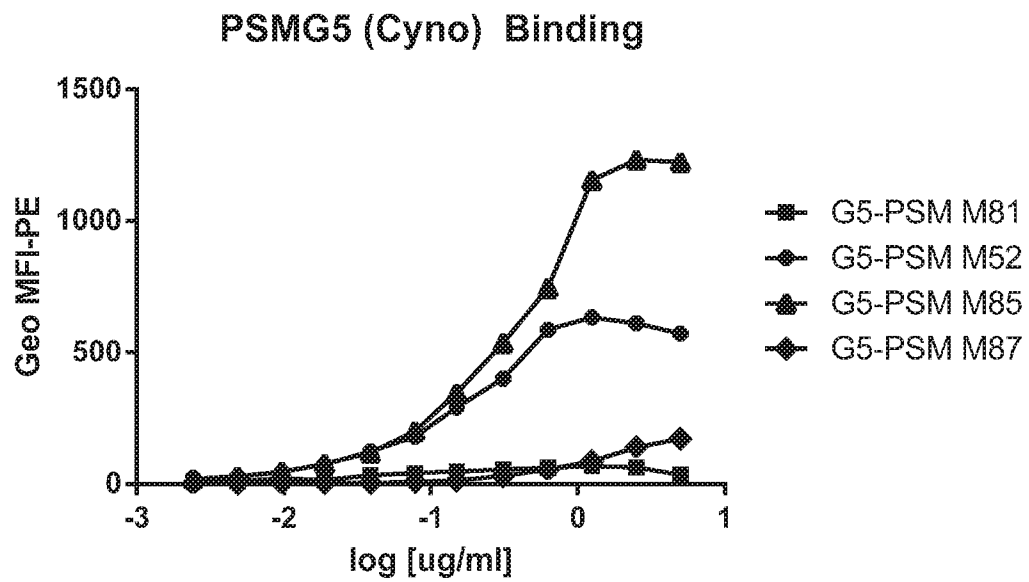


Fig. 25D

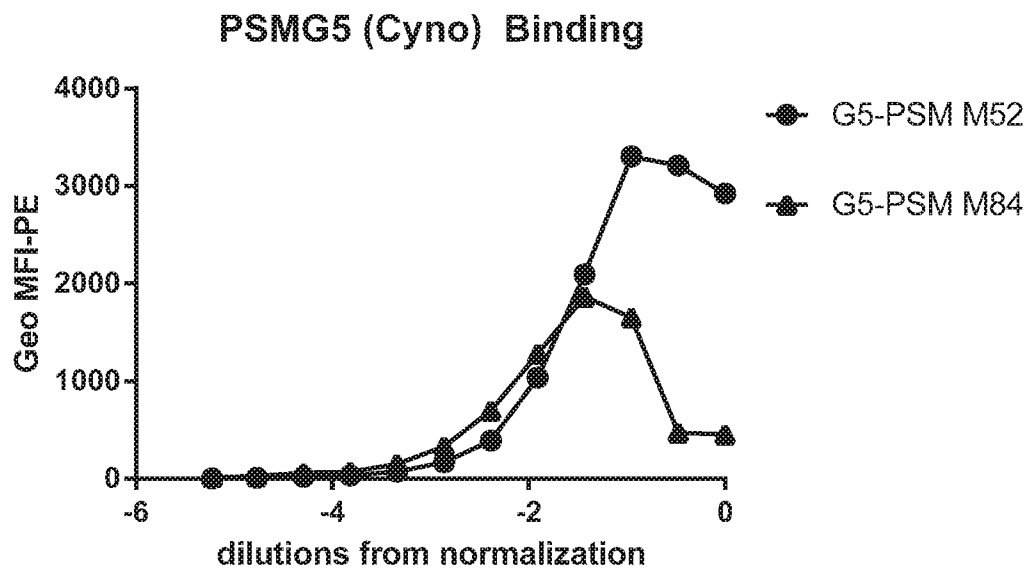


Fig. 26

Overall structure of PSMM84 Fab bound to PSMA

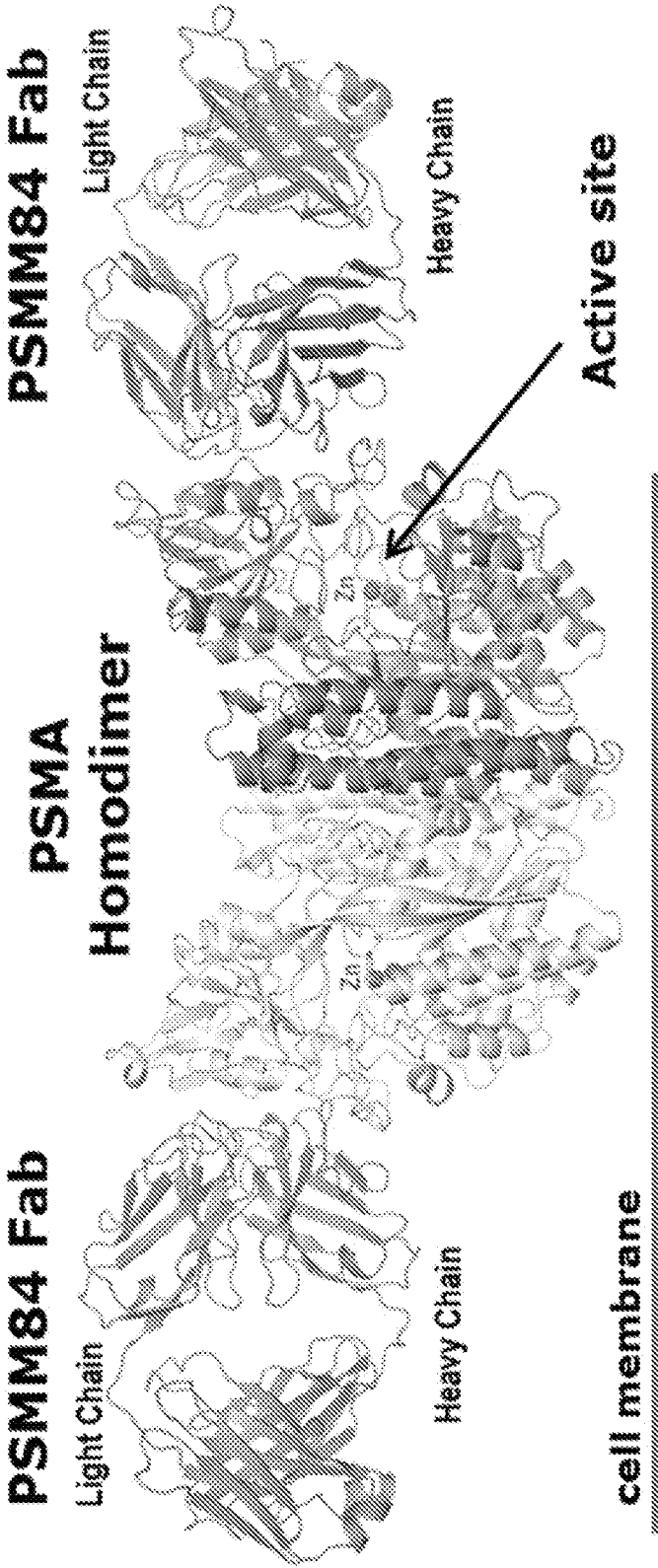


Fig. 27

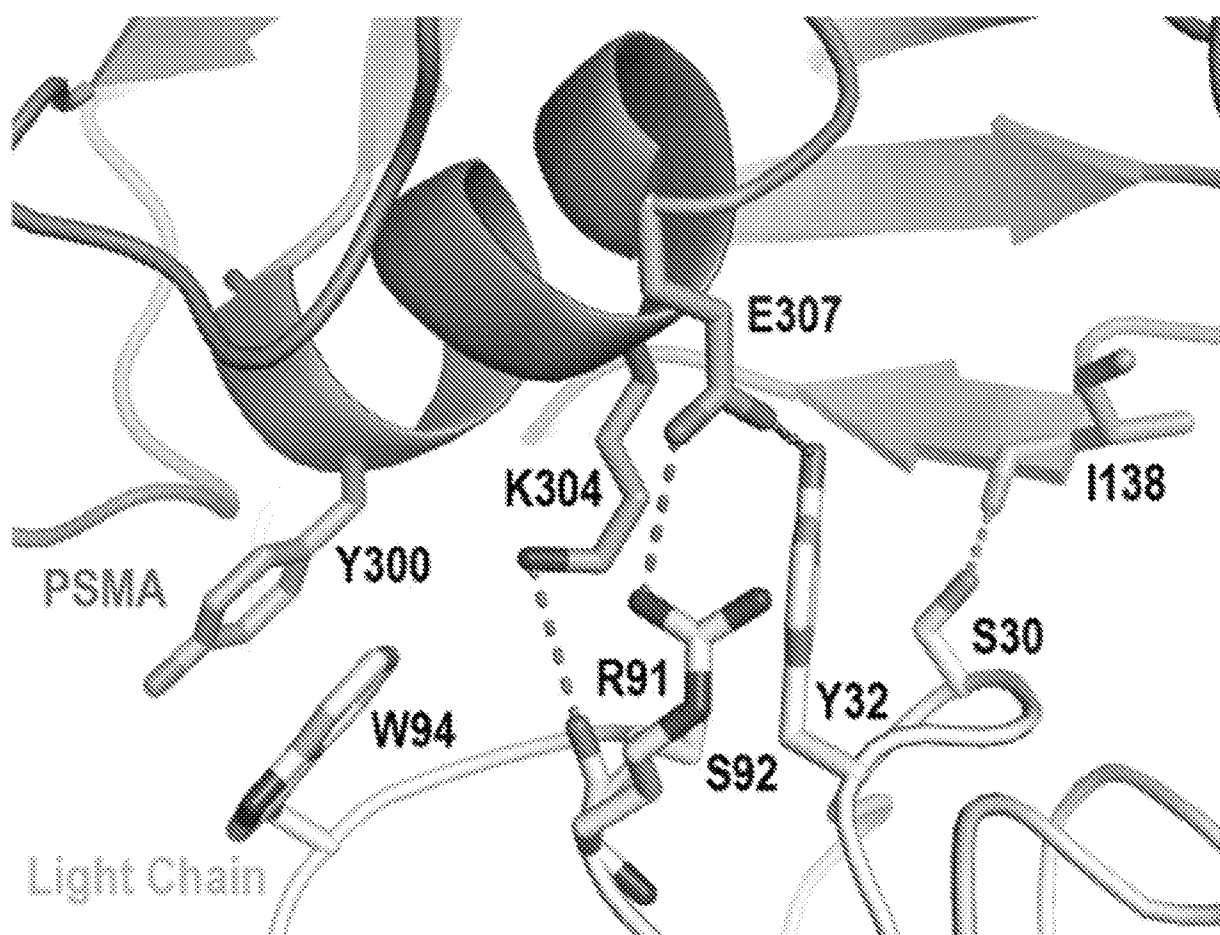


Fig. 28

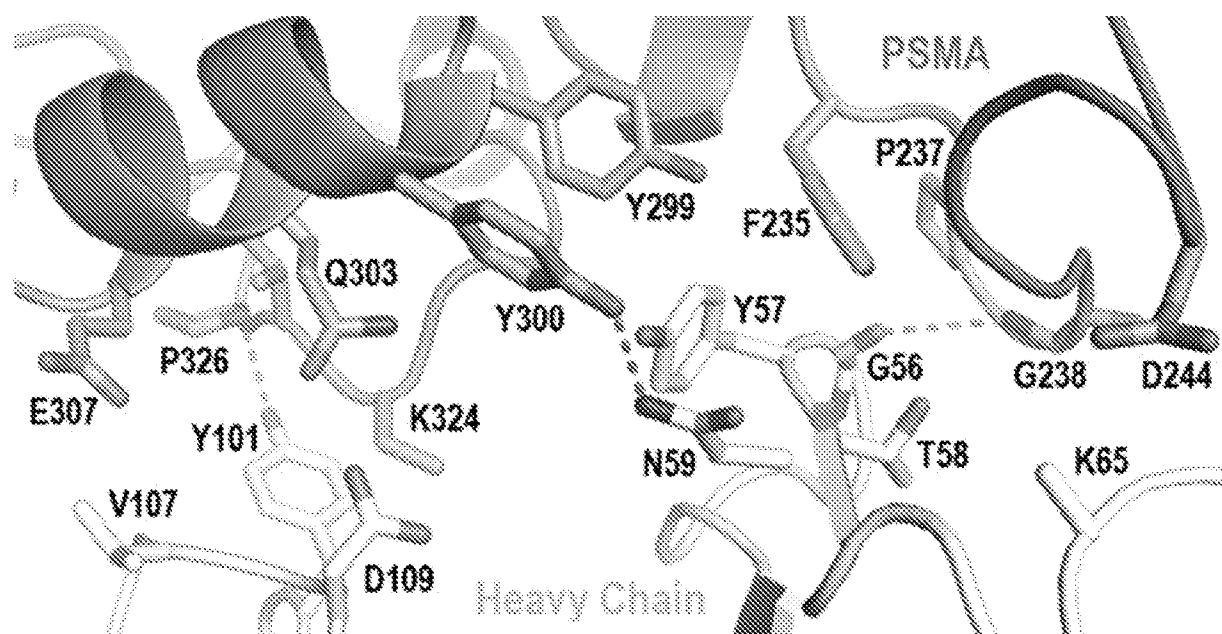


Fig. 29

Epitope residues of PSNM84

humanPSMA	(1)	MWNLHETDSAVATARRPRWLCAGALVLAG-GFFLLGFLFGWF	IKSNEAT-NITPKHNMKAFDELKAENIKKFLXNFTQIPHLACTEQNFQL
mousePSMA	(1)	MWNLQDSDSAEVLGHRQRWLRGILVLAITGTLIGLFGWF	IKPSNEAIGNVSHSGMKKFLHELKAENIKKFLXNFTRTRPHLAGTQNNFEL
cynoPSMA	(1)	MWNLHETDSAVATARRPRWLCAGALVLAG-GFFLLGFLFGWF	IKSSSEAT-NITPKHNMKAFDELKAENIKKFLHNFHTQIPHLACTEQNFQL
humanPSMA	(93)	AKQIQSQWKEFGLDSEVELAHYDVLLSYPNKTHPNYI	ISIINEDGNEFNTSLFEPPPPGEYENVSIVPPPSAFSPQGMPEGDLVYVNVYARTEDFF
mousePSMA	(95)	AKQIHDQWKEFGLDLVELSHYDVLLSYPNKTHPNYI	ISIINEDGNEFNTSLSEQPPPGYENISDVVPYSAPSPQGTPEGDLVYVNVYARTEDFF
cynoPSMA	(93)	AKQIQSQWKEFGLDSEVELTHYDVLLSYPNKTHPNYI	ISIINEDGNEFNTSLFEPPPAGYENVSIVPPPSAFSPQGMPEGDLVYVNVYARTEDFF
humanPSMA	(187)	KLERDMKINC SGKIVIARYGKVFGRGNKVKNAQLAGAKGV	ILLYSDPADYKAPGVKSYDDGWNLPGGGVQVRGNILNLNGAGDPLTPGYPANEYAYR
mousePSMA	(189)	KLEREMKISC SGKIVIARYGKVFGRGNMVKNAQLAGAKGM	ILLYSDPADYKVPVAVKSYDDGWNLPGGGVQVRGNVLNLNGAGDPLTPGYPANEHAYR
cynoPSMA	(187)	KLERDMKINC SGKIVIARYGKVFGRGNKVKNAQLAGATG	VLVLYSDPDDYKAPGVKSYDDGWNLPGGGVQVRGNILNLNGAGDPLTPGYPANEYAYR
humanPSMA	(281)	RGIAEAVGLPSIPVHP	IGYDDAQKLLKMGGSAPPDSSNRGSLKVPYNVGPGFTGNFSTQVKRMHIHSTNEVTRIYNVIGTLRGAVEPDRYVIL
mousePSMA	(283)	HELTNAVGLPSIPVHP	IGYDDAQKLLKMGGPAPPDSSWKGGLLKVPYNVGPGFAGNFSTQVKRMHIHSTYKVTIRIYNVIGILKGALEPDRYVIL
cynoPSMA	(281)	RGMAEAVGLPSIPVHP	IGYDDAQKLLKMGGSASPDSSWRGSLKVPYNVGPGFTGNFSTQVKRMHIHSTSEVTRIYNVIGILRGAVEPDRYVIL
humanPSMA	(375)	GGHRDSWVFGGIDPQSGAAVVEIVRSFGILKKEGWRPR	TILFASWDAAEEFGLLGSTEWAEENSRLQLQERGVAYINADSSIEGNYTLRVDCCTP
mousePSMA	(377)	GGHRDAWVFGGIDPQSGAAVVEIVRSFGILKKRRRPR	TILFASWDAAEEFGLLGSTEWAEHSRLQLQERGVAYINADSSIEGNYTLRVDCCTP
cynoPSMA	(375)	GGHRDSWVFGGIDPQSGAAVVEIVRSFGMLKKEGWR	PRRTILFASWDAAEEFGLLGSTEWAEENSRLQLQERGVAYINADSSIEGNYTLRVDCCTP
humanPSMA	(469)	LMYSLVNLTKELKSPDEGEFGKSLYESWTKKSPSP	SPESGMPRISKLGSGNDFEVFFQRLGIASGRARYTKNWEINKFSGYPLYHSVYETIELV
mousePSMA	(471)	LMYSLVNLTKELQSPDEGEFGKSLYDSWKESKSP	SPEFGMPRISKLGSGNDFEVFFQRLGIASGRARYTKNWKTNKVSYPPLYHSVYETIELV
cynoPSMA	(469)	LMYSLVNLTKELQSPDEGEFGKSLYESWTKKSP	SPEFGMPRISKLGSGNDFEVFFQRLGIASGRARYTKNWEINKFSGYPLYHSVYETIELV
humanPSMA	(563)	EKFYDPMFKYHLTVAQVRGGMVFEANSLVLPFDCR	OYAVVLRKYADKIYISIMKHPQEMKITYSVSFDSLFSAVKNFTEIASKFSERLQDFDKS
mousePSMA	(565)	VKFYDPTFKYHLTVAQVRGAMVFEANSLVLPFDCQ	SYAVALKKYADTIYNISMKHPQEMKAYMISFDSLFSAVNNFTDVASKFNORLQELDKS
cynoPSMA	(563)	EKFYDPMFKYHLTVAQVRGGMVFEANSLVLPFDCR	OYAVVLRKYADKIYNISMKHPQEMKITYSVSFDSLFSAVKNFTEIASKFSERLQDFDKS
humanPSMA	(657)	NPILVRMNDQLMFLERAFIDP	LGLPDRPFYRHHVIYAPSSHNKYAGSFPGIYDALFDIESKVDPSQAWGEVVKRQIYVAAFTVQAAAEITLSEVA
mousePSMA	(659)	NPILLRIMNDQLMYLERAFIDP	LGLPGRPFYRHHIYAPSSHNKYAGSFPGIYDALFDISSKNVASKAWNEVKRQISIAFTFTVQAAAEITLREVA
cynoPSMA	(657)	NPILLRIMNDQLMFLERAFIDP	LGLPDRPFYRHHVIYAPSSHNKYAGSFPGIYDALFDIESKVDPSQAWGEVVKRQISIAFTFTVQAAAEITLSEVA

Epitope residues are shaded. Sequence divergence shown by underline.

Fig. 30

Paratope residues of PSM84

Paratope of PSM84

PSM84_HC (1) EVQLLESGGGLVQPGGSLRLSCAASGFTFKSDAMHWVRQAPGKGLEWVSEISGSGCXTN~~YADSVKGR~~FTISRDNK
PSM84_HC (77) NTLYLQMNSLRAEDTAVYYCARDSDSSLYVGGDYFDYWGQGTILVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL
PSM84_HC (153) VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQYICNVNHKPSNTKVDKKVEPKSC

PSM84_IC (1) EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASN~~RATGIPARFSGSGGTDFT~~
PSM84_IC (73) LTISSEPEDEFAVYYCQQRSSN~~WPLTF~~GGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA
PSM84_IC (145) KVQWKVDNALQSGNSQESVTEQDSKDSSTLSLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

CDR regions underlined. Paratope residues shaded.

Fig. 31

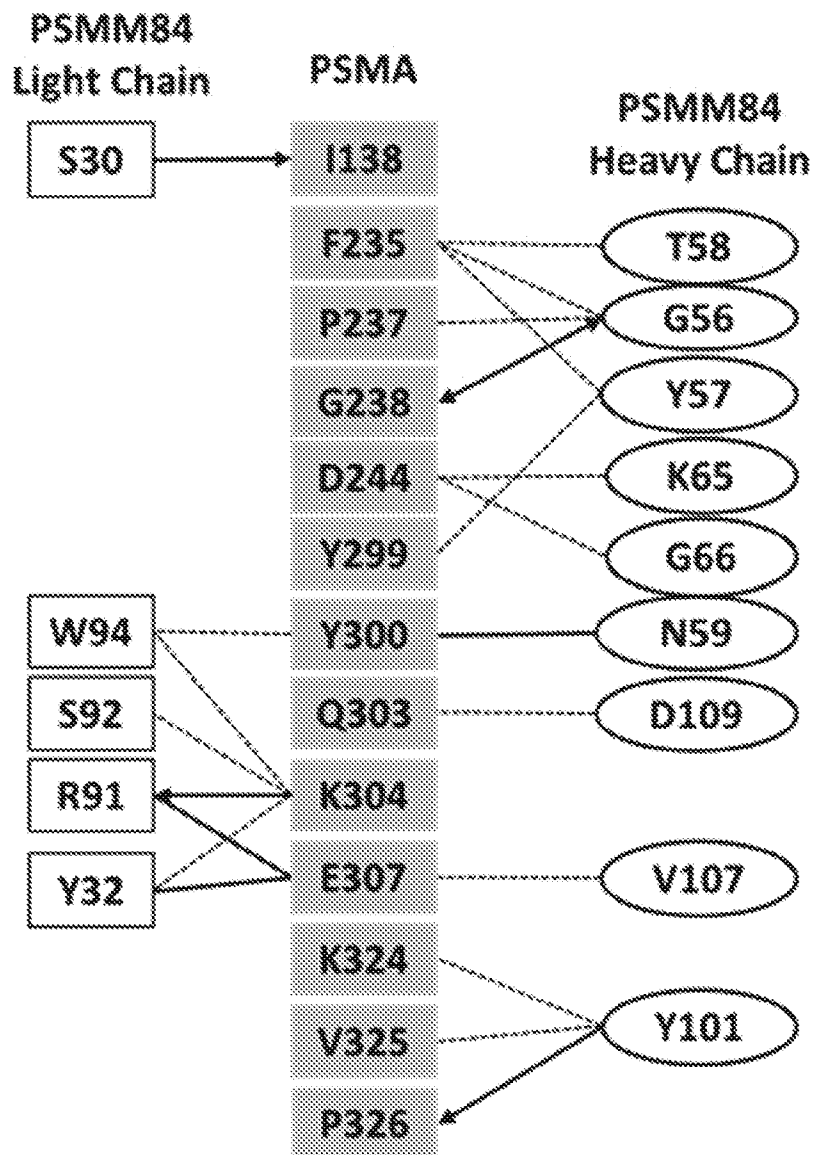


Fig. 32

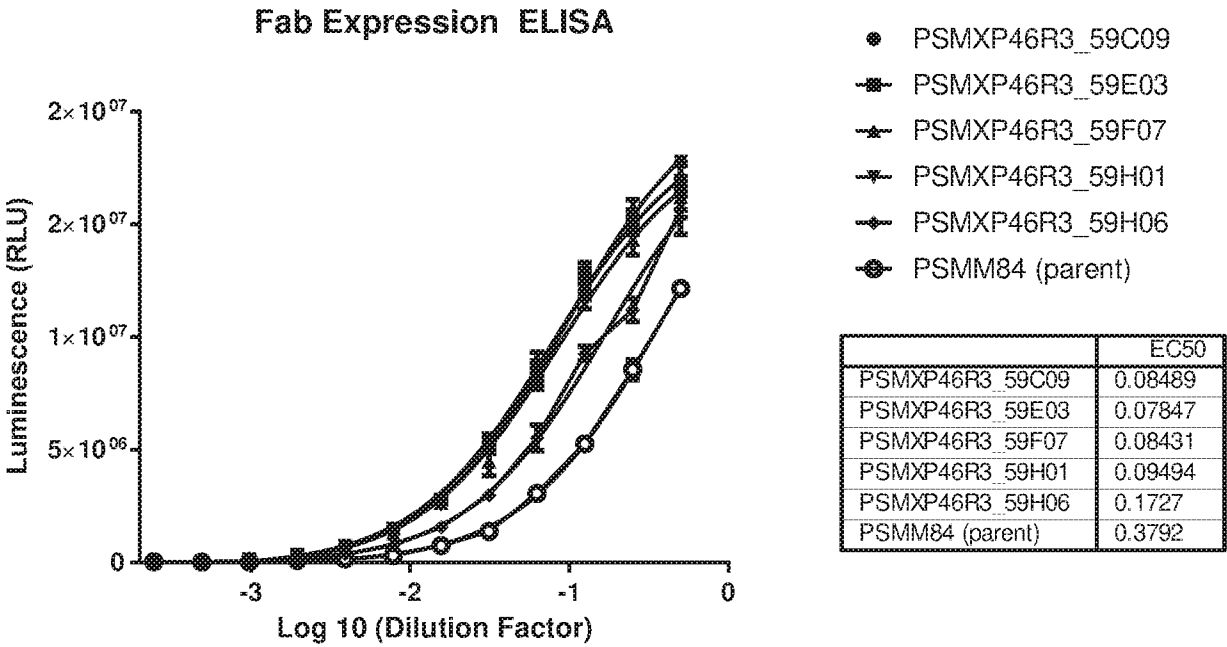


Fig. 33

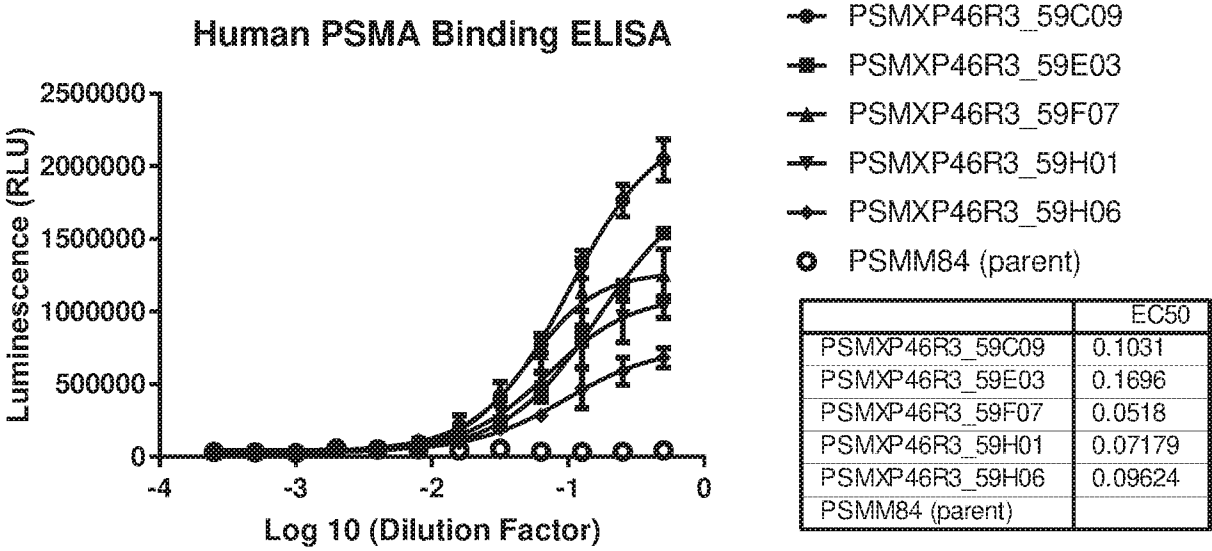


Fig. 34

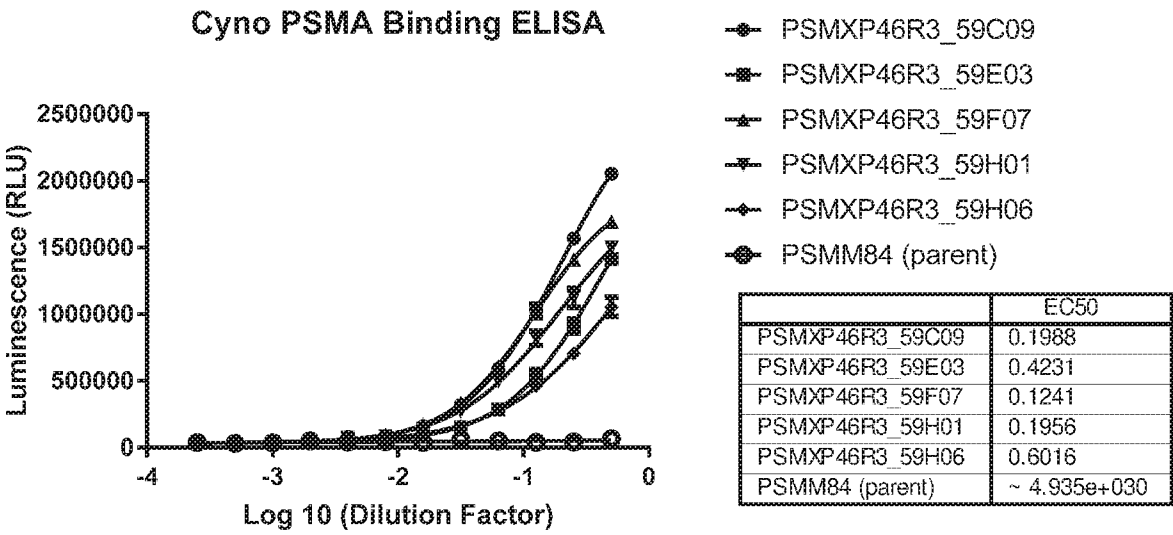
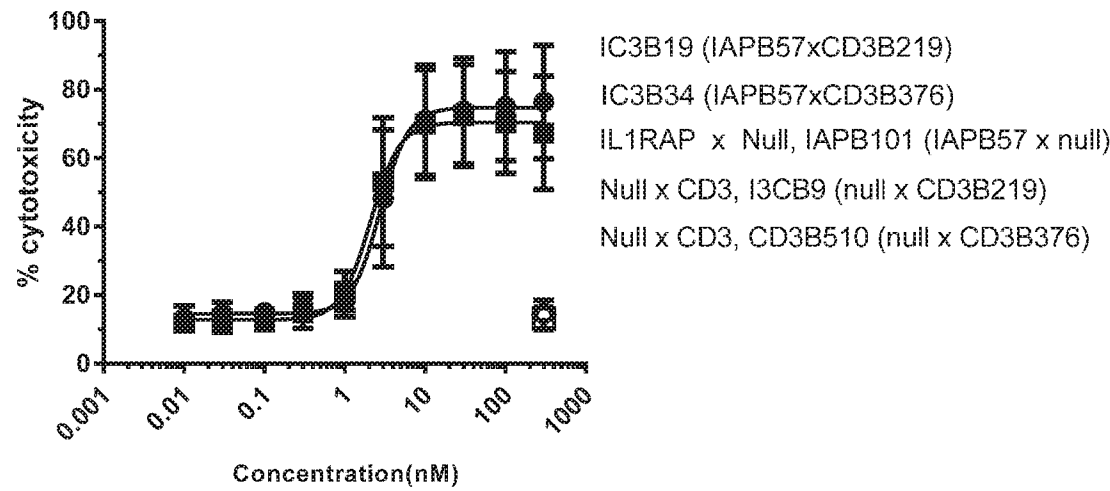


Fig. 35



uM	0.0100	0.0300	0.1000	0.3000	1.0000	3.0000	10.0000	30.0000	100.0000	300.0000
ug/mL	0.0015	0.0045	0.0150	0.0450	0.1500	0.4500	1.5000	4.5000	15.0000	45.0000

Fig. 36

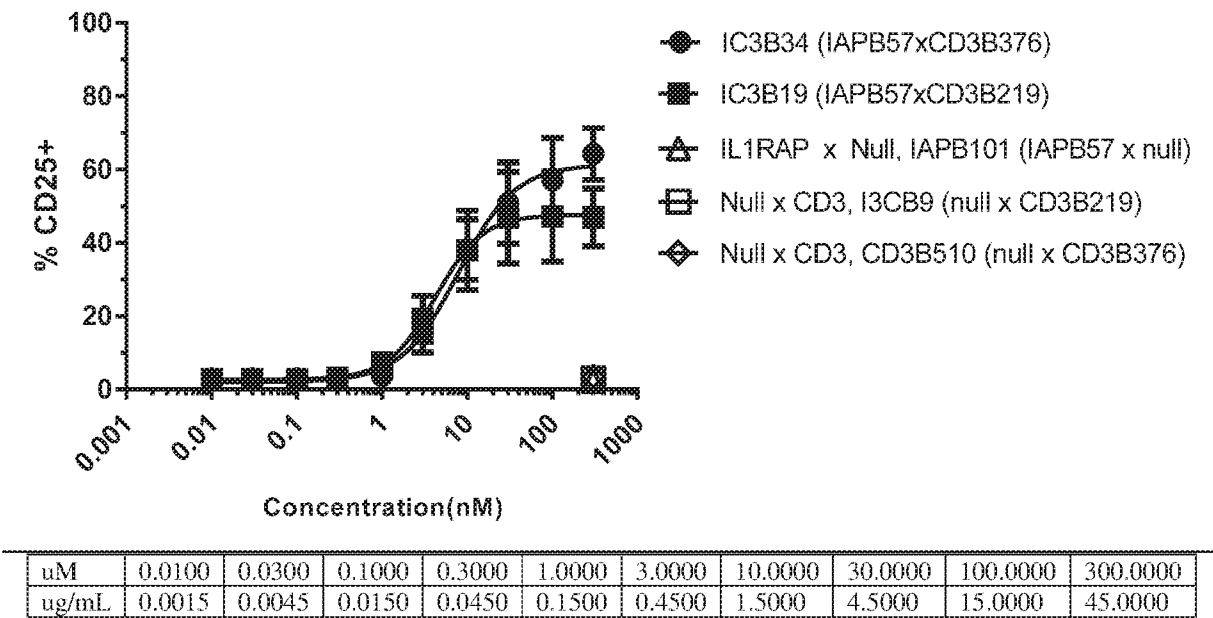
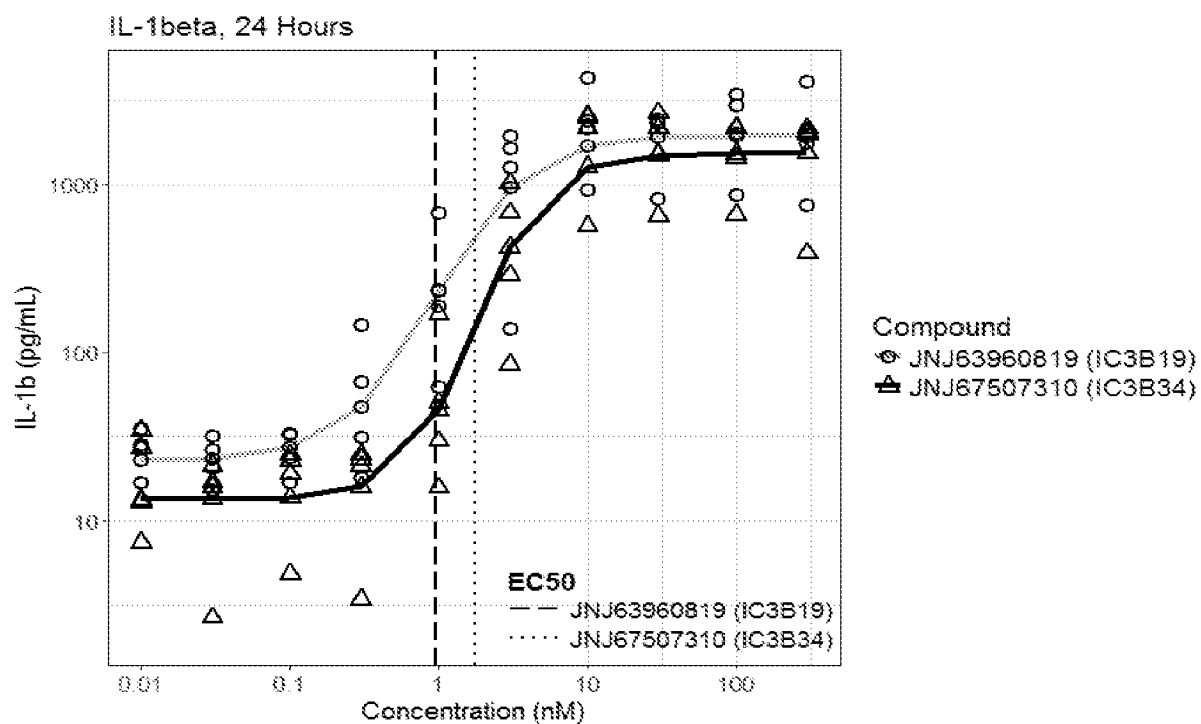
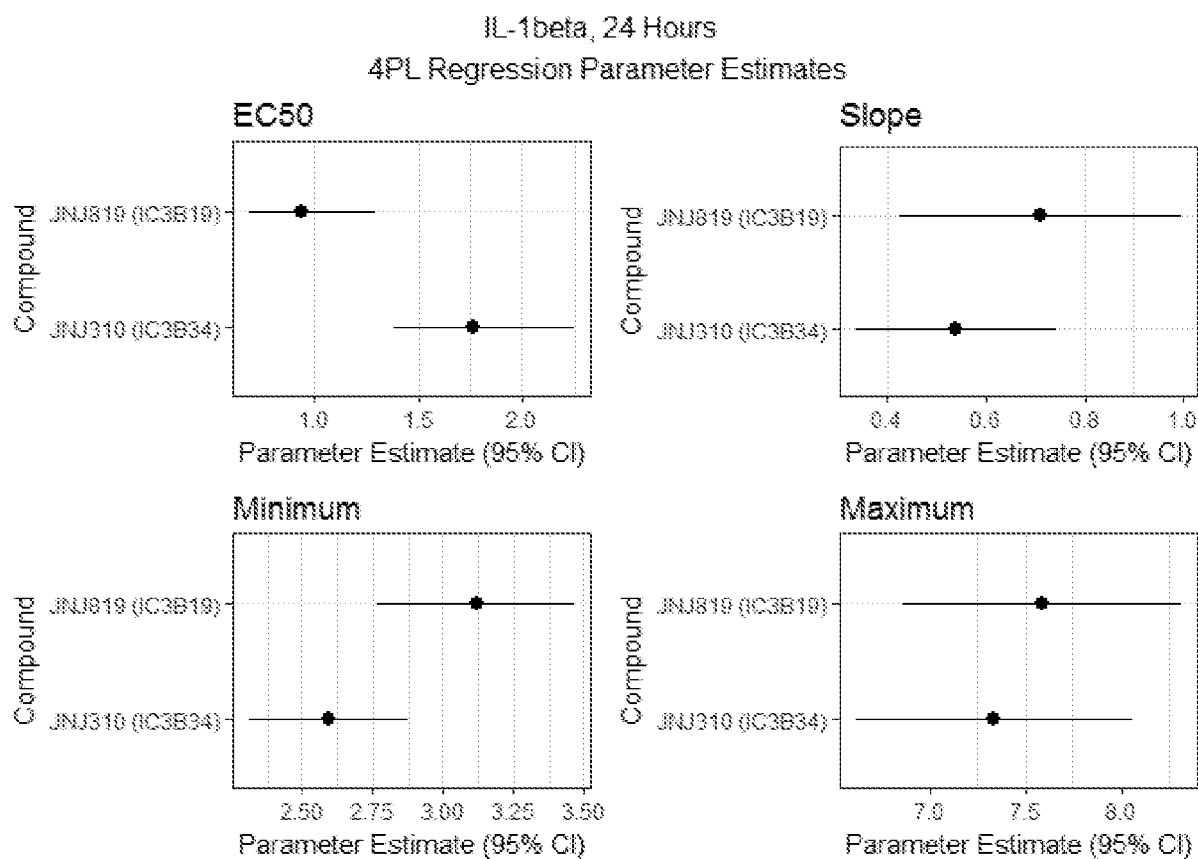


Fig. 37A



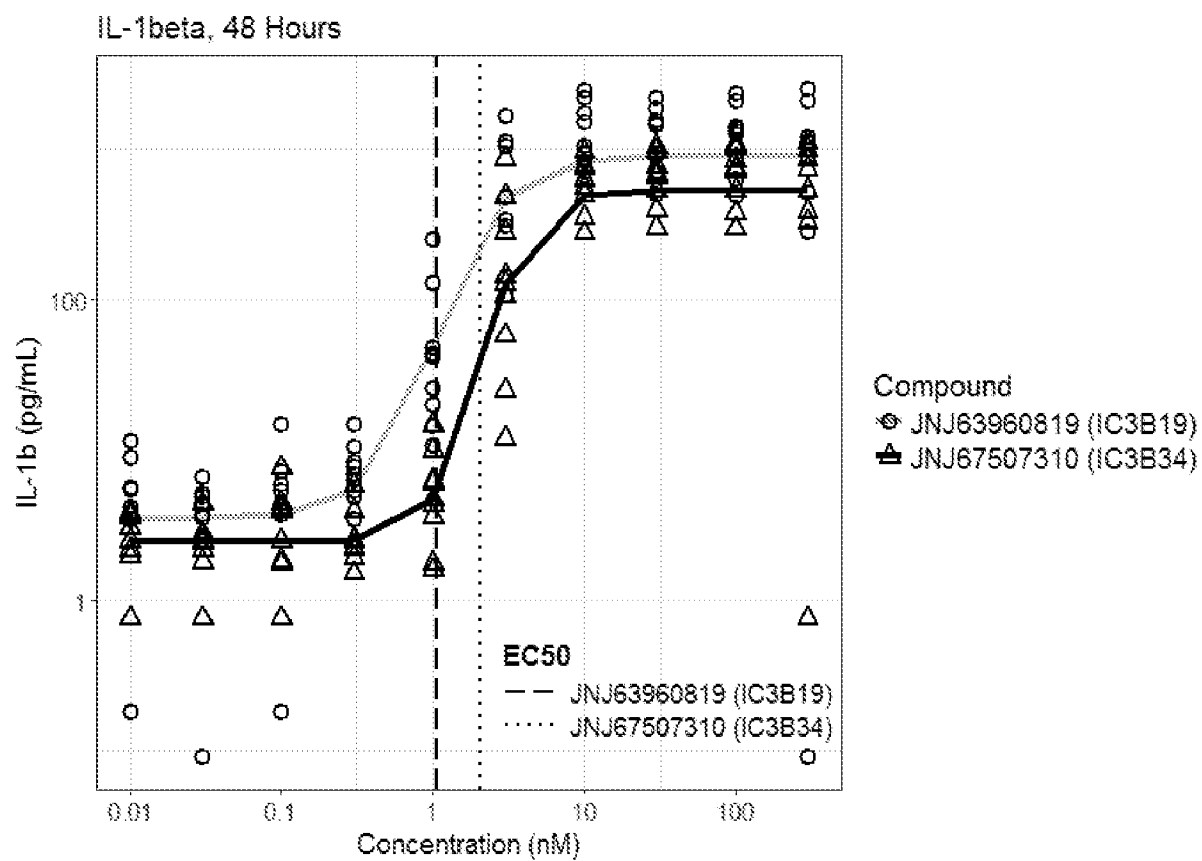
	Difference	Sigma	p-value
Difference at 0.01	-0.414	0.553	0.9439
Difference at 0.03	-0.718	0.553	0.5723
Difference at 0.1	-0.537	0.553	0.8182
Difference at 0.3	-1.227	0.553	0.1172
Difference at 1	-1.547	0.553	0.0281
Difference at 3	-0.875	0.553	0.3817
Difference at 10	-0.248	0.553	0.9983
Difference at 30	-0.164	0.553	0.9999
Difference at 100	-0.348	0.553	0.9797
Difference at 300	-0.281	0.553	0.9955

Fig. 37B



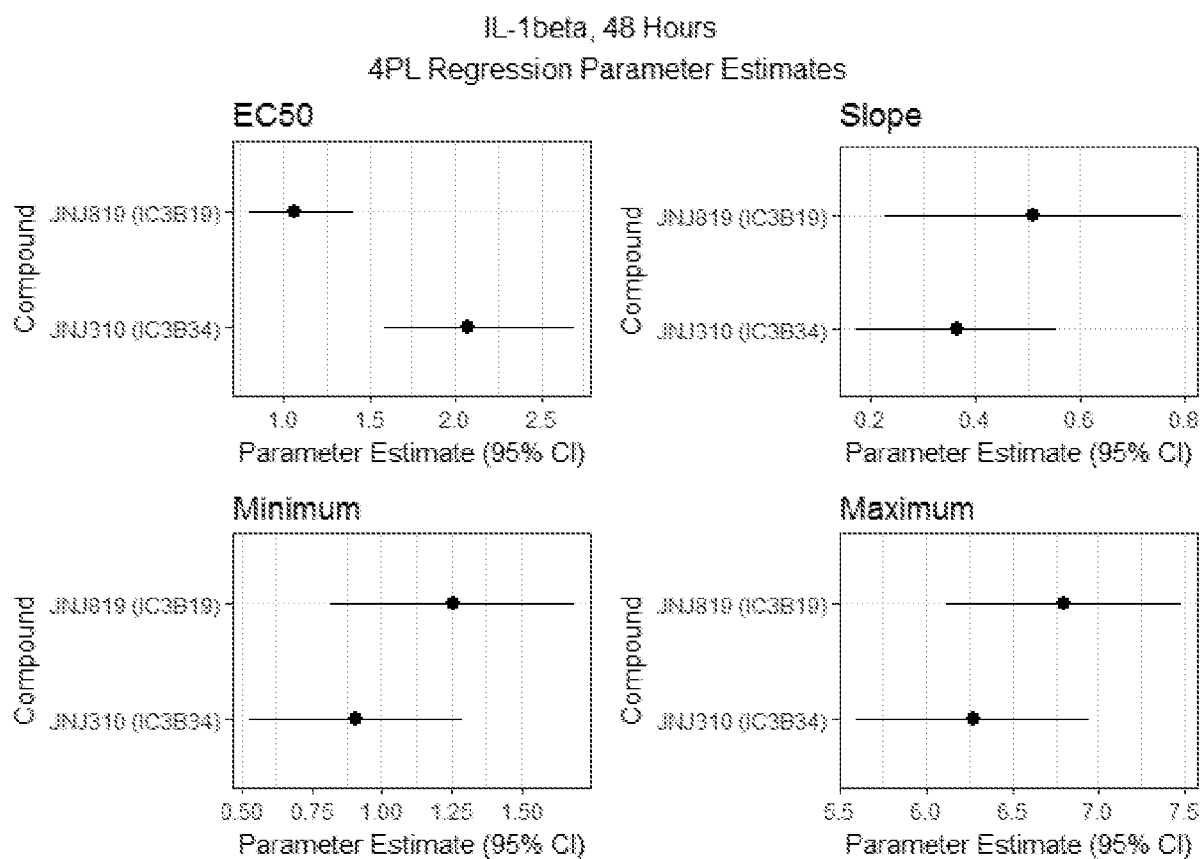
	JNJ819 (IC3B19)	JNJ310 (IC3B34)	p-value
EC50	0.940 (0.682, 1.295)	1.763 (1.381, 2.252)	0.0027
Slope	0.710 (0.423, 0.996)	0.540 (0.335, 0.744)	0.3046
Minimum	3.119 (2.769, 3.469)	2.592 (2.309, 2.875)	0.0268
Maximum	7.589 (6.865, 8.313)	7.335 (6.613, 8.058)	0.2033

Fig. 38A



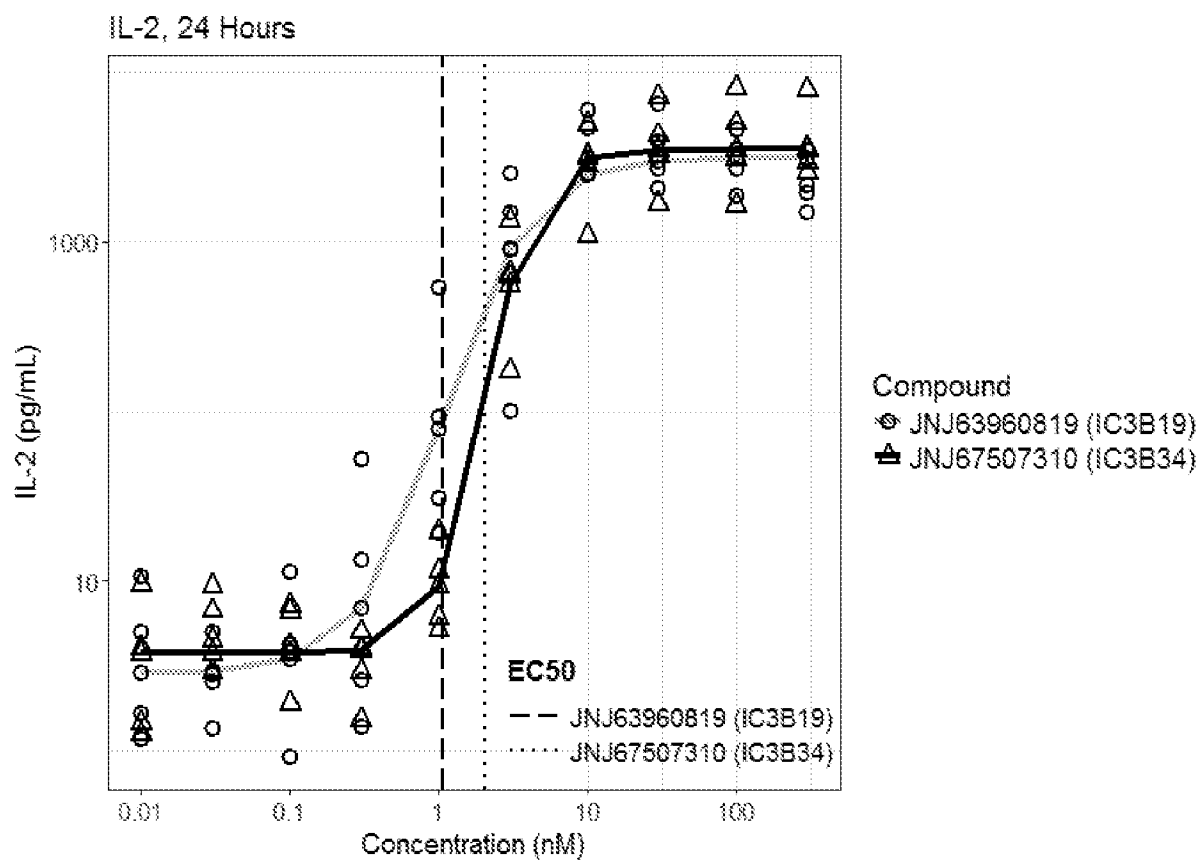
	Difference	Sigma	p-value
Difference at 0.01	-0.431	0.618	0.9976
Difference at 0.03	-0.183	0.618	1.0000
Difference at 0.1	-0.321	0.618	0.9998
Difference at 0.3	-1.020	0.618	0.5913
Difference at 1	-2.105	0.618	0.0064
Difference at 3	-1.508	0.618	0.1255
Difference at 10	-0.806	0.618	0.8424
Difference at 30	-0.624	0.618	0.9635
Difference at 100	-0.556	0.618	0.9834
Difference at 300	-0.049	0.618	1.0000

Fig. 38B



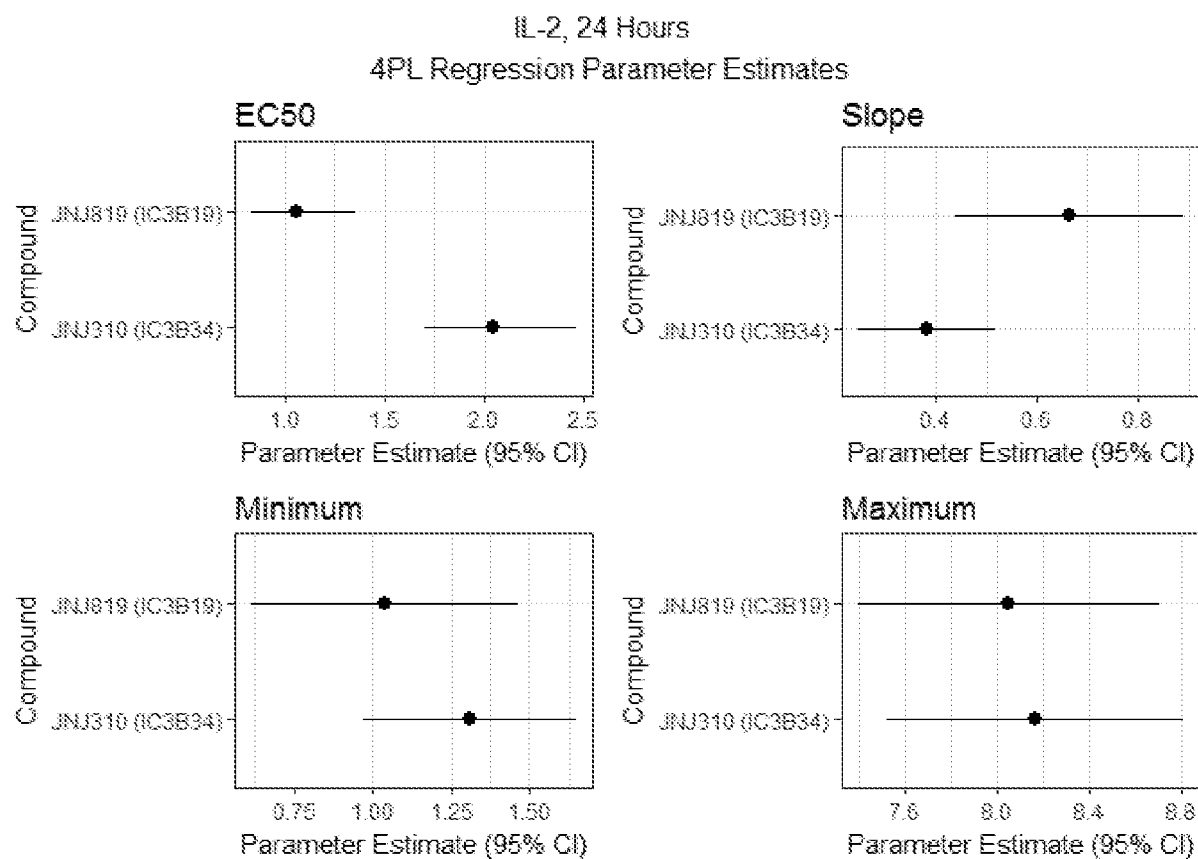
	JNJ819 (IC3B19)	JNJ310 (IC3B34)	p-value
EC50	1.060 (0.798, 1.408)	2.068 (1.587, 2.695)	0.0010
Slope	0.512 (0.230, 0.794)	0.365 (0.173, 0.557)	0.3951
Minimum	1.254 (0.818, 1.690)	0.905 (0.525, 1.286)	0.2543
Maximum	6.798 (6.117, 7.478)	6.268 (5.589, 6.947)	0.0528

Fig. 39A



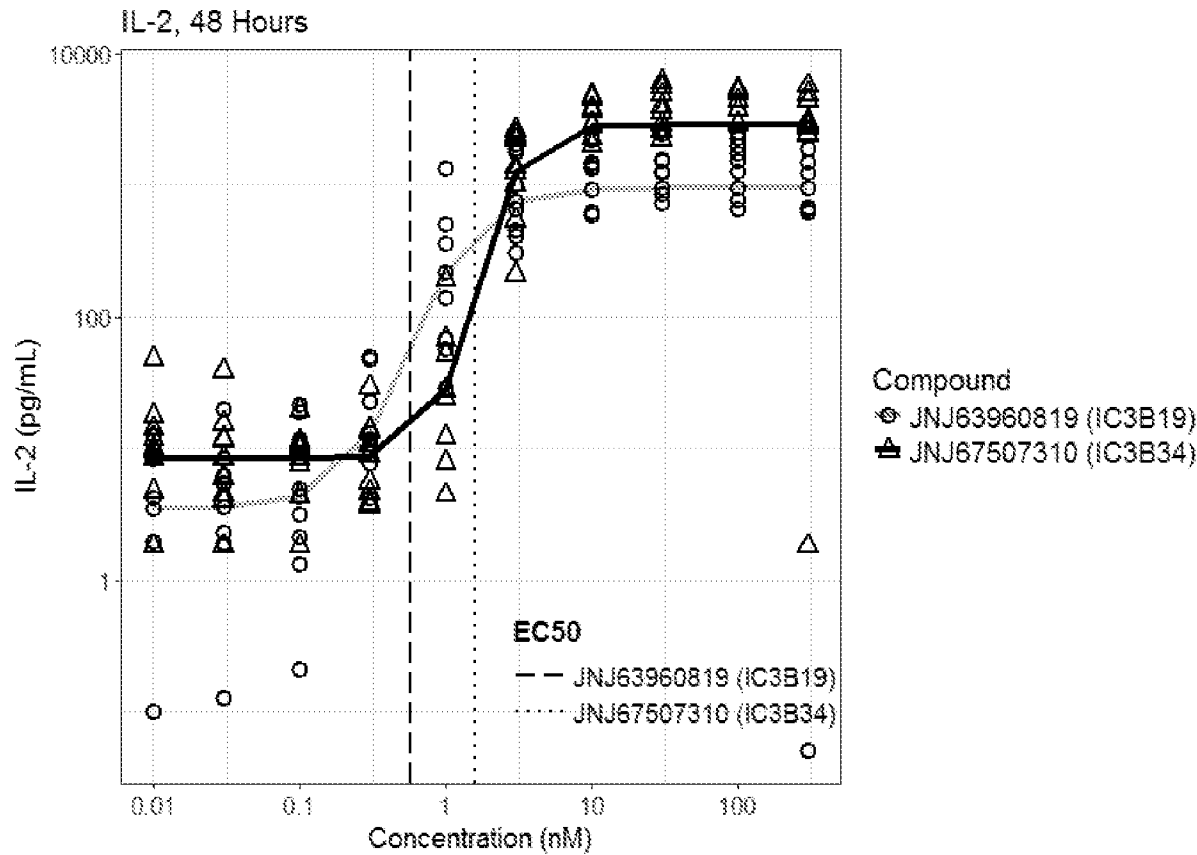
	Difference	Sigma	p-value
Difference at 0.01	-0.105	0.599	1.0000
Difference at 0.03	0.704	0.599	0.8315
Difference at 0.1	0.198	0.599	1.0000
Difference at 0.3	-0.841	0.599	0.6679
Difference at 1	-2.095	0.599	0.0041
Difference at 3	-0.330	0.599	0.9989
Difference at 10	-0.382	0.599	0.9963
Difference at 30	0.026	0.599	1.0000
Difference at 100	0.222	0.599	1.0000
Difference at 300	0.568	0.599	0.9440

Fig. 39B



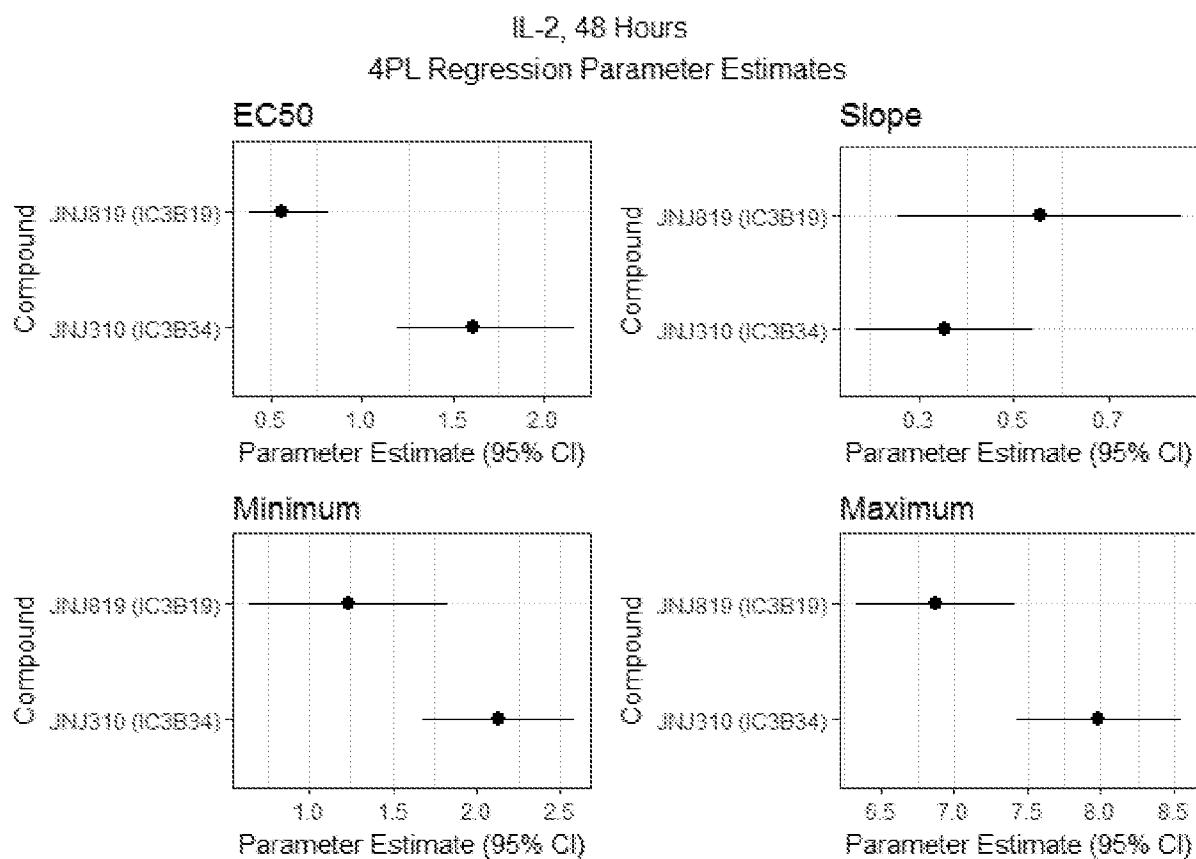
	JNJ819 (IC3B19)	JNJ310 (IC3B34)	p-value
EC50	1.063 (0.829, 1.361)	2.044 (1.697, 2.463)	0.0001
Slope	0.665 (0.440, 0.890)	0.383 (0.247, 0.520)	0.0256
Minimum	1.038 (0.613, 1.463)	1.311 (0.973, 1.650)	0.3103
Maximum	8.053 (7.398, 8.707)	8.168 (7.527, 8.809)	0.6466

Fig. 40A



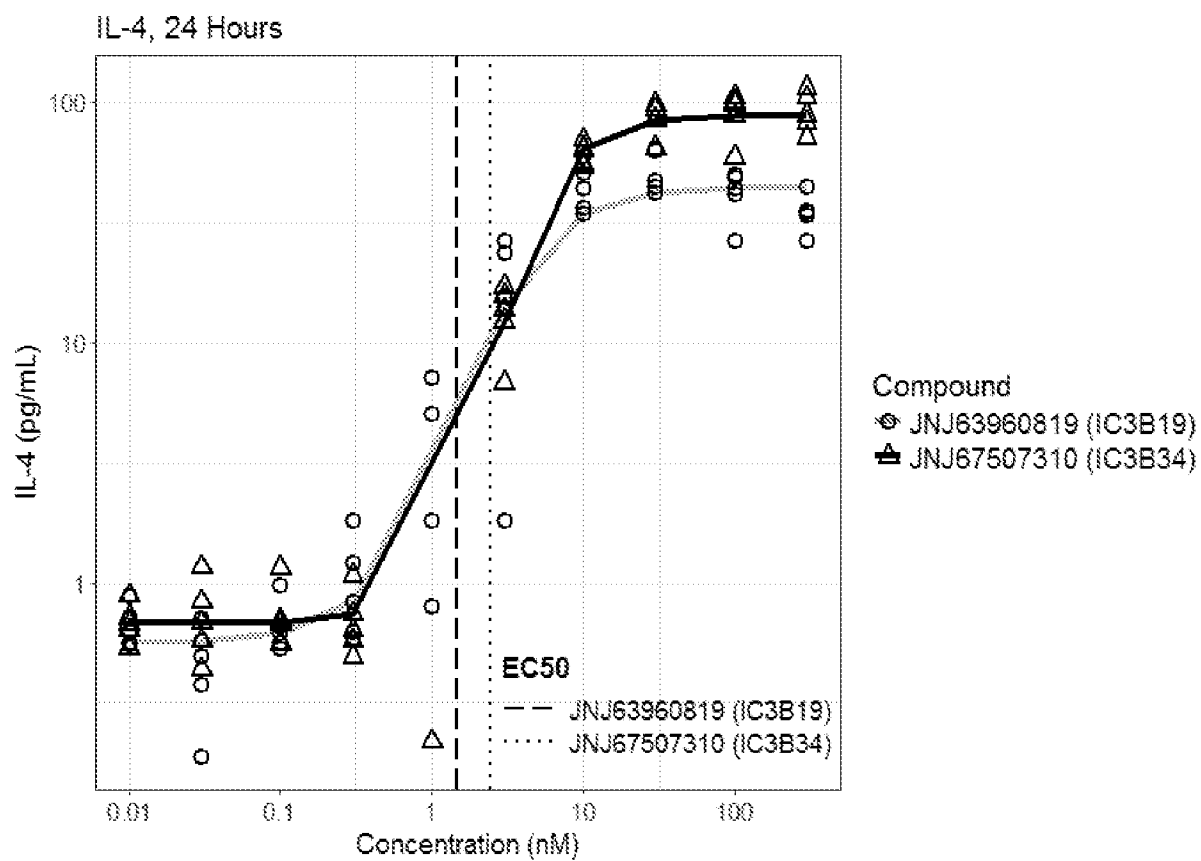
	Difference	Sigma	p-value
Difference at 0.01	0.928	0.676	0.8169
Difference at 0.03	0.859	0.676	0.8755
Difference at 0.1	0.737	0.676	0.9485
Difference at 0.3	-0.567	0.676	0.9917
Difference at 1	-1.950	0.676	0.0370
Difference at 3	0.372	0.676	0.9998
Difference at 10	0.954	0.676	0.7914
Difference at 30	0.987	0.676	0.7576
Difference at 100	1.066	0.676	0.6693
Difference at 300	1.488	0.676	0.2289

Fig. 40B



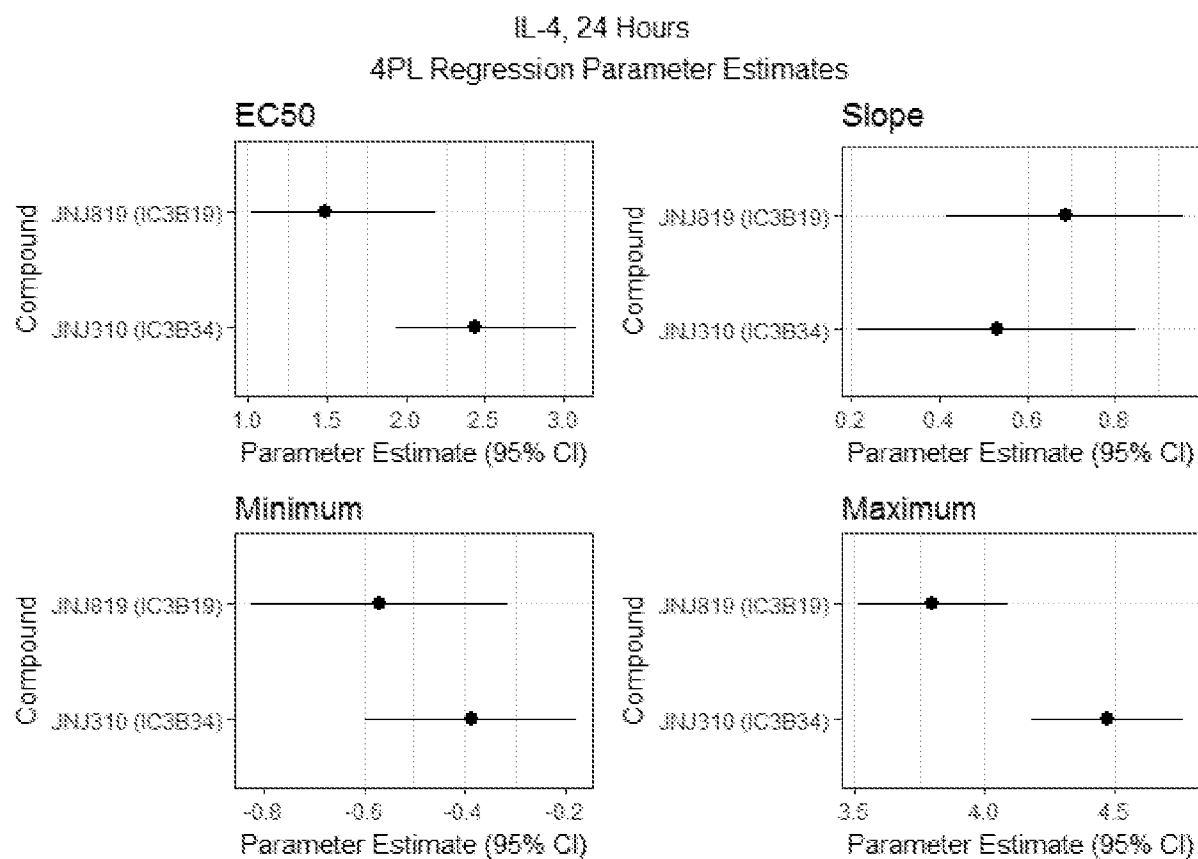
	JNJ819 (IC3B19)	JNJ310 (IC3B34)	p-value
EC50	0.558 (0.380, 0.821)	1.611 (1.199, 2.166)	Sig.
Slope	0.554 (0.256, 0.851)	0.353 (0.168, 0.539)	0.2079
Minimum	1.231 (0.638, 1.824)	2.129 (1.674, 2.584)	0.0158
Maximum	6.874 (6.327, 7.421)	7.988 (7.425, 8.551)	0.0008

Fig. 41A



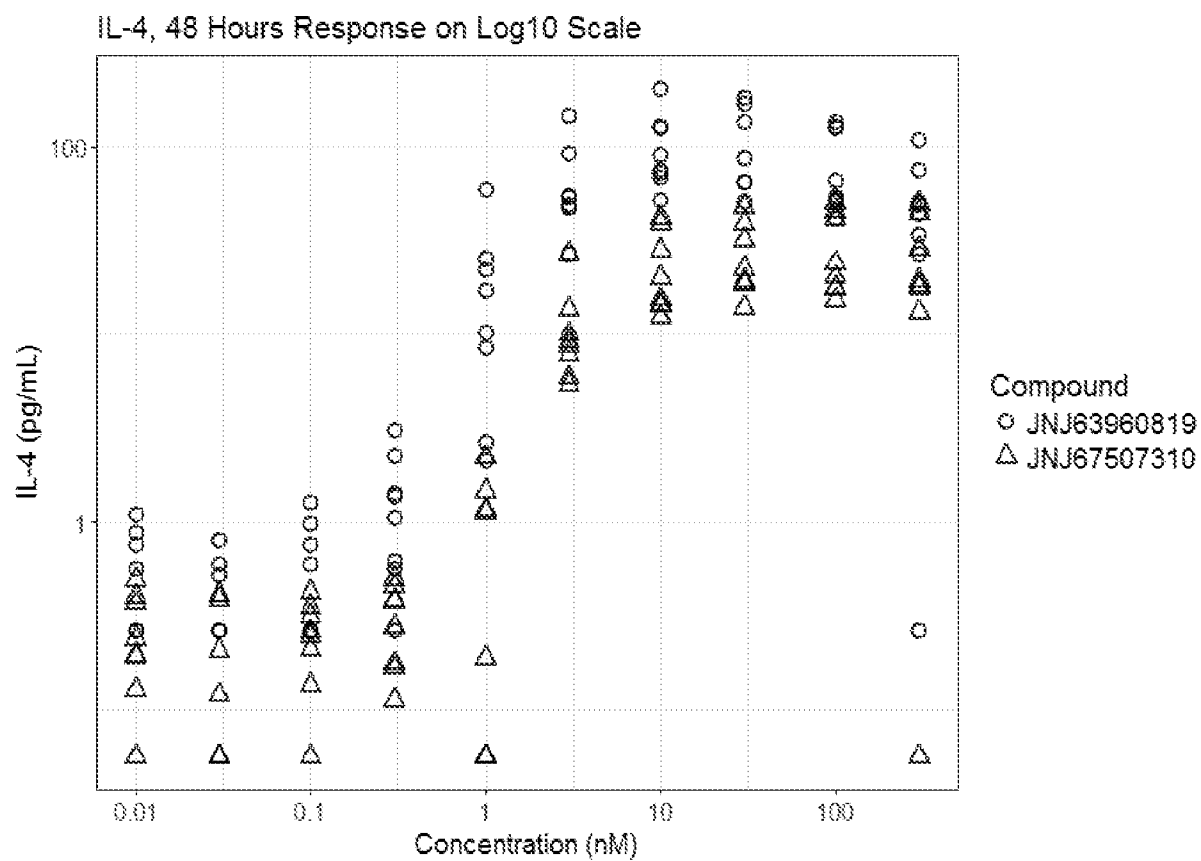
	Difference	Sigma	p-value
Difference at 0.01	-0.010	0.301	1.0000
Difference at 0.03	0.563	0.301	0.3761
Difference at 0.1	0.110	0.301	1.0000
Difference at 0.3	-0.361	0.301	0.8592
Difference at 3	0.081	0.301	1.0000
Difference at 10	0.253	0.301	0.9815
Difference at 30	0.439	0.301	0.6850
Difference at 100	0.780	0.301	0.0749
Difference at 300	1.031	0.301	0.0054

Fig. 41B



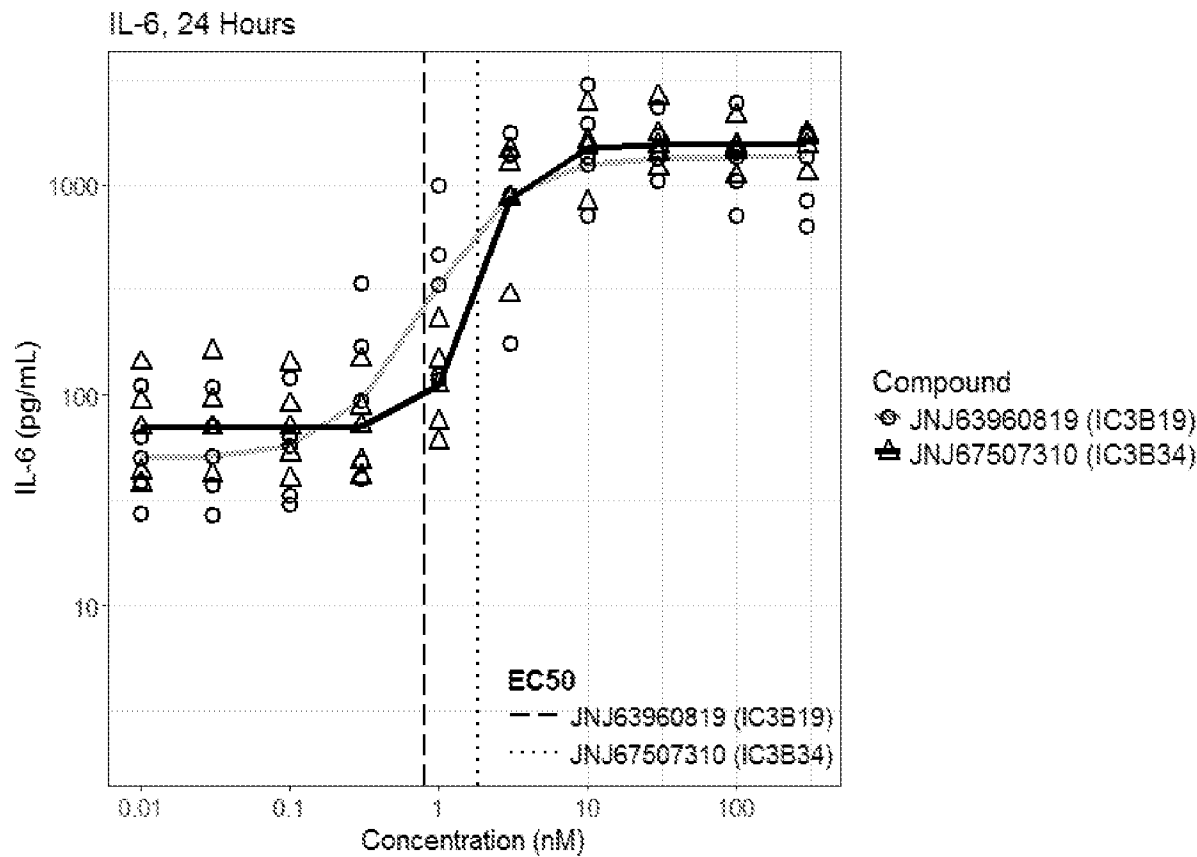
	JNJ819 (IC3B19)	JNJ310 (IC3B34)	p-value
EC50	1.493 (1.016, 2.192)	2.440 (1.932, 3.081)	0.2415
Slope	0.686 (0.416, 0.957)	0.532 (0.214, 0.849)	0.4668
Minimum	-0.570 (-0.827, -0.313)	-0.387 (-0.598, -0.176)	0.2942
Maximum	3.799 (3.510, 4.088)	4.476 (4.183, 4.769)	0.0043

Fig. 42



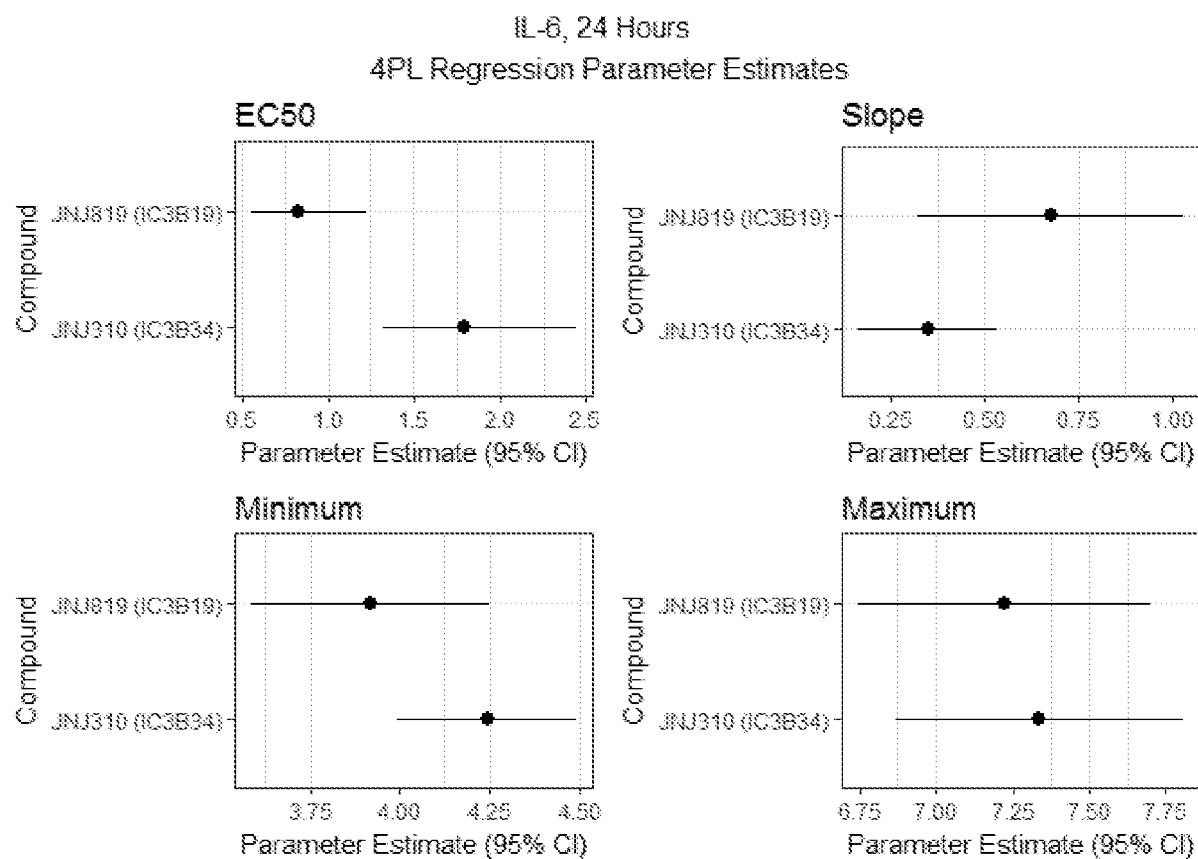
	Difference	Sigma	p-value
Difference at 0.01	-0.756	0.474	0.6568
Difference at 0.03	-0.882	0.474	0.4482
Difference at 0.1	-0.795	0.474	0.5915
Difference at 0.3	-1.337	0.474	0.0454
Difference at 1	-3.54	0.474	<0.0001
Difference at 3	-1.786	0.474	0.0016
Difference at 10	-1.504	0.474	0.0146
Difference at 30	-1.329	0.474	0.0475
Difference at 100	-1.043	0.474	0.2301
Difference at 300	-0.831	0.474	0.5305

Fig. 43A



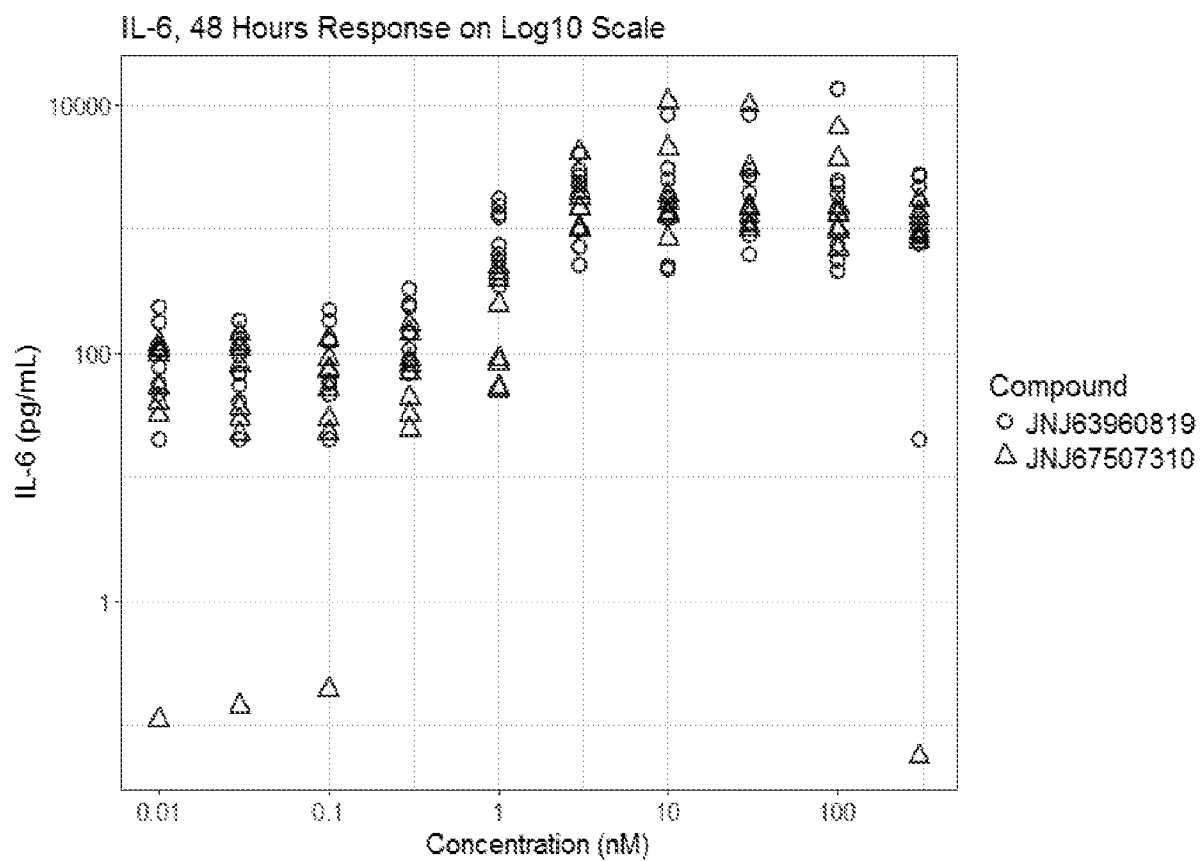
	Difference	Sigma	p-value
Difference at 0.01	0.263	0.456	0.9990
Difference at 0.03	0.302	0.456	0.9970
Difference at 0.1	0.304	0.456	0.9968
Difference at 0.3	-0.367	0.456	0.9866
Difference at 1	-0.962	0.456	0.2340
Difference at 3	-0.059	0.456	1.0000
Difference at 10	-0.037	0.456	1.0000
Difference at 30	0.056	0.456	1.0000
Difference at 100	0.156	0.456	1.0000
Difference at 300	0.314	0.456	0.9958

Fig. 43B



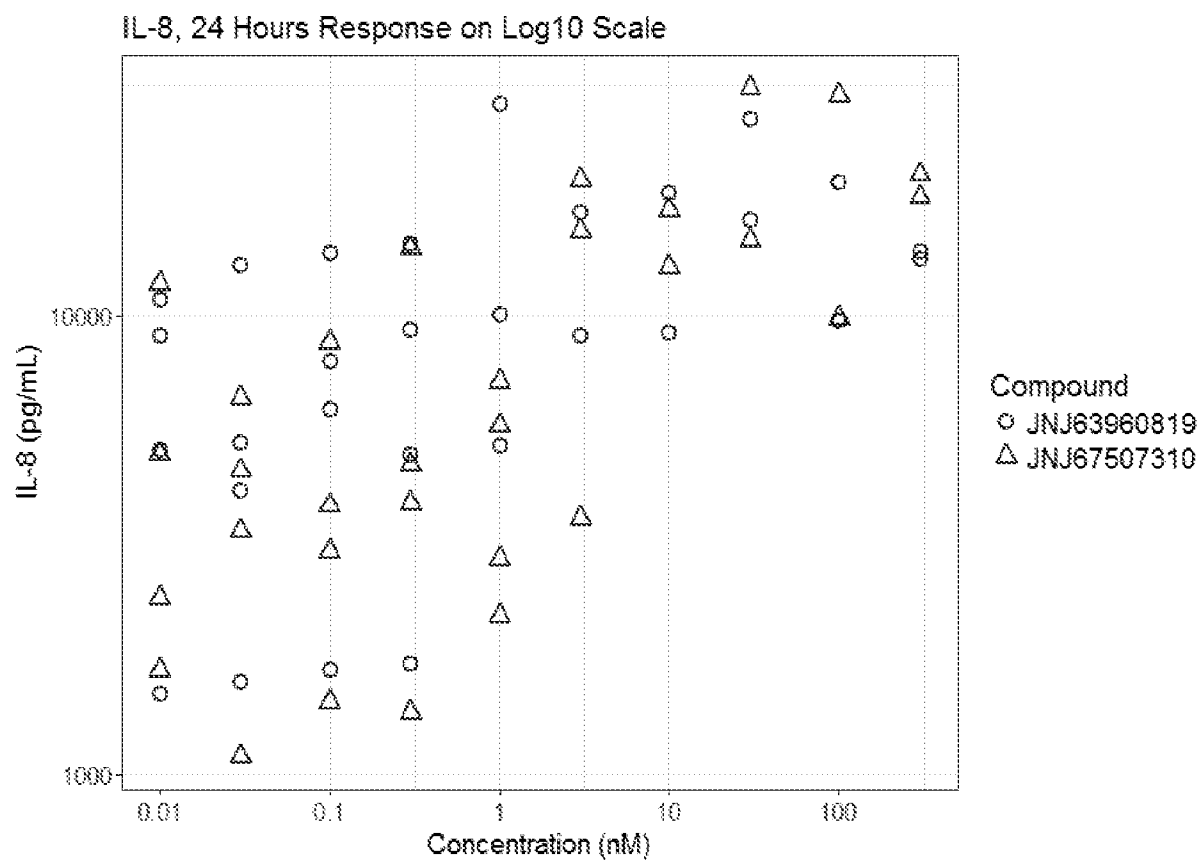
	JNJ819 (IC3B19)	JNJ310 (IC3B34)	p-value
EC50	0.821 (0.549, 1.229)	1.796 (1.320, 2.444)	Sig.
Slope	0.678 (0.324, 1.031)	0.349 (0.162, 0.536)	0.0819
Minimum	3.917 (3.582, 4.252)	4.243 (3.993, 4.493)	0.1151
Maximum	7.221 (6.742, 7.700)	7.337 (6.865, 7.808)	0.5224

Fig. 44



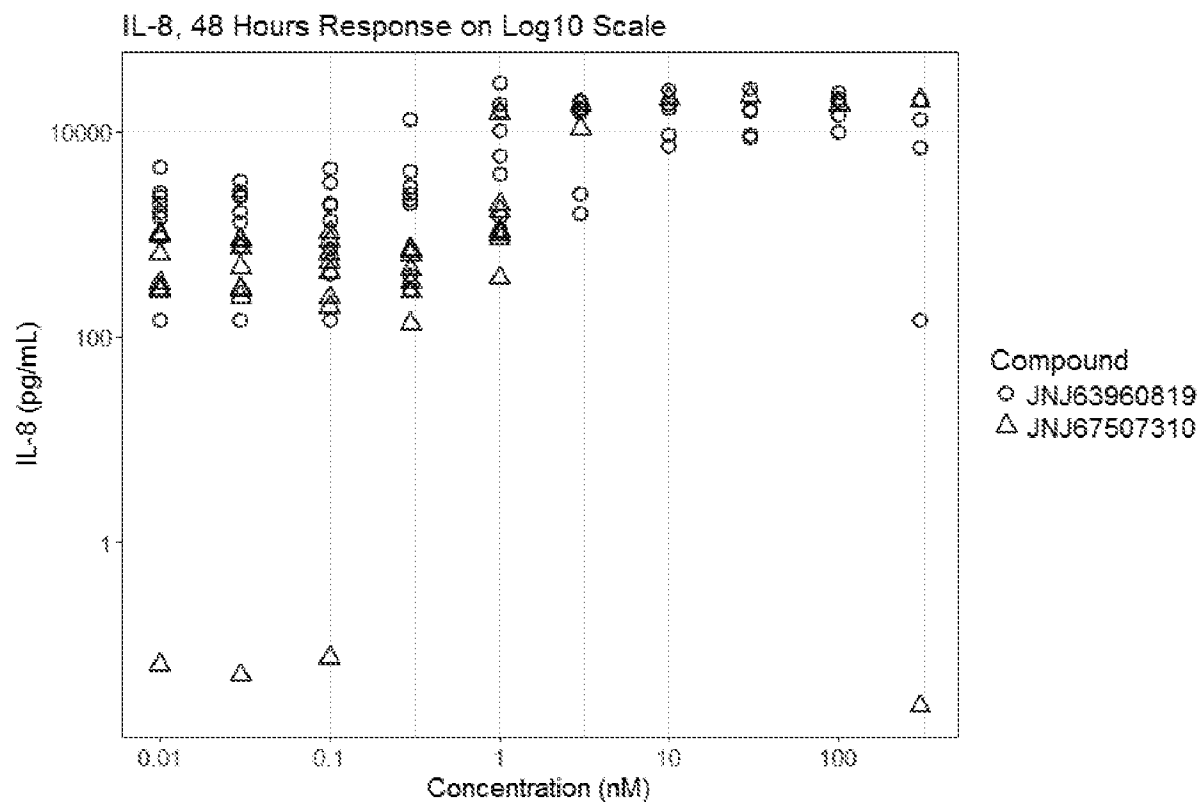
	Difference	Sigma	p-value
Difference at 0.01	-0.948	0.698	0.8438
Difference at 0.03	-0.875	0.698	0.8982
Difference at 0.1	-1.071	0.698	0.7261
Difference at 0.3	-0.811	0.698	0.9349
Difference at 1	-1.724	0.698	0.1254
Difference at 3	-0.090	0.698	1.0000
Difference at 10	0.207	0.698	1.0000
Difference at 30	-0.061	0.698	1.0000
Difference at 100	-0.001	0.698	1.0000
Difference at 300	-1.001	0.698	0.7966

Fig. 45



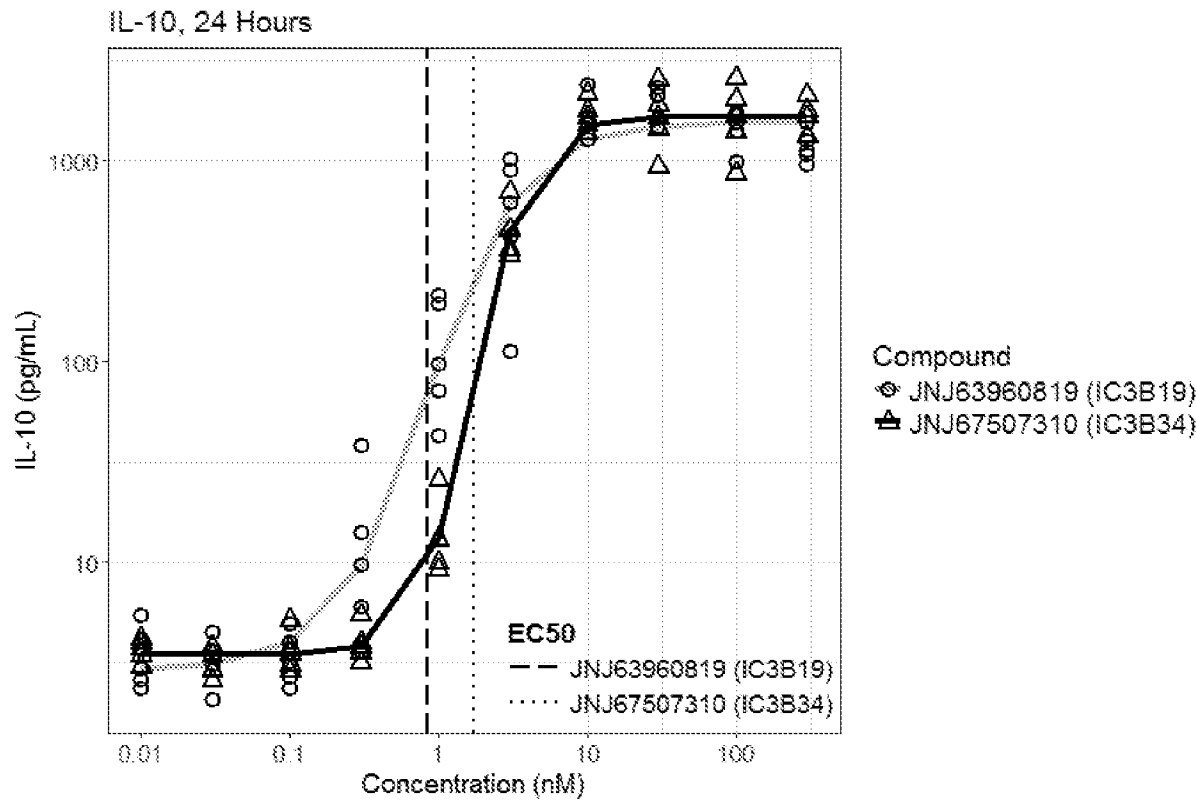
	Difference	Sigma	p-value
Difference at 0.01	-0.285	0.560	0.9985
Difference at 0.03	-0.349	0.560	0.9927
Difference at 0.1	-0.512	0.560	0.9192
Difference at 0.3	-0.299	0.560	0.9977
Difference at 1	-1.276	0.576	0.1433
Difference at 3	-0.311	0.621	0.9986
Difference at 10	0.158	0.649	1.0000
Difference at 30	0.062	0.649	1.0000
Difference at 100	0.259	0.649	0.9998
Difference at 300	0.386	0.649	0.9948

Fig. 46



	Difference	Sigma	p-value
Difference at 0.01	-2.073	1.303	0.3365
Difference at 0.03	-2.198	1.303	0.2873
Difference at 0.1	-1.972	1.303	0.3811
Difference at 0.3	-2.753	1.309	0.1302
Difference at 1	-2.650	1.309	0.1533
Difference at 3	-0.834	1.419	0.9715
Difference at 10	-0.880	1.551	0.9766
Difference at 30	-0.819	1.551	0.9847
Difference at 100	-1.189	1.551	0.8961
Difference at 300	-1.909	1.445	0.5029

Fig. 47A



	Difference	Sigma	p-value
Difference at 0.01	0.098	0.325	1.0000
Difference at 0.03	-0.077	0.325	1.0000
Difference at 0.1	0.127	0.325	1.0000
Difference at 0.3	-0.963	0.325	0.0293
Difference at 1	-2.09	0.325	<0.0001
Difference at 3	-0.026	0.325	1.0000
Difference at 10	-0.037	0.325	1.0000
Difference at 30	-0.245	0.325	0.9967
Difference at 100	0.098	0.325	1.0000
Difference at 300	0.375	0.325	0.9308

Fig. 47B

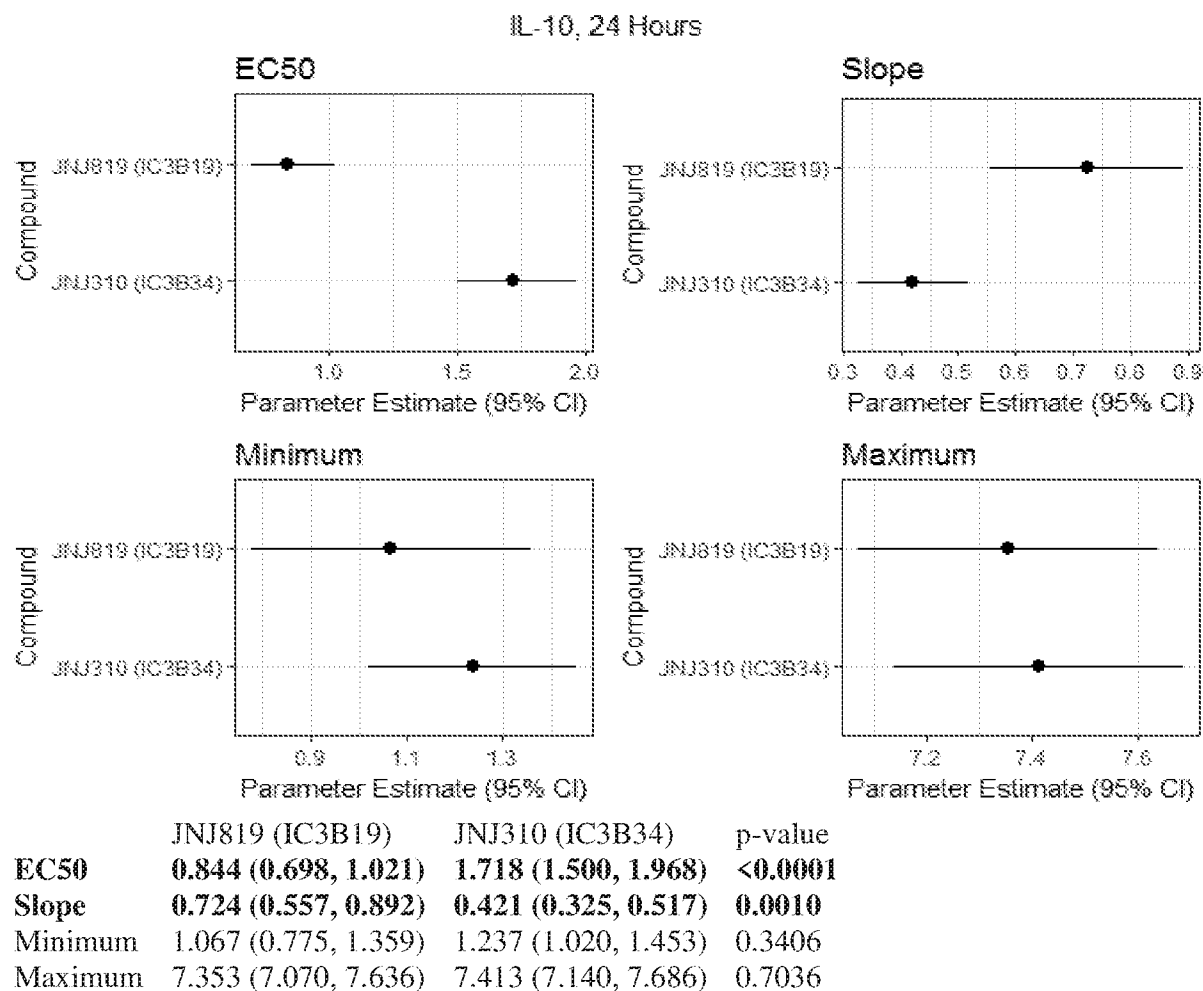
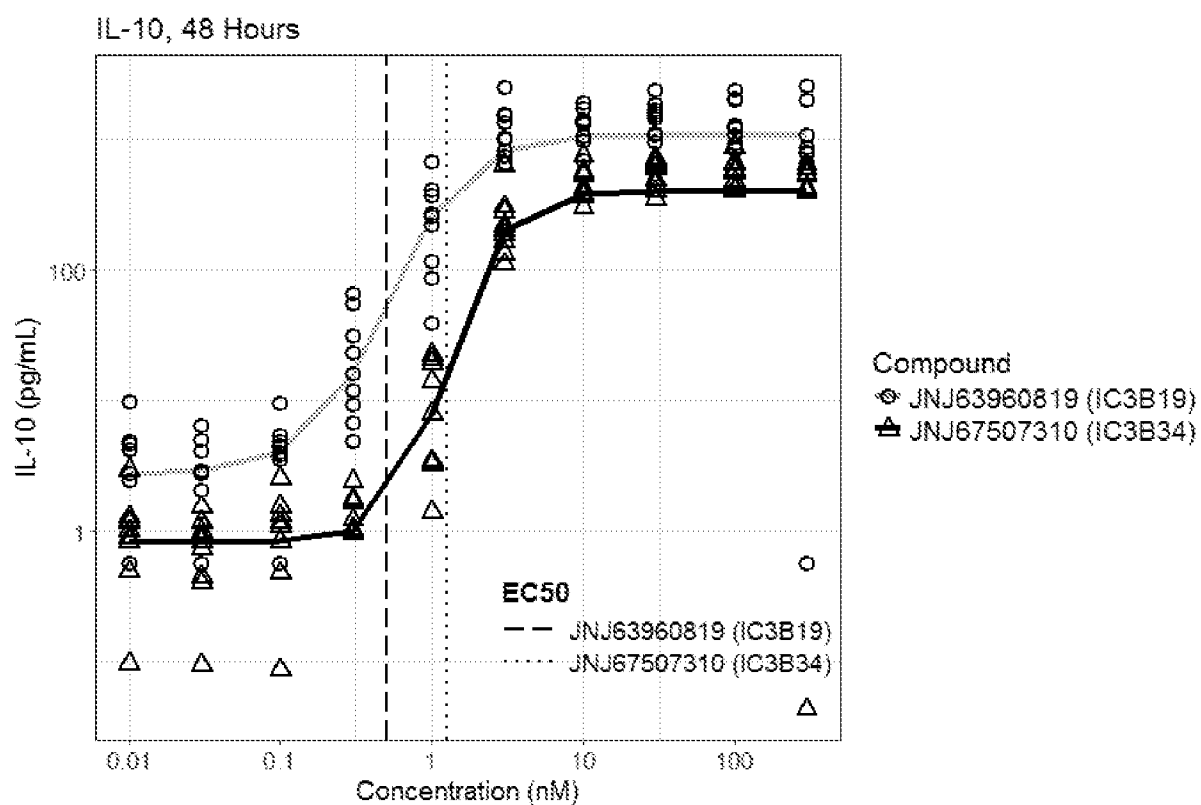


Fig. 48A



	Difference	Sigma	p-value
Difference at 0.01	-1.404	0.583	0.1405
Difference at 0.03	-1.391	0.583	0.1484
Difference at 0.1	-1.472	0.583	0.1043
Difference at 0.3	-2.546	0.583	1e-04
Difference at 1	-3.33	0.583	<0.0001
Difference at 3	-1.693	0.583	0.0352
Difference at 10	-0.98	0.583	0.5852
Difference at 30	-1.011	0.583	0.5434
Difference at 100	-0.898	0.583	0.6952
Difference at 300	-0.956	0.583	0.6178

Fig. 48B

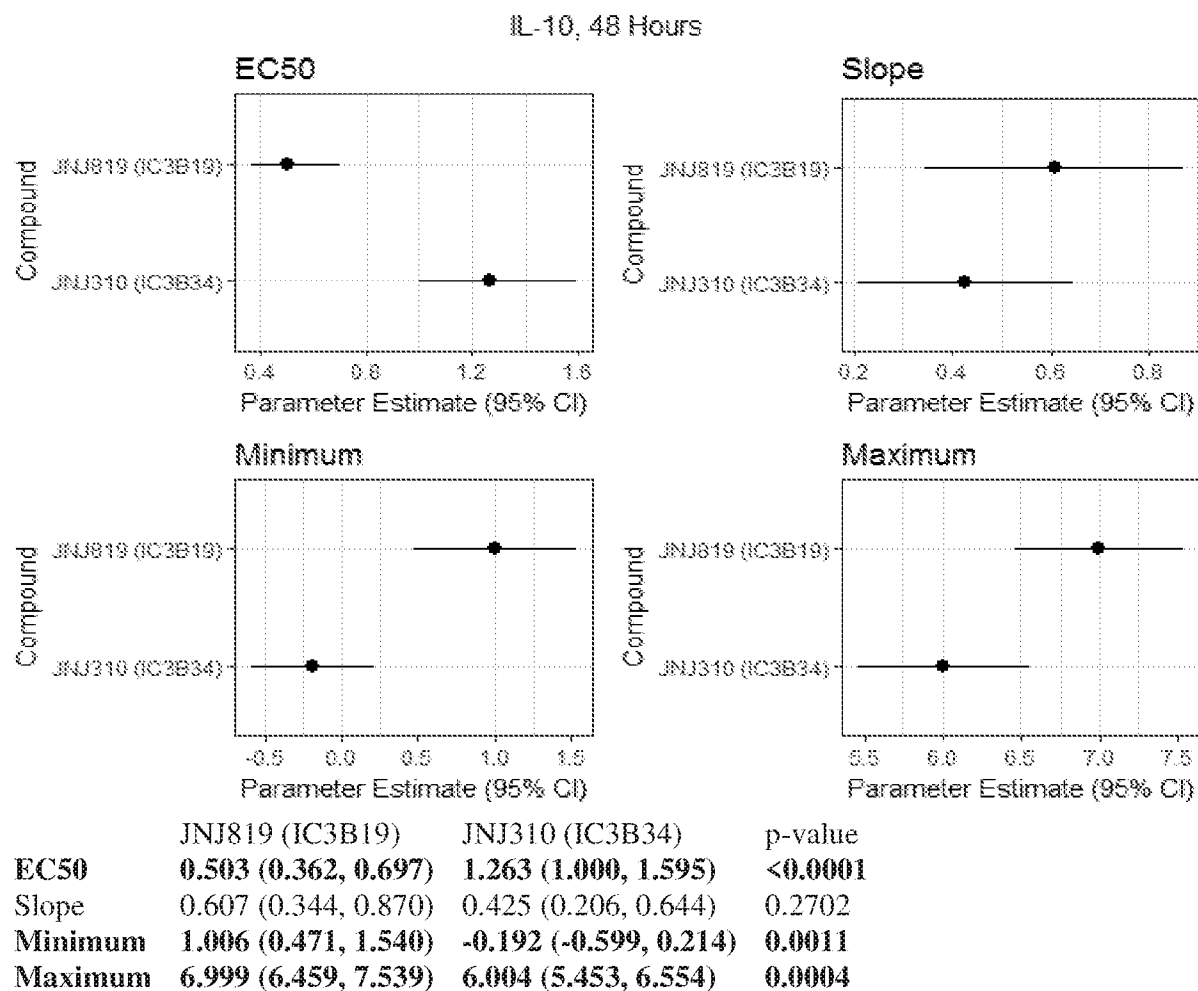
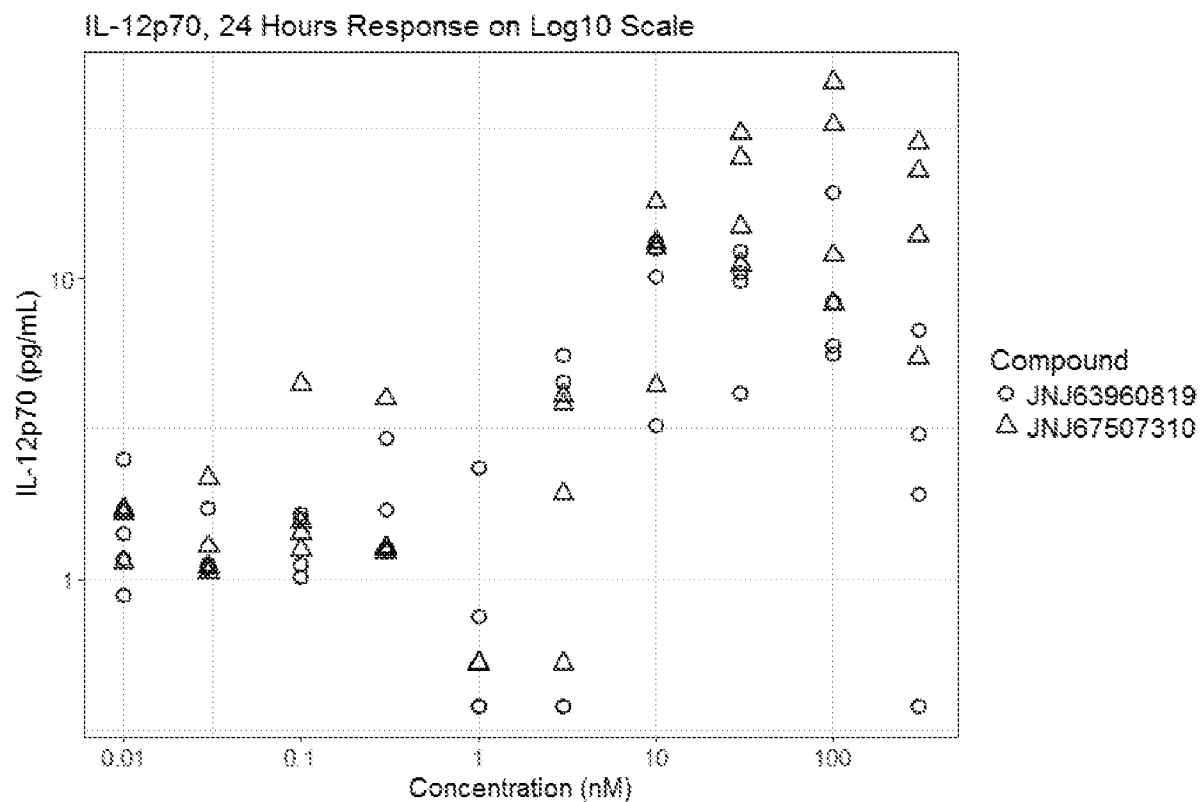
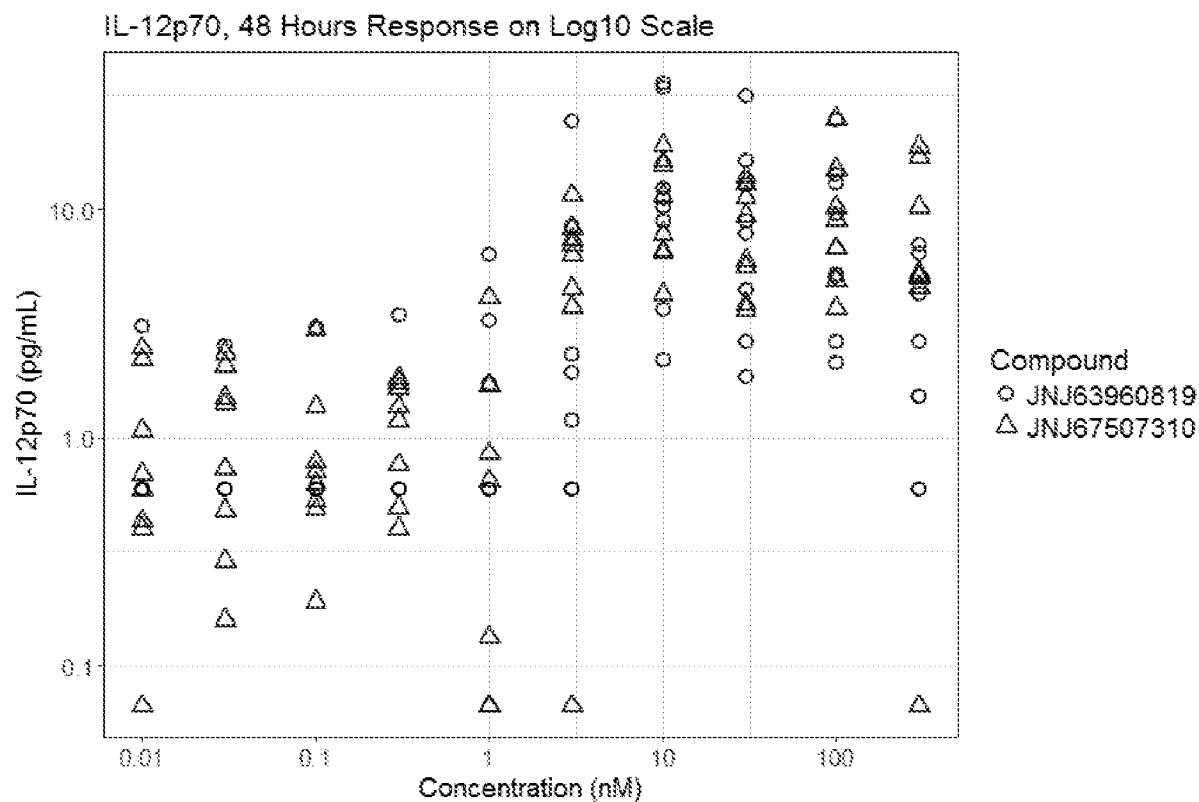


Fig. 49



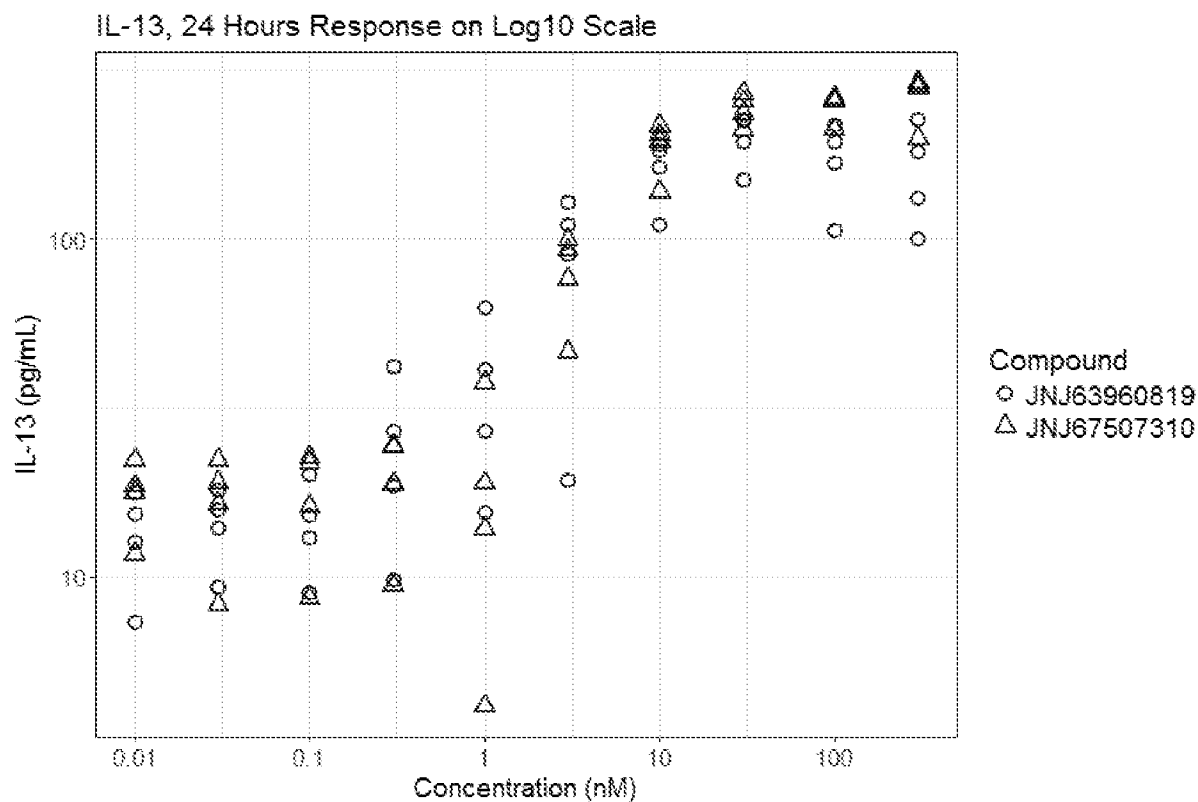
	Difference	Sigma	p-value
Difference at 0.01	0.096	0.485	1.0000
Difference at 0.03	0.081	0.485	1.0000
Difference at 0.1	0.351	0.485	0.9953
Difference at 0.3	0.002	0.485	1.0000
Difference at 1	-0.302	0.485	0.9986
Difference at 3	0.369	0.485	0.9931
Difference at 10	0.216	0.485	0.9999
Difference at 30	0.792	0.485	0.5672
Difference at 100	0.814	0.485	0.5321
Difference at 300	2.024	0.485	0.0003

Fig. 50



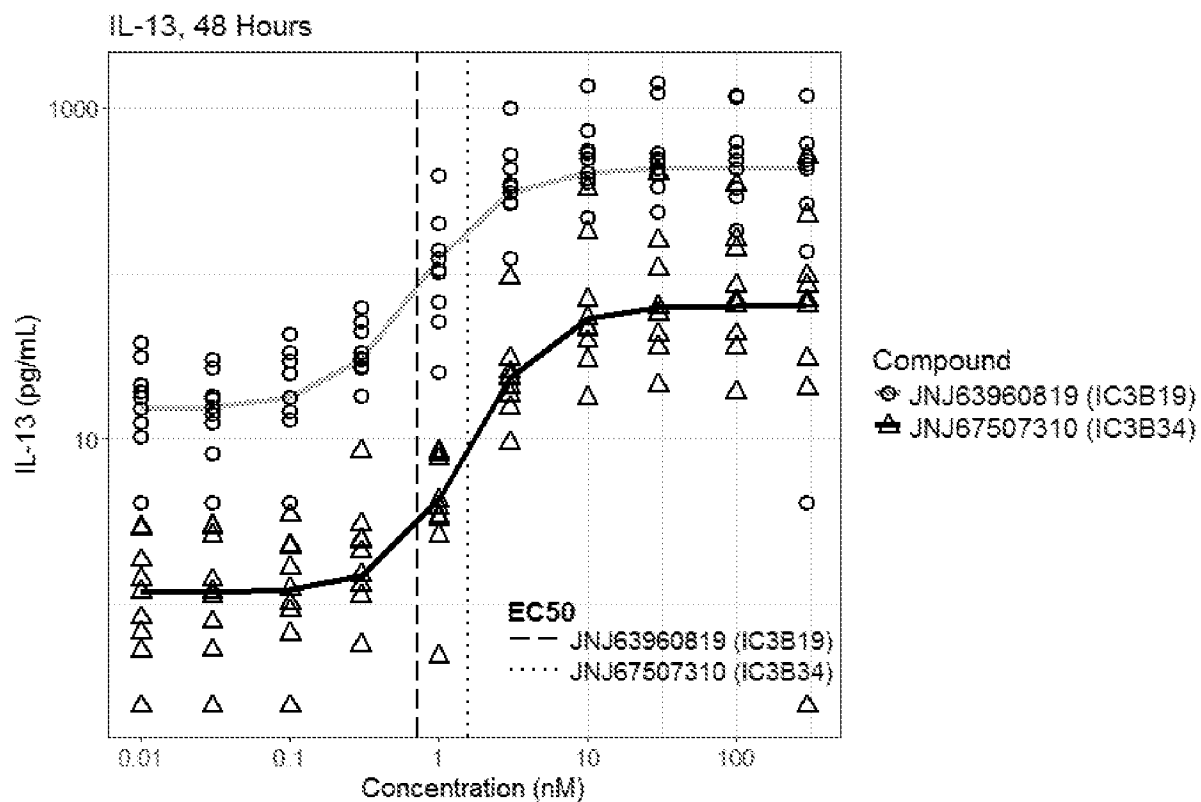
	Difference	Sigma	p-value
Difference at 0.01	-0.140	0.503	1.0000
Difference at 0.03	0.108	0.503	1.0000
Difference at 0.1	-0.022	0.503	1.0000
Difference at 0.3	0.324	0.503	0.9988
Difference at 1	-0.822	0.503	0.6083
Difference at 3	0.623	0.503	0.8814
Difference at 10	-0.059	0.503	1.0000
Difference at 30	-0.022	0.503	1.0000
Difference at 100	0.178	0.503	1.0000
Difference at 300	0.718	0.503	0.7659

Fig. 51



	Difference	Sigma	p-value
Difference at 0.01	0.307	0.312	0.8941
Difference at 0.03	0.108	0.312	1.0000
Difference at 0.1	0.161	0.312	0.9985
Difference at 0.3	-0.170	0.312	0.9978
Difference at 1	-0.817	0.312	0.0565
Difference at 3	0.071	0.312	1.0000
Difference at 10	0.159	0.312	0.9987
Difference at 30	0.212	0.312	0.9886
Difference at 100	0.393	0.312	0.7092
Difference at 300	0.536	0.312	0.3785

Fig. 52A



	Difference	Sigma	p-value
Difference at 0.01	-2.735	0.49	<0.0001
Difference at 0.03	-2.489	0.49	<0.0001
Difference at 0.1	-2.726	0.49	<0.0001
Difference at 0.3	-2.846	0.49	<0.0001
Difference at 1	-3.337	0.49	<0.0001
Difference at 3	-2.707	0.49	<0.0001
Difference at 10	-2.132	0.49	1e-04
Difference at 30	-2.005	0.49	4e-04
Difference at 100	-1.869	0.49	0.0014
Difference at 300	-1.753	0.49	0.0034

Fig. 52B

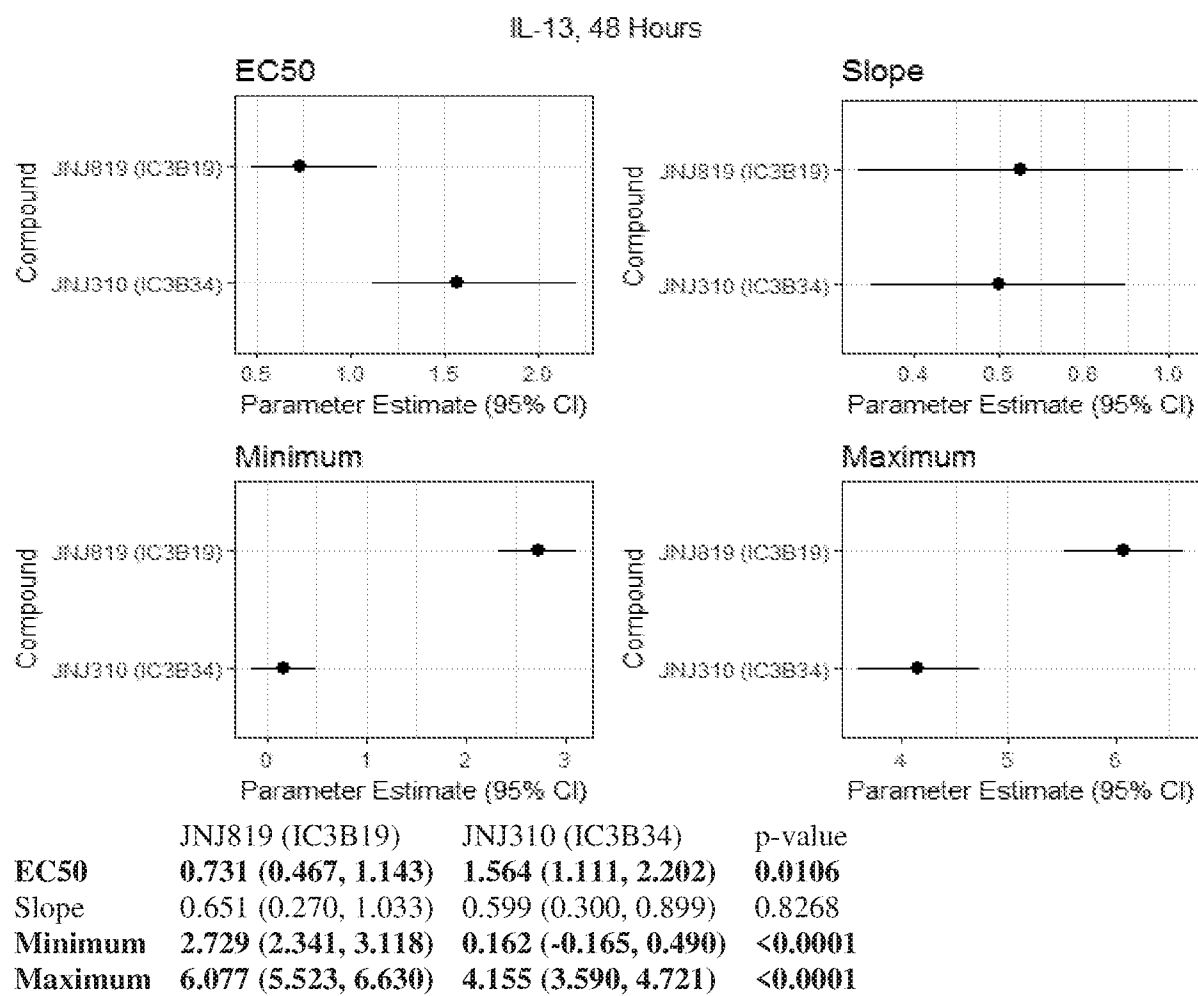
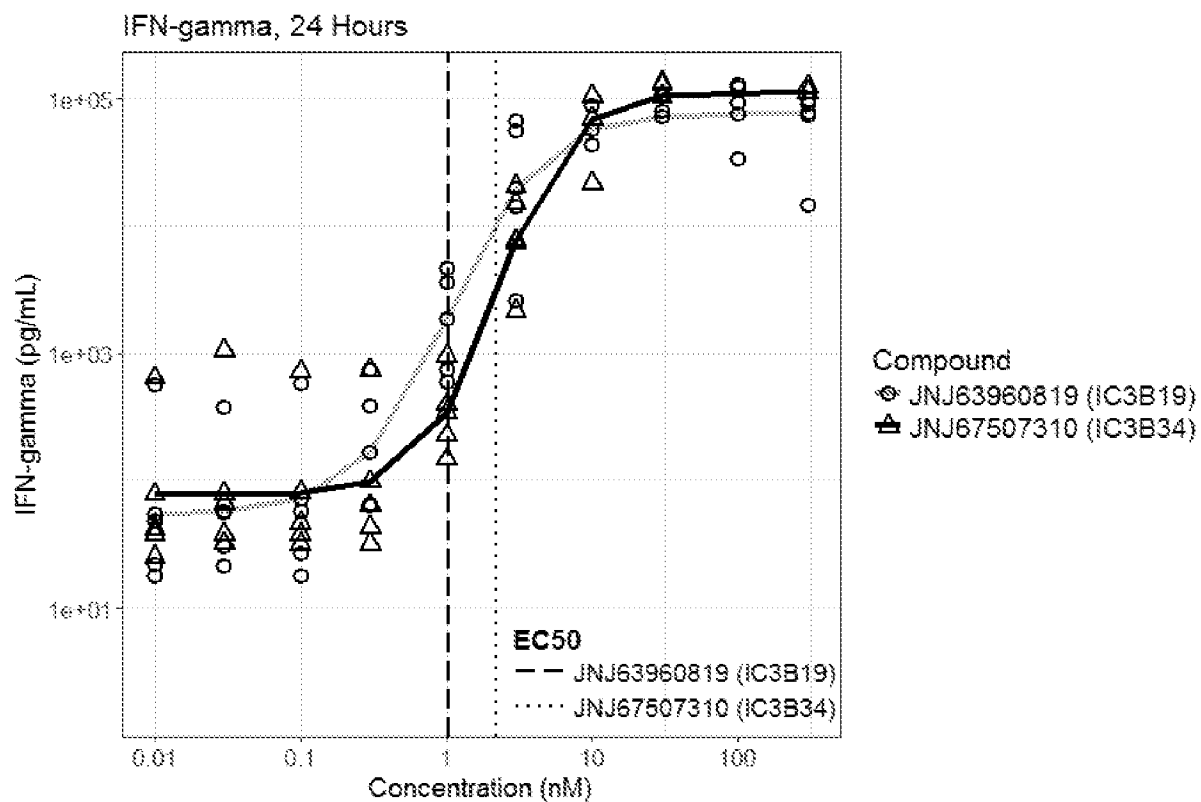


Fig. 53A



	Difference	Sigma	p-value
Difference at 0.01	0.220	0.927	1.0000
Difference at 0.03	0.448	0.927	0.9991
Difference at 0.1	0.225	0.927	1.0000
Difference at 0.3	-0.735	0.927	0.9718
Difference at 1	-1.596	0.927	0.4007
Difference at 3	-0.836	0.927	0.9413
Difference at 10	-0.060	1.123	1.0000
Difference at 30	0.538	1.123	0.9992
Difference at 300	1.510	1.206	0.7439

Fig. 53B

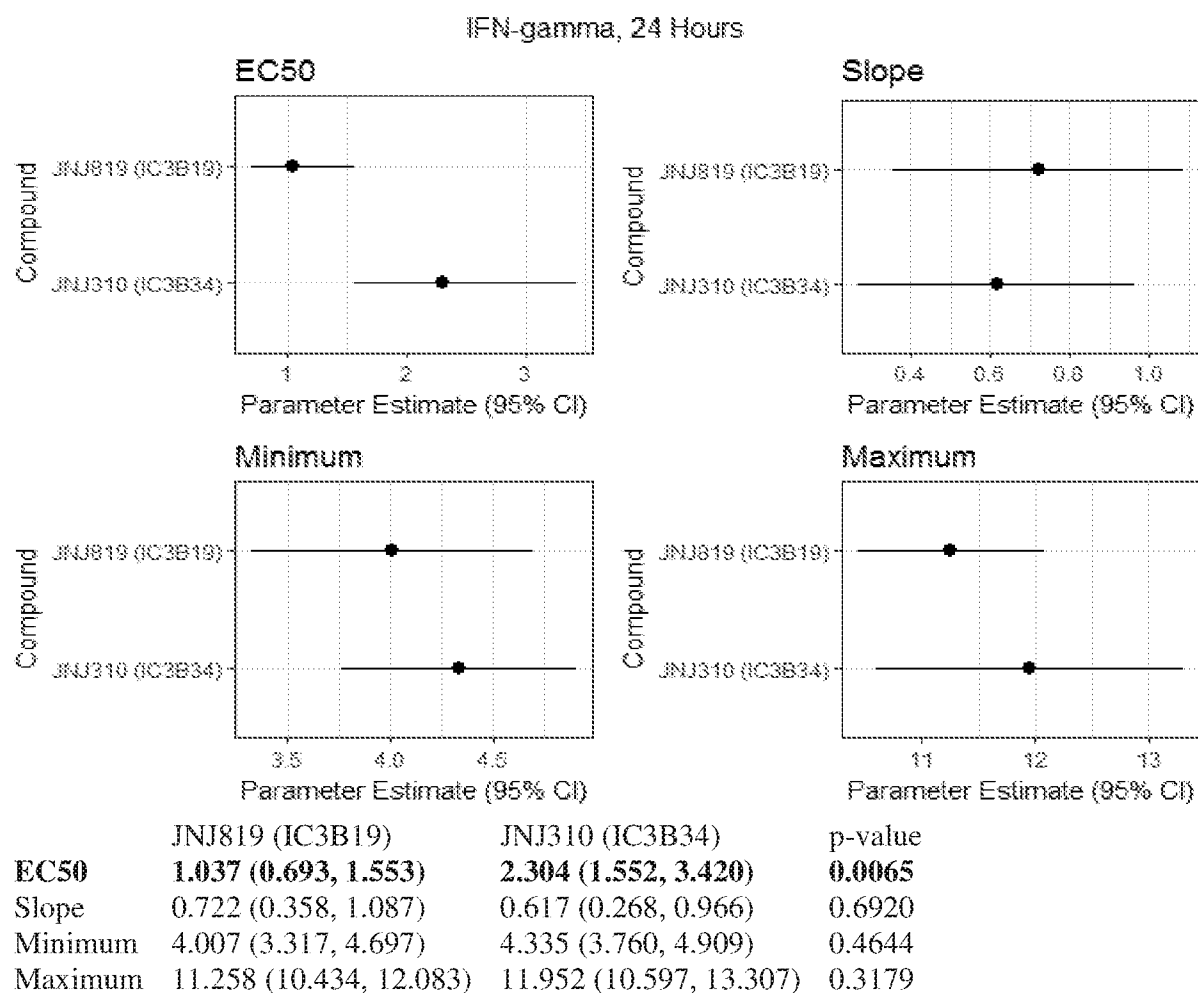
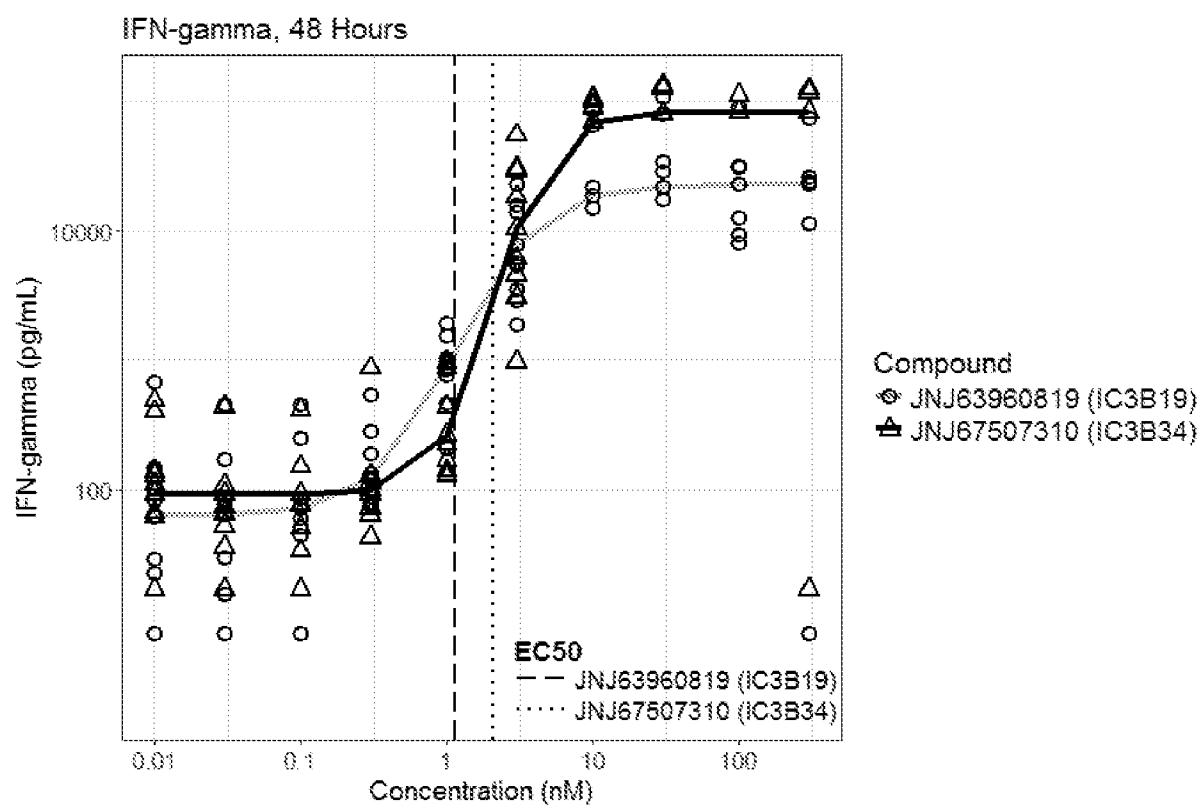


Fig. 54A



	Difference	Sigma	p-value
Difference at 0.01	0.576	0.699	0.9926
Difference at 0.03	0.406	0.699	0.9996
Difference at 0.1	0.034	0.699	1.0000
Difference at 0.3	-0.329	0.699	0.9999
Difference at 1	-1.084	0.699	0.6880
Difference at 3	0.401	0.699	0.9996
Difference at 10	1.056	0.869	0.9007
Difference at 30	0.804	0.942	0.9903
Difference at 100	1.253	1.389	0.9854
Difference at 300	-0.082	0.922	1.0000

Fig. 54B

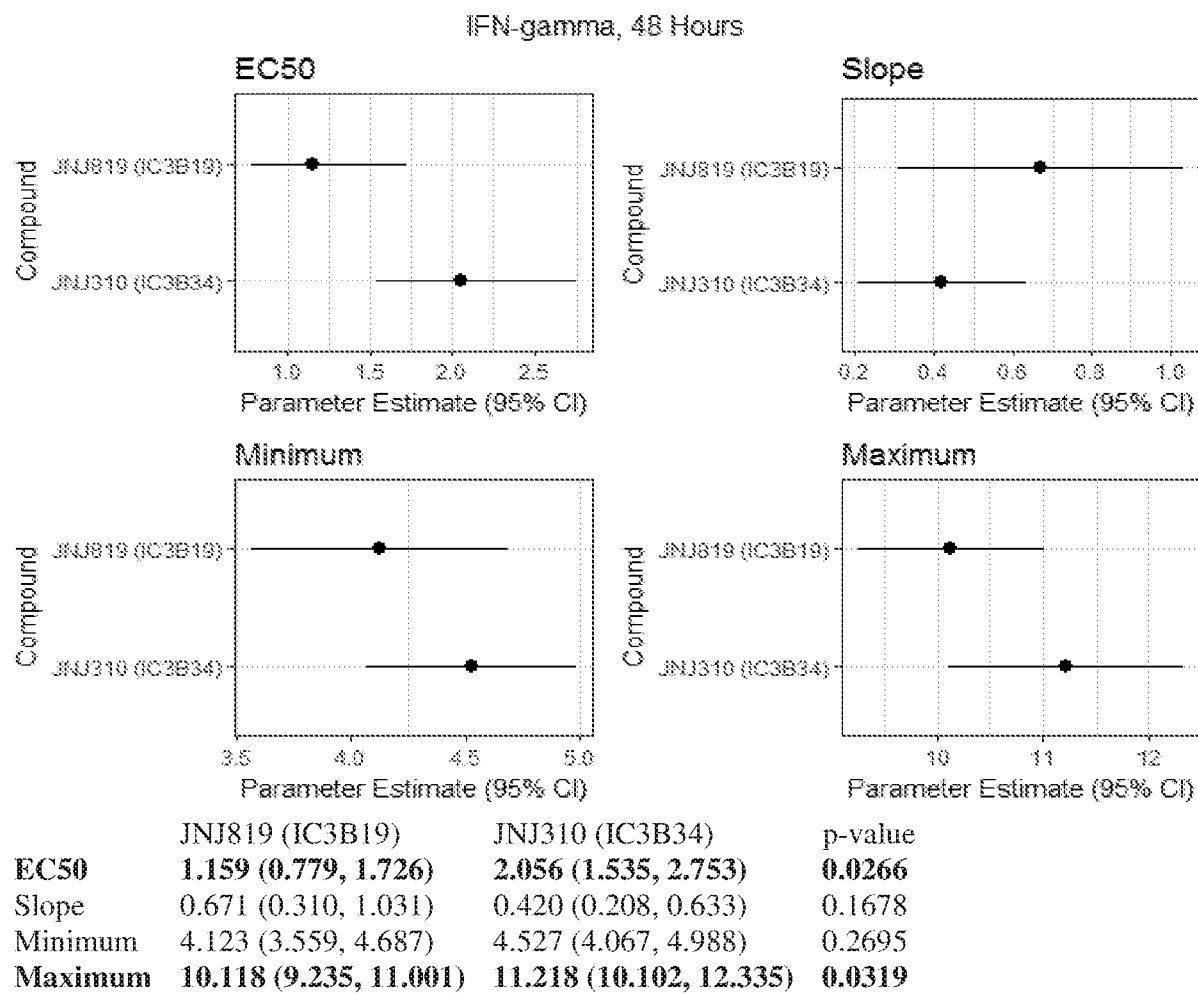
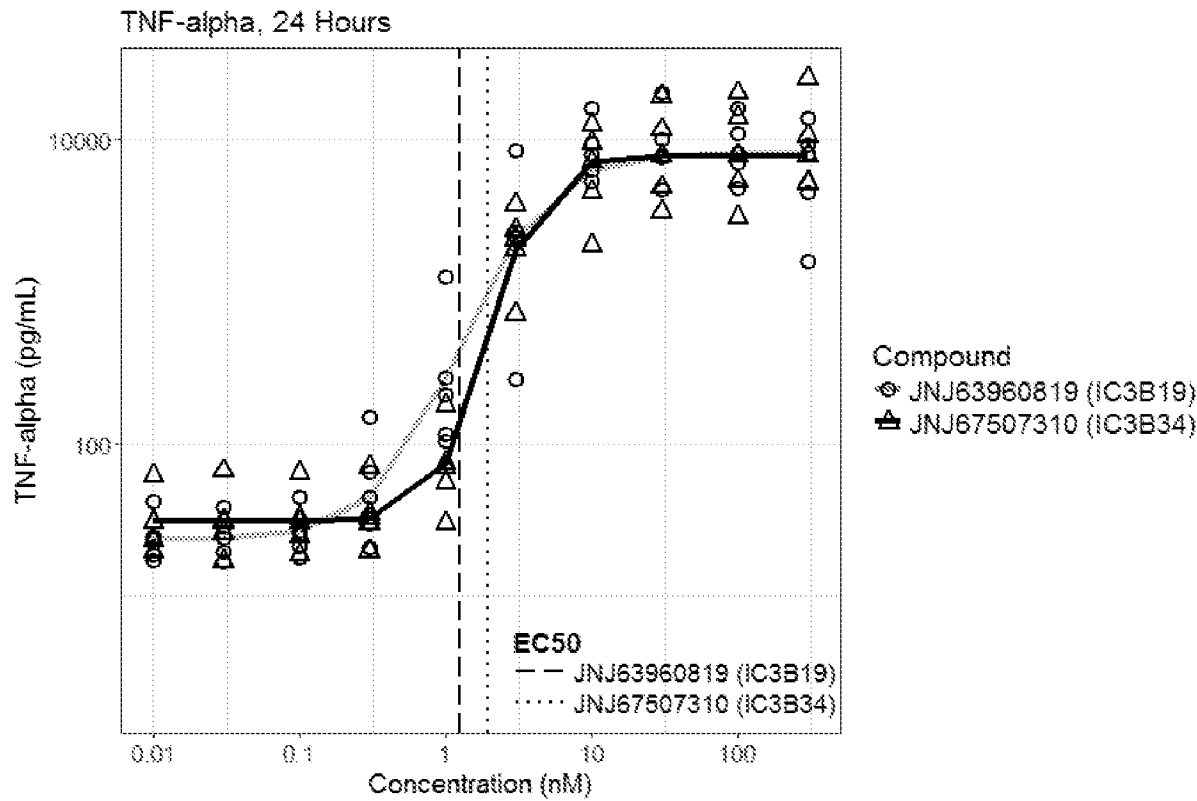


Fig. 55A



	Difference	Sigma	p-value
Difference at 0.01	0.242	0.53	0.9997
Difference at 0.03	0.233	0.53	0.9998
Difference at 0.1	0.203	0.53	0.9999
Difference at 0.3	-0.362	0.53	0.9918
Difference at 1	-1.258	0.53	0.1120
Difference at 3	0.035	0.53	1.0000
Difference at 10	-0.446	0.53	0.9660
Difference at 30	-0.175	0.53	1.0000
Difference at 100	-0.058	0.53	1.0000
Difference at 300	0.521	0.53	0.9172

Fig. 55B

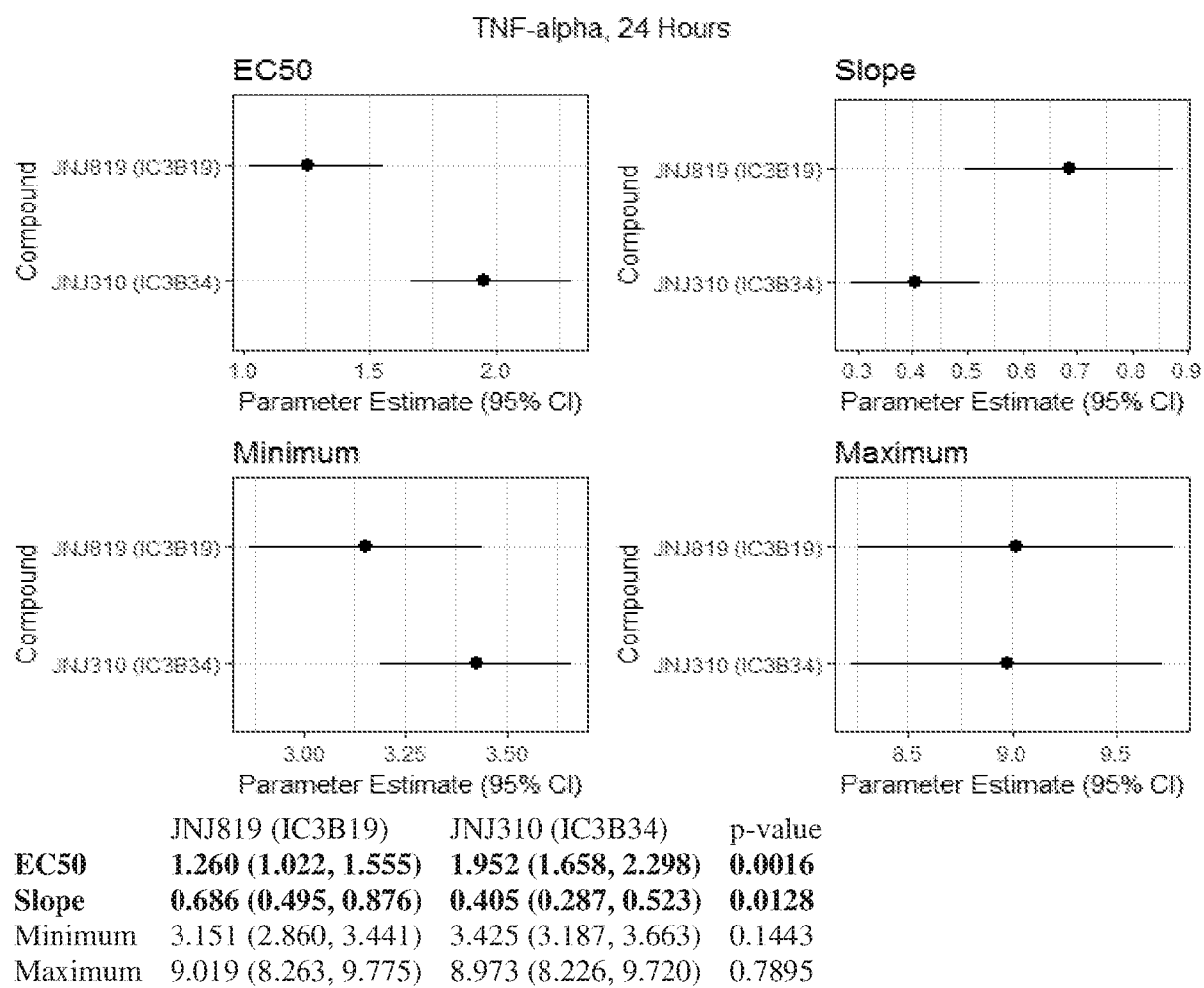
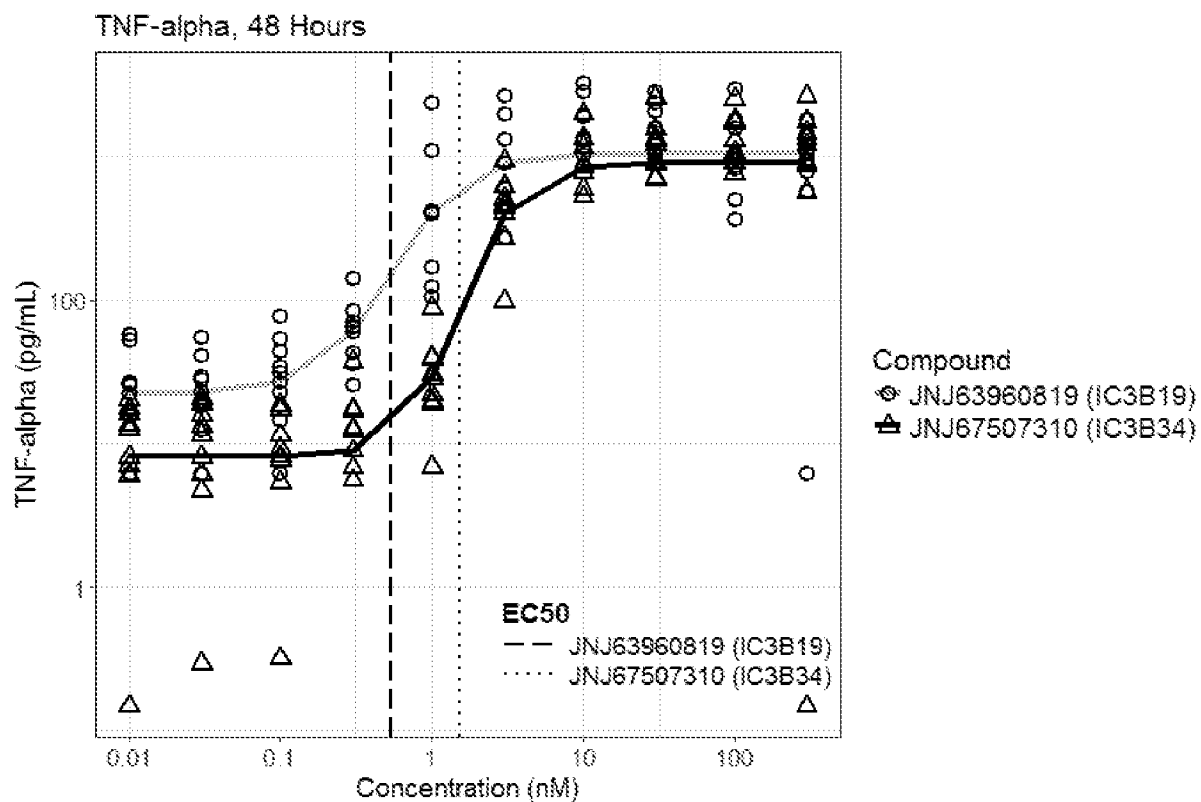


Fig. 56A



	Difference	Sigma	p-value
Difference at 0.01	-1.21	0.579	0.2840
Difference at 0.03	-1.099	0.579	0.4088
Difference at 0.1	-1.365	0.579	0.1560
Difference at 0.3	-1.471	0.579	0.0982
Difference at 1	-2.66	0.579	<0.0001
Difference at 3	-0.718	0.579	0.8826
Difference at 10	-0.497	0.579	0.9889
Difference at 30	-0.245	0.579	1.0000
Difference at 100	0.243	0.579	1.0000
Difference at 300	-0.33	0.579	0.9996

Fig. 56B

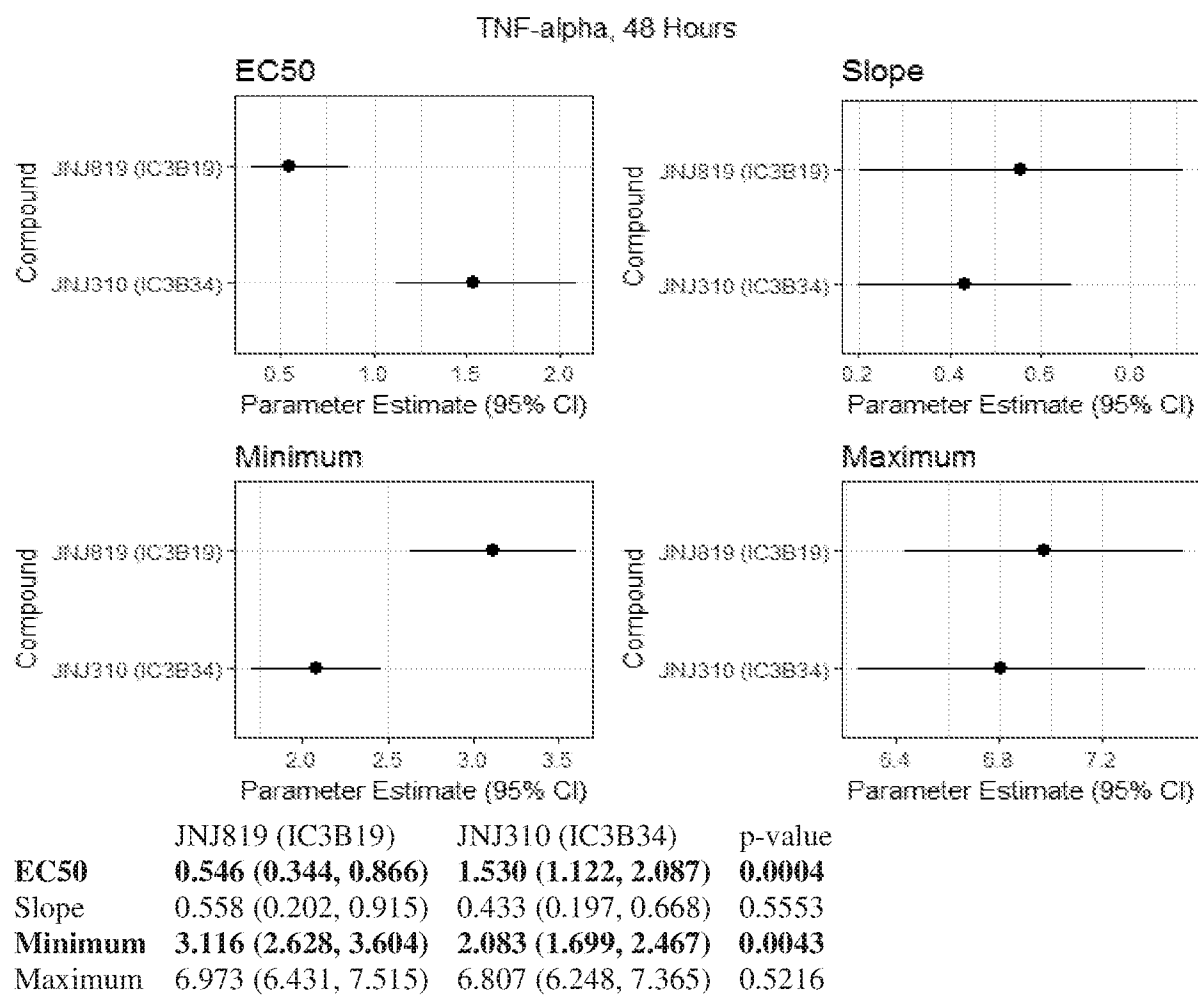
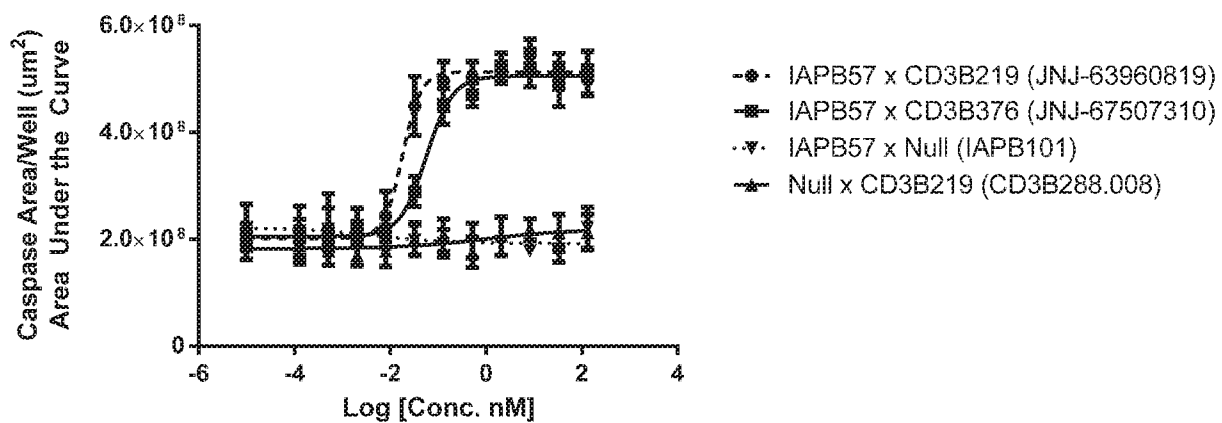


Fig. 57



	IL1RAP Affinity (nM)	Cytotox EC ₅₀ (nM)
JNJ-63960819	0.04	0.018
JNJ-67507310	0.02	0.057

Fig. 58

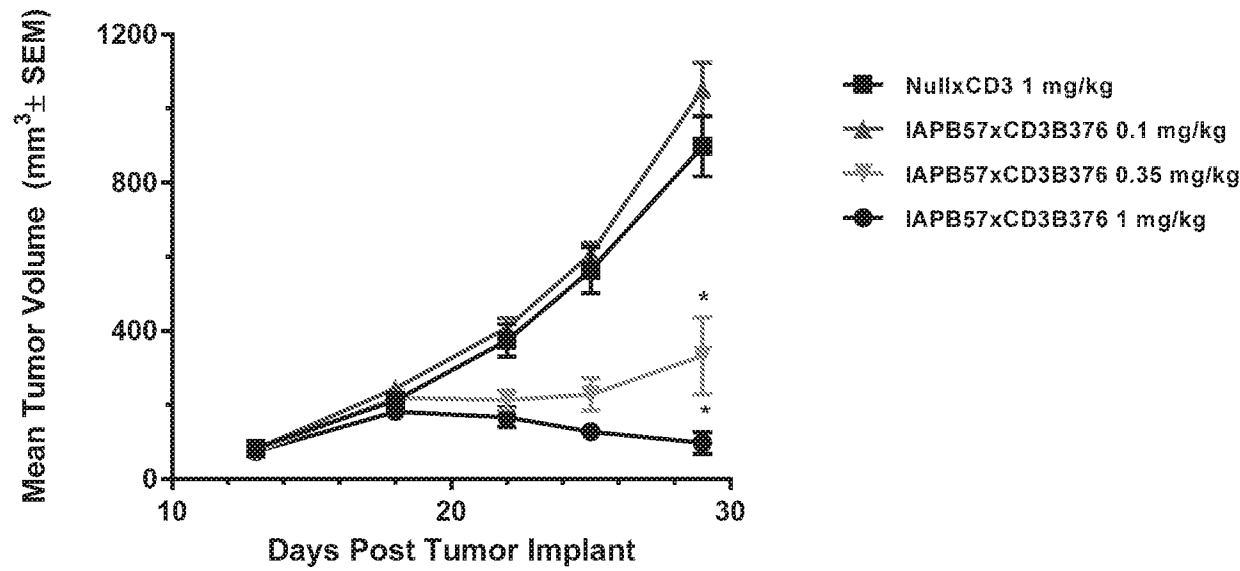


Fig. 59

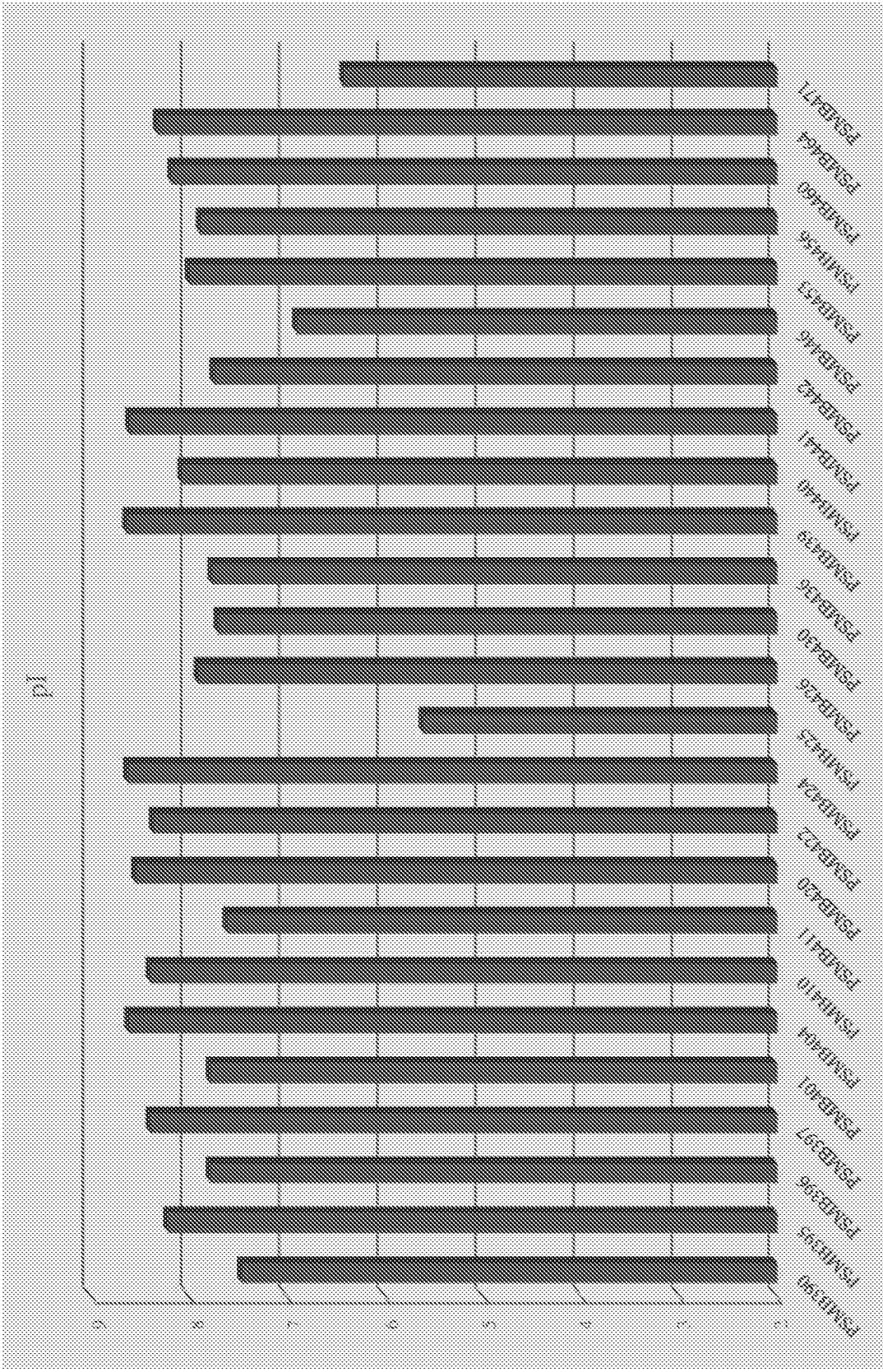


Fig. 60

Self-association propensity of PSMA mAbs
(against CNTO5825)

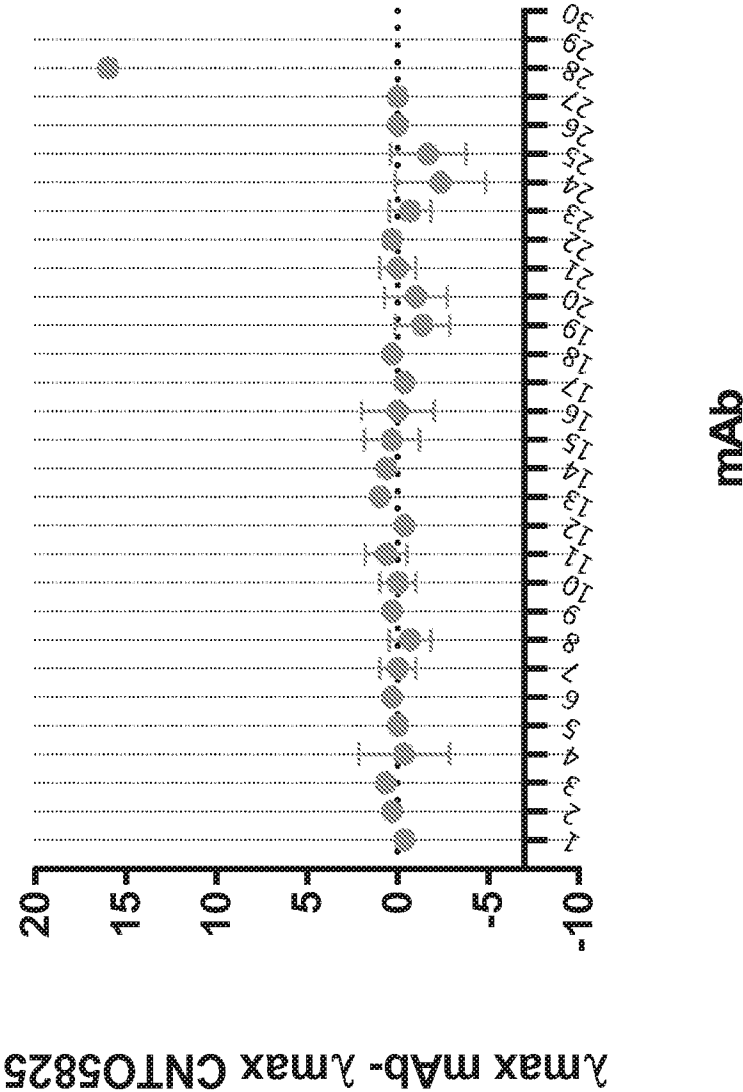


Fig. 61

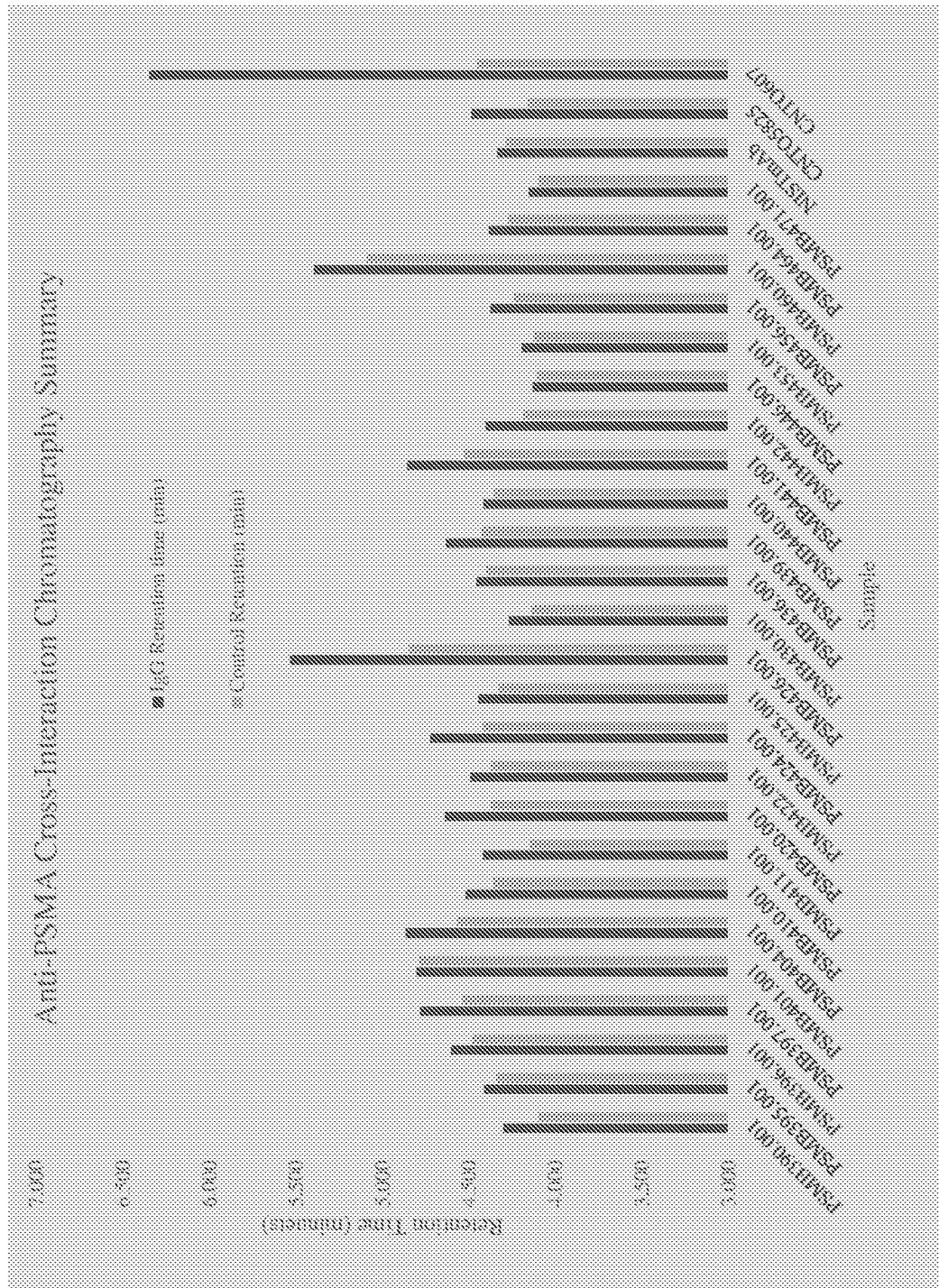


Fig. 62

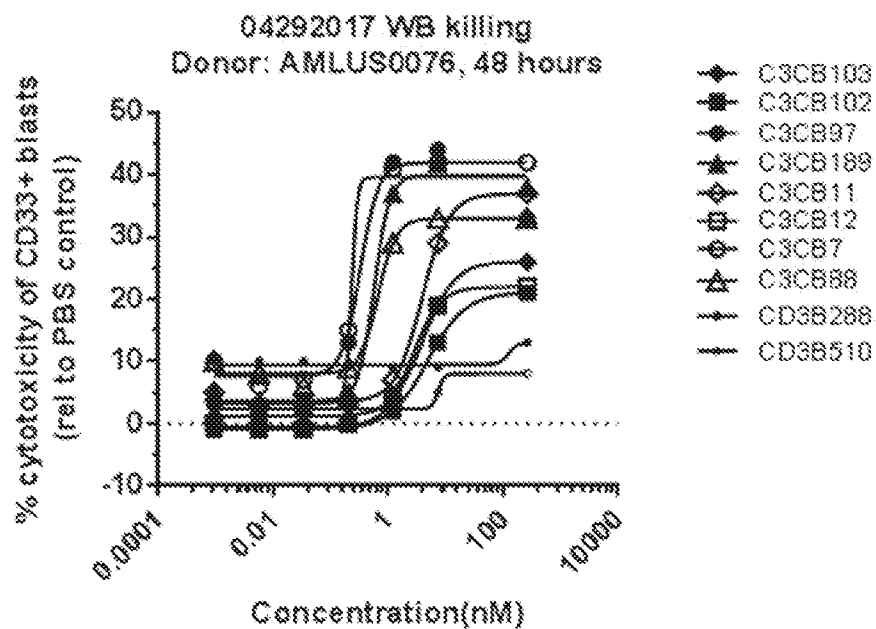


FIG. 62A

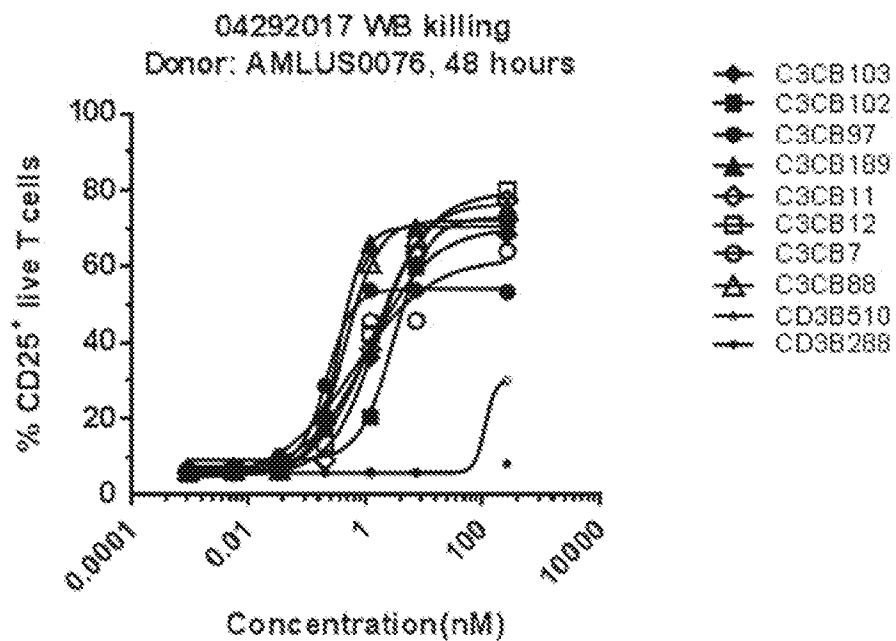


FIG. 62B

Fig. 63

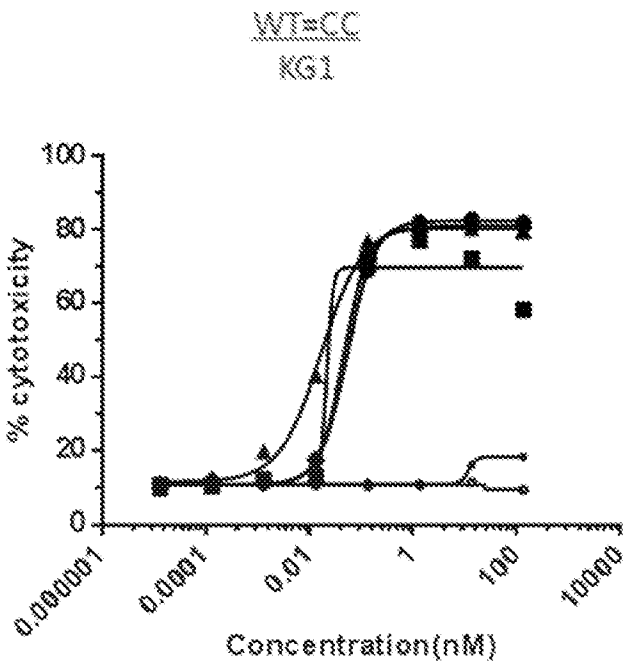


FIG. 63A

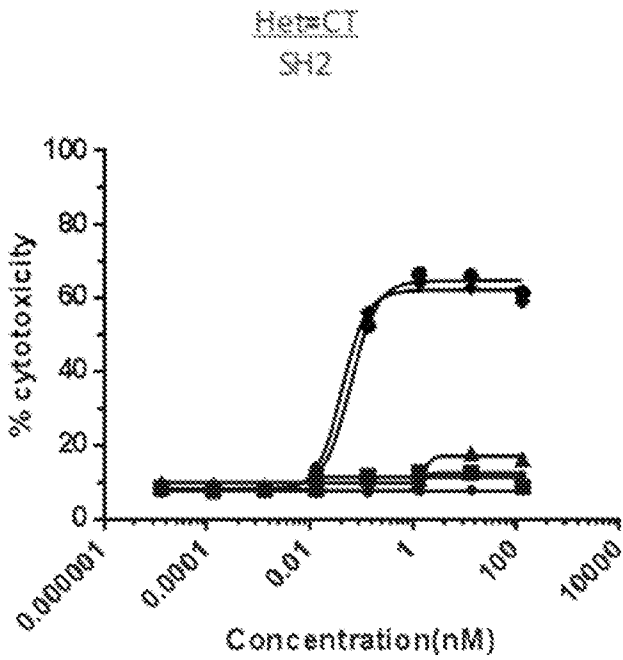


FIG. 63B

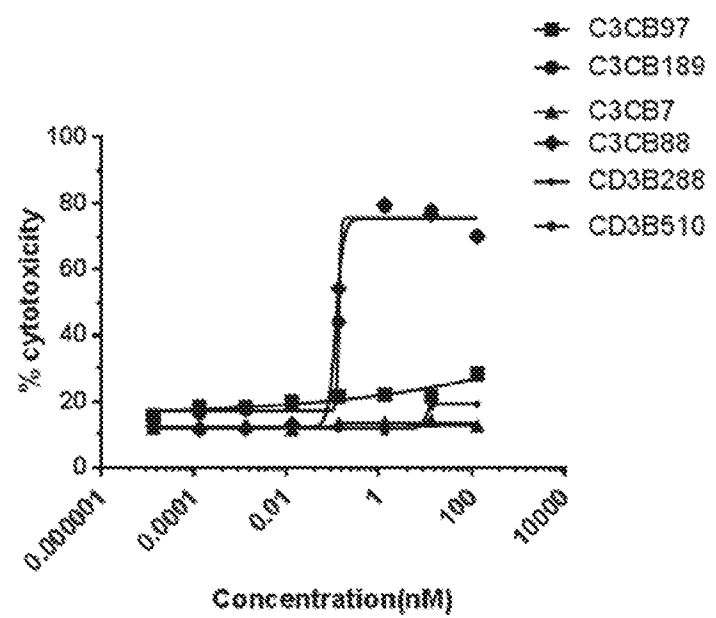


FIG. 63C

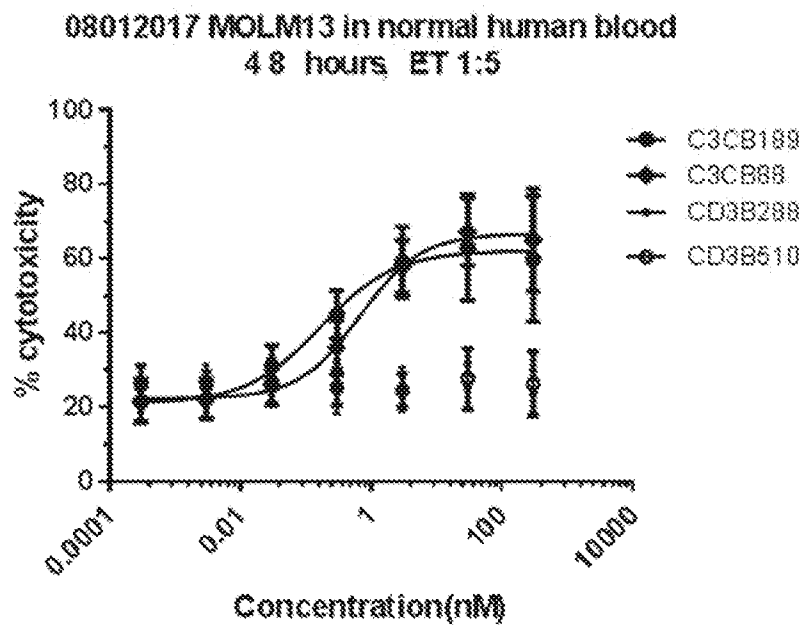


FIG. 64A

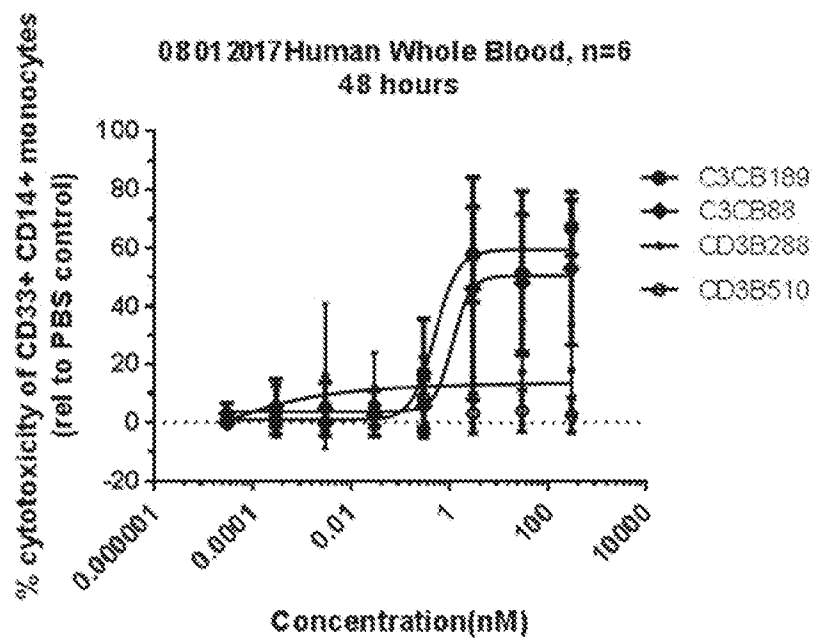


FIG. 64B

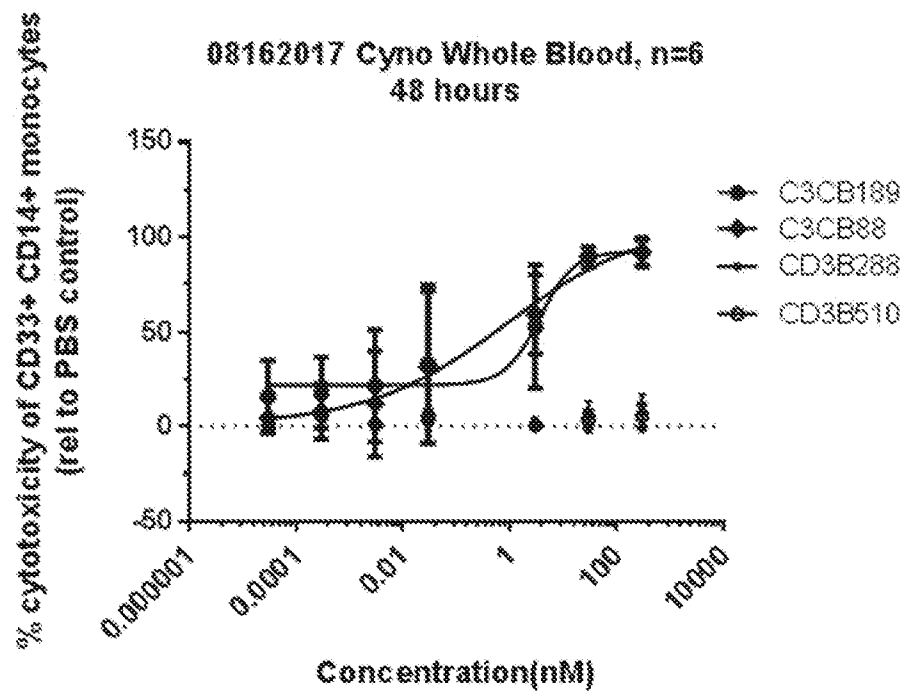


FIG. 65A

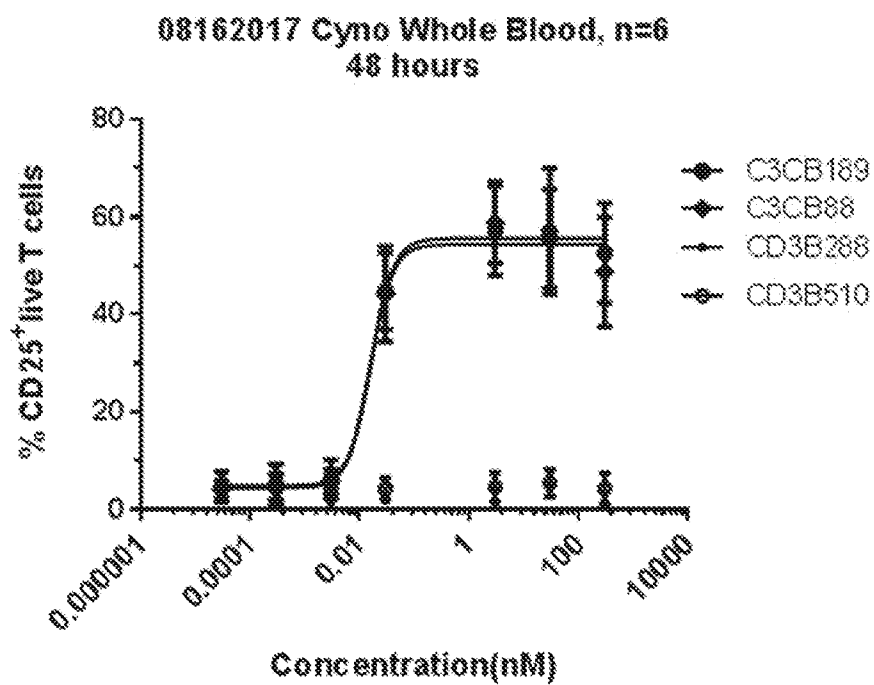


FIG. 65B

Fig. 66

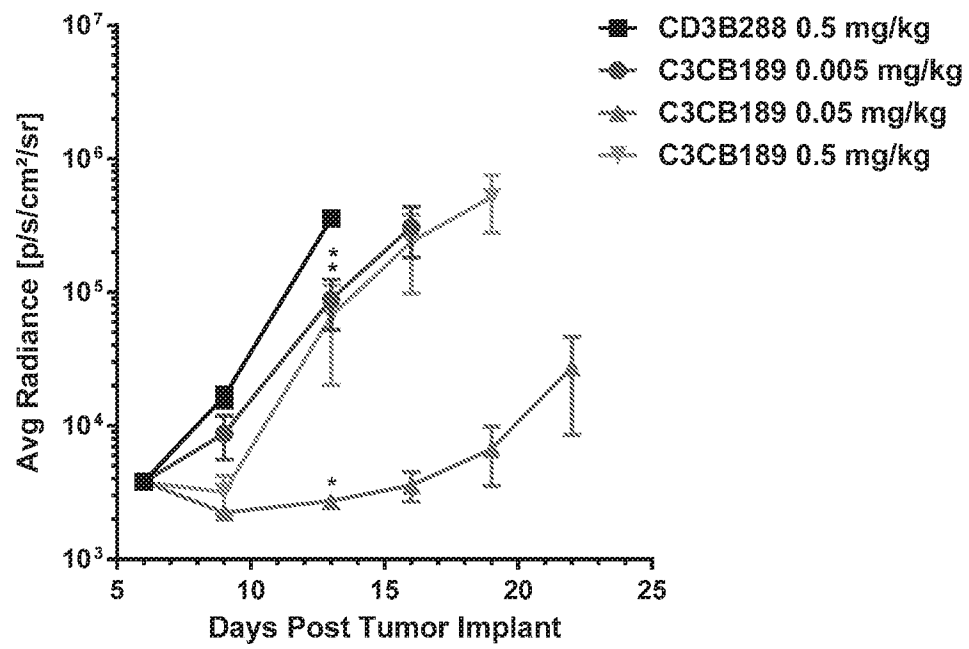


Fig. 67

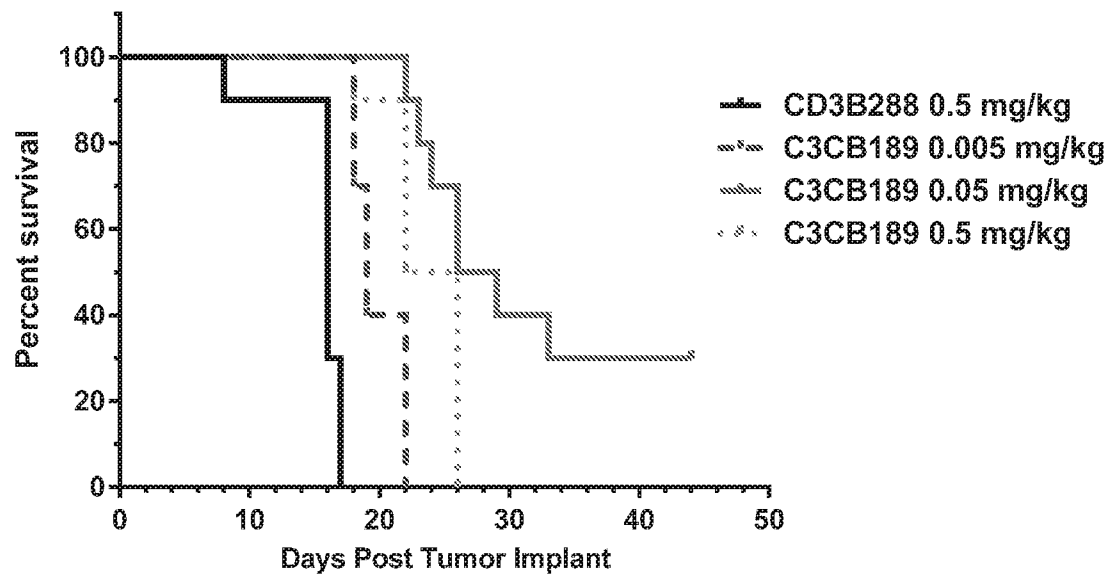


Fig. 68

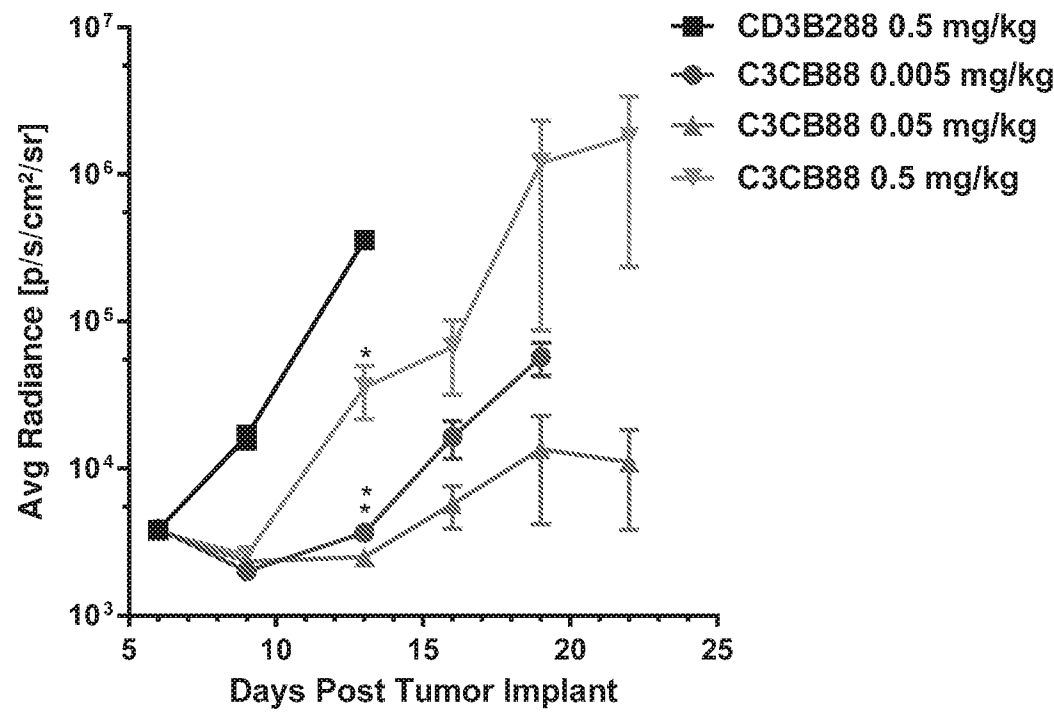


Fig. 69

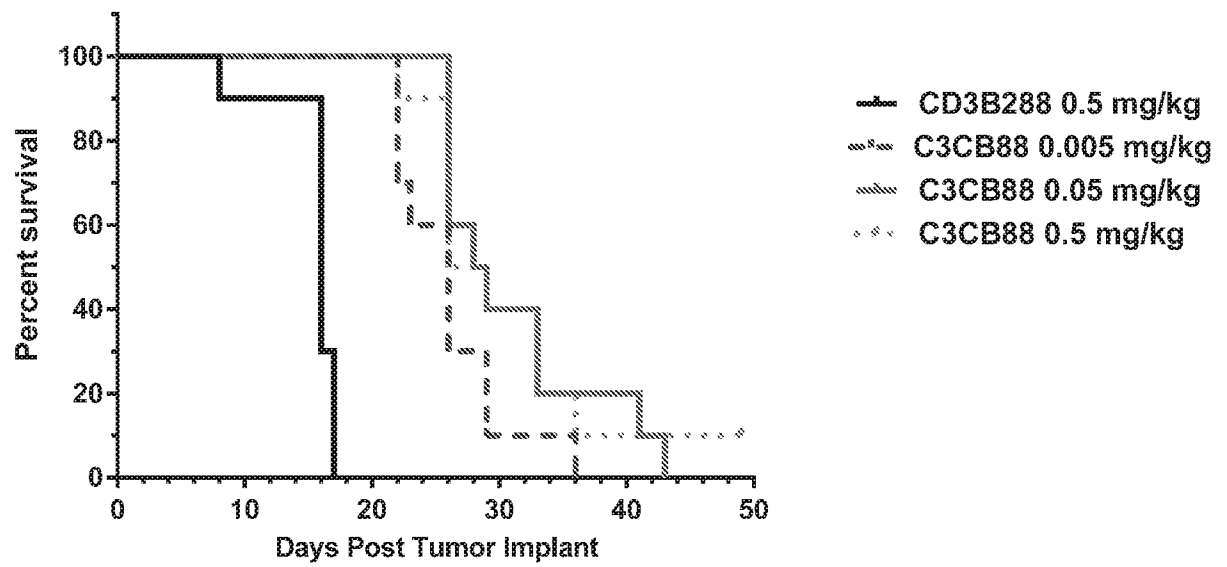


Fig. 70

```
25      EVQLLESGGGLVQR-GGSLRPSCAASGFTFS
27      EVQLLESGGGLVQPPGGSLRLSCAASGFTFS
87      EVQLLESGGGLVQP-GGSLRLSCAASGFTFS
89      EVQLLESGGGLVQP-GGSLRLSCAASGFTFS
      *****

25      SYMSWVRQAPGKGLEWVSVISGGGFTDY
27      SYMSWVRQAPGKGLEWVSVISGGGSFTSY
87      SYMSWVRQAPGKGLEWVSVISGGGFTDY
89      SYMSWVRQAPGKGLEWVSVISGGGFTDY
      *****.*.*.*

25      ADSVKGRFTISRDN SKNTLYLHMNSLRAED
27      ADSVKGRFTISRDN SNNTLYLQMSSLRAED
87      ADSVKGRFTISRDN SKNTLYLQMNSLRAED
89      ADSVKGRFTISRDN SKNTLYLHMNSLRAED
      *****.*.*.*

25      TAVYYCARMPLNSPHDYWGQGLTVTVSS
27      TAVYYCARMPLNSPHDCWGQGLTVTVSS
87      TAVYYCARMPLNSPHDYWGQGLTVTVSS
89      TAVYYCARMPLNSPHDYWGQGLTVTVSS
      **.******
```

Fig. 71

```
28      AIQMTQSPSSLSASVGDRVTTTCRASQGIR
30      AIQMTQSPSSLSASVGDRVTTTCRASQGIR
88      DIQMTQSPSSLSASVGDRVTTTCRASQGIR
90      AIQMTQSPSSLSASVGDRVTTTCRASQGIR
          *****

28      NDLGWYQQKPGKAPKLLIYAASSLQSGVPS
30      NDLGWYQQKPGKAPKLLIYAASSLQSGVPS
88      NDLGWYQQKPGKAPKLLIYAASSLQSGVPS
90      NDLGWYQQKPGKAPKLLIYAASSLQSGVPS
          *****

28      RFSGSGSGTDFTLTISSLQPEDFATYYCLQ
30      RFSGSGSGTDFTLTISSLQPEDFATYYCLQ
88      RFSGSGSGTDFTLTISSLQPEDFATYYCLQ
90      RFSGSGSGTDFTLTISSLQPEDFATYYCLQ
          *****

28      DYNIALTFGGGTKVEIK
30      DYNISLTFGGGTKVEIR
88      DYNYPLTFGGGTKVEIK
90      DYNYPLTFGGGTKVEIK
          ****.*****;
```

Fig. 72

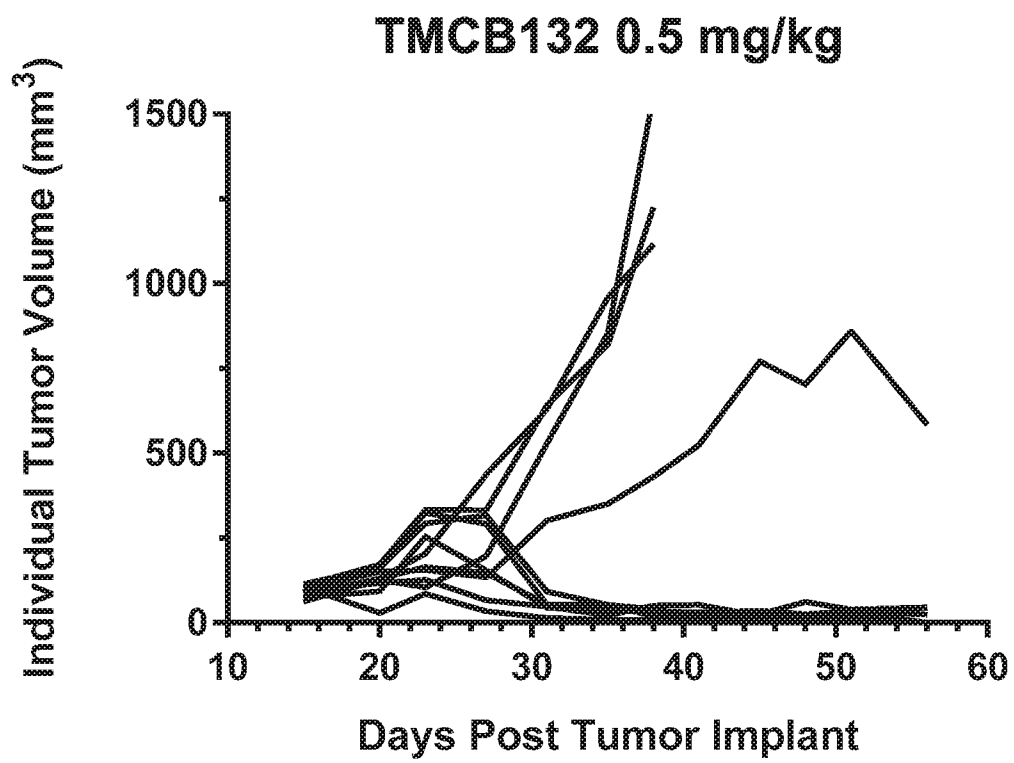
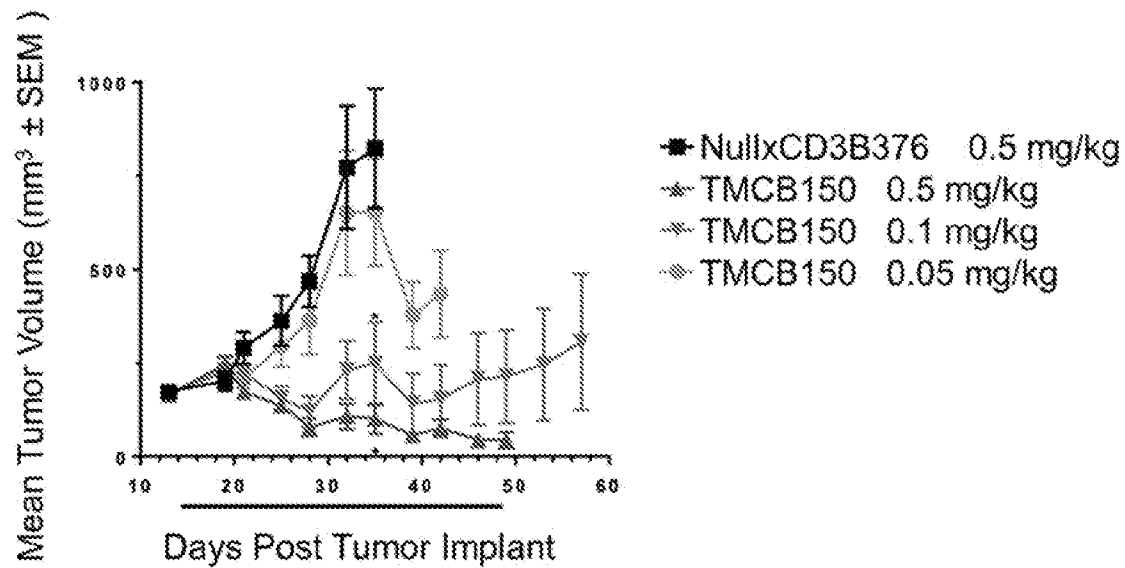


Fig. 73



* $p \leq 0.0001$ for treatment vs. control, calculated by the Linear Mixed-Effects analysis followed by pairwise comparisons. Bar below the X-axis represents the dosing period.

Fig. 74

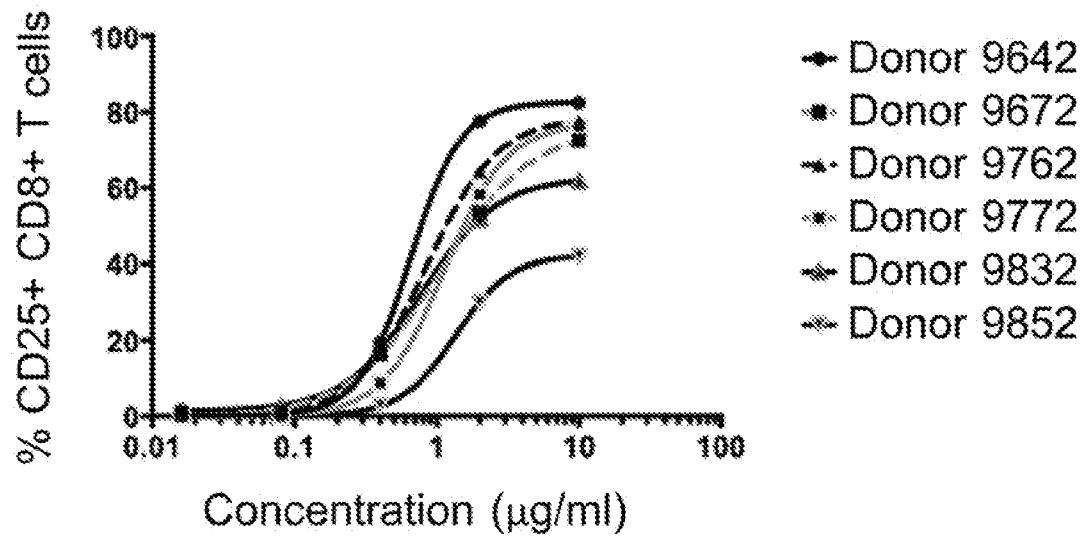


Fig. 75

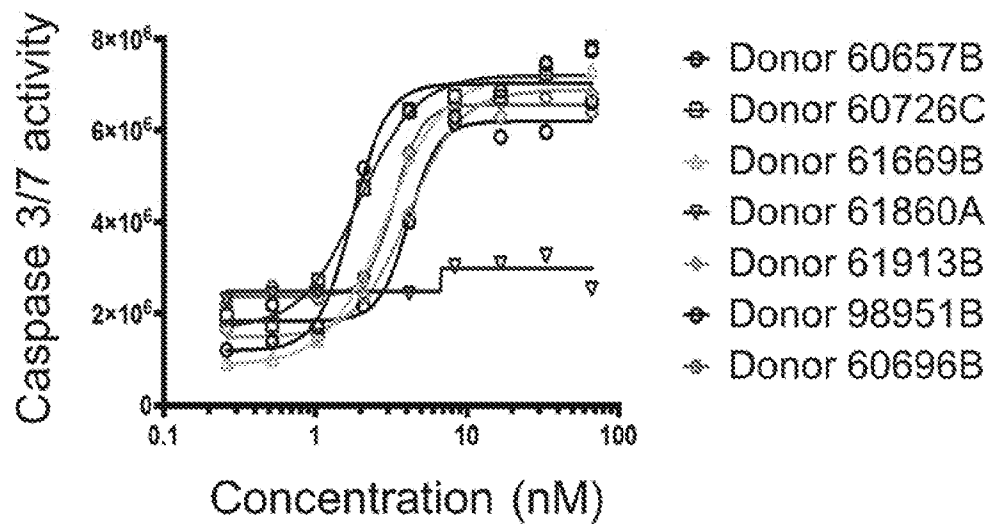
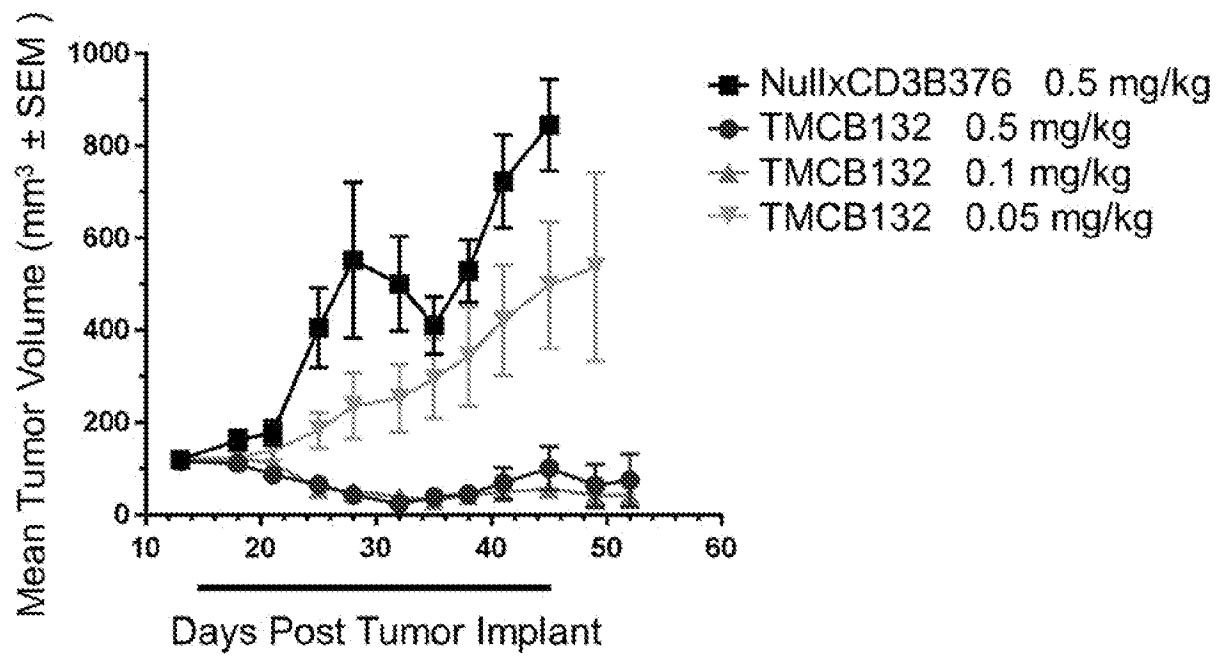


Fig. 76



SEQUENCE LISTING

<110> GAUDET, FRANCOIS
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<120> ANTI-CD3 ANTIBODIES AND USES THEREOF

<130> JBI5135WOPCT1

<150> 62/676,081

<151> 2018-05-24

<160> 729

<170> PatentIn version 3.5

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<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 1

Glu	Ile	Ser	Gly	Ser	Gly	Gly	Tyr	Thr	Asn	Tyr	Ala	Asp	Ser	Met	Lys
1				5					10					15	

Gly

<210> 2

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 2

Glu	Ile	Ser	Gly	Ser	Gly	Gly	Tyr	Thr	Asn	Tyr	Ala	Asp	Ser	Met	Lys
1				5					10					15	

Ser

<210> 3
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 3

Glu Ile Ser Gly Ser Gly Gly Tyr Thr Asn Tyr Ala Asp Ser Leu Lys
1 5 10 15

Gly

<210> 4
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 4

Arg Ala Ser Gln Ser Val Ser Asn Tyr Leu Ala
1 5 10

<210> 5
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 5

Gln Gln Arg Gly Asn Trp Pro Leu Thr
1 5

<210> 6
<211> 124
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 6

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Lys Ser Asp
20 25 30

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

Ser Glu Ile Ser Gly Ser Gly Gly Tyr Thr Asn Tyr Ala Asp Ser Met
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

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

Ala Arg Asp Ser Tyr Asp Ser Ser Leu Tyr Val Gly Asp Tyr Phe Asp
100 105 110

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 7

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 7

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Lys Ser Asp
20 25 30

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

Ser Glu Ile Ser Gly Ser Gly Gly Tyr Thr Asn Tyr Ala Asp Ser Met
50 55 60

Lys Ser Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

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

Ala Arg Asp Ser Tyr Asp Ser Ser Leu Tyr Val Gly Asp Tyr Phe Asp
100 105 110

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 8

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 8

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Lys Ser Asp
20 25 30

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

Ser Glu Ile Ser Gly Ser Gly Gly Tyr Thr Asn Tyr Ala Asp Ser Leu
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

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

Ala Arg Asp Ser Tyr Asp Ser Ser Leu Tyr Val Gly Asp Tyr Phe Asp
100 105 110

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 9

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 9

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

His 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 Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 10

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 10

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 Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 11

<211> 451

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 11

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Lys Ser Asp
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

35

40

45

Ser Glu Ile Ser Gly Ser Gly Gly Tyr Thr Asn Tyr Ala Asp Ser Met
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80

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

Ala Arg Asp Ser Tyr Asp Ser Ser Leu Tyr Val Gly Asp Tyr Phe Asp
 100 105 110

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys
 115 120 125

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

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

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

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
 180 185 190

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

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

Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
 225 230 235 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
 245 250 255

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

Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val
275 280 285

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

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305 310 315 320

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

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

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

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
370 375 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385 390 395 400

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

Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met
420 425 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
435 440 445

Leu Gly Lys
450

<210> 12

<211> 451
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 12

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Lys Ser Asp
20 25 30

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

Ser Glu Ile Ser Gly Ser Gly Gly Tyr Thr Asn Tyr Ala Asp Ser Met
50 55 60

Lys Ser Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

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

Ala Arg Asp Ser Tyr Asp Ser Ser Leu Tyr Val Gly Asp Tyr Phe Asp
100 105 110

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys
115 120 125

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

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

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

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val

180					185					190					
Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn
		195					200					205			
Val	Asp	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser
	210					215					220				
Lys	Tyr	Gly	Pro	Pro	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	Gly
225					230					235					240
Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met
				245					250					255	
Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	Gln
			260					265					270		
Glu	Asp	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val
		275					280					285			
His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Tyr
	290					295					300				
Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly
305					310					315					320
Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	Ser	Ser	Ile
				325					330					335	
Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val
			340					345					350		
Tyr	Thr	Leu	Pro	Pro	Ser	Gln	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser
		355					360					365			
Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu
						375					380				
Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro
385					390					395					400

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

Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met
420 425 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
435 440 445

Leu Gly Lys
450

<210> 13

<211> 451

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 13

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Lys Ser Asp
20 25 30

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

Ser Glu Ile Ser Gly Ser Gly Gly Tyr Thr Asn Tyr Ala Asp Ser Leu
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

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

Ala Arg Asp Ser Tyr Asp Ser Ser Leu Tyr Val Gly Asp Tyr Phe Asp
100 105 110

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys
115 120 125

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

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

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

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
180 185 190

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

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

Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
225 230 235 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
245 250 255

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

Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val
275 280 285

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

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305 310 315 320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile

325

330

335

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

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

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
 370 375 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
 385 390 395 400

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

Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met
 420 425 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
 435 440 445

Leu Gly Lys
 450

<210> 14

<211> 214

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 14

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

His 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 Leu
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
 100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
 115 120 125

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

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
 145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
 165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
 180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
 195 200 205

Phe Asn Arg Gly Glu Cys
 210

<210> 15

<211> 214

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 15

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 Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

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

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 16
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 16

Asp Gly Tyr Ser Ser Gly Arg Ser Thr Thr Tyr Ala Phe Asp Tyr
1 5 10 15

<210> 17
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 17

Met Pro Leu Asn Ser Pro His Asp Cys
1 5

<210> 18
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 18

Arg Ala Ser Gln Gly Ile Arg Asn Asp Leu Gly
1 5 10

<210> 19
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 19

Arg Ala Ser Gln Ser Val Ser Thr Tyr Tyr Leu Ala
1 5 10

<210> 20

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 20

Gln Val Gln Leu Gln Gln Ser Gly Pro Arg Leu Val Arg Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Phe Asn Asn
20 25 30

Asn Ala Ala Trp Ser 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 Leu Tyr Asp Tyr Ala
50 55 60

Val Ser Val Lys Ser Arg Ile Thr Val Asn Pro Asp Thr Ser Arg Asn
65 70 75 80

Gln Phe Thr Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Leu
85 90 95

Tyr Tyr Cys Ala Arg Gly Tyr Ser Ser Ser Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 21

<211> 7

<212> PRT

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 21

Gly Ala Ser Tyr Arg Ala Thr
1 5

<210> 22
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 22

Leu Gln Asp Tyr Asn Tyr Ala Leu Thr
1 5

<210> 23
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 23

Gln Gln Tyr Gly His Ser Pro Ile Thr
1 5

<210> 24
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 24

Leu Gln Asp Tyr Asn Tyr Ser Leu Thr
1 5

<210> 25
<211> 118
<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 25

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Arg Gly Gly
1 5 10 15

Ser Leu Arg Pro Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

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

Ser Val Ile Ser Gly Ser Gly Gly Phe Thr Asp Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

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

Ala Arg Met Pro Leu Asn Ser Pro His Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 26

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 26

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Ser

65		70		75		80									
Tyr	Leu	Gln	Met	Ser	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Phe	Tyr	Tyr
			85						90					95	
Cys	Ala	Arg	Met	Pro	Leu	Asn	Ser	Pro	His	Asp	Cys	Trp	Gly	Gln	Gly
			100					105					110		
Thr	Leu	Val	Thr	Val	Ser	Ser									
		115													

<210> 28
 <211> 107
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic polypeptide

<400> 28

Ala	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
1				5					10					15	
Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Gly	Ile	Arg	Asn	Asp
			20					25					30		
Leu	Gly	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	Leu	Gln	Asp	Tyr	Asn	Tyr	Ala	Leu
				85					90					95	
Thr	Phe	Gly	Gly	Gly	Thr	Lys	Val	Glu	Ile	Lys					
			100					105							

<210> 29

<211> 108
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 29

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 Thr Tyr
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 Tyr 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 His Ser Pro
85 90 95

Ile Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 30
<211> 107
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 30

Ala Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
20 25 30

Leu Gly 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 Leu Gln Asp Tyr Asn Tyr Ser Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Arg
100 105

<210> 31

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 31

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 Ala Thr Tyr
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 Tyr Asn Pro
85 90 95

Ile Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 32
<211> 445
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 32

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Arg Gly Gly
1 5 10 15

Ser Leu Arg Pro Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

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

Ser Val Ile Ser Gly Ser Gly Gly Phe Thr Asp Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

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

Ala Arg Met Pro Leu Asn Ser Pro His Asp Tyr Trp Gly Gln Gly Thr
100 105 110

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln

370

375

380

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

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

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

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

<210> 33

<211> 451

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 33

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

Tyr Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45

Gly Gly Ile Ile Pro Ile Ser Gly Arg Ala Asn Tyr Ala Gln Lys Phe
 50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu 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 Asp Gly Tyr Ser Ser Gly Arg Ser Thr Thr Tyr Ala Phe Asp

100				105				110							
Tyr	Trp	Gly 115	Gln	Gly	Thr	Leu	Val 120	Thr	Val	Ser	Ser	Ala 125	Ser	Thr	Lys
Gly	Pro 130	Ser	Val	Phe	Pro	Leu 135	Ala	Pro	Cys	Ser	Arg 140	Ser	Thr	Ser	Glu
Ser 145	Thr	Ala	Ala	Leu	Gly 150	Cys	Leu	Val	Lys	Asp 155	Tyr	Phe	Pro	Glu	Pro 160
Val	Thr	Val	Ser	Trp 165	Asn	Ser	Gly	Ala 170	Leu	Thr	Ser	Gly	Val	His 175	Thr
Phe	Pro	Ala	Val 180	Leu	Gln	Ser	Ser	Gly 185	Leu	Tyr	Ser	Leu	Ser 190	Ser	Val
Val	Thr 195	Val	Pro	Ser	Ser	Ser	Leu 200	Gly	Thr	Lys	Thr	Tyr 205	Thr	Cys	Asn
Val 210	Asp	His	Lys	Pro	Ser	Asn 215	Thr	Lys	Val	Asp	Lys 220	Arg	Val	Glu	Ser
Lys 225	Tyr	Gly	Pro	Pro	Cys 230	Pro	Pro	Cys	Pro	Ala 235	Pro	Glu	Ala	Ala	Gly 240
Gly	Pro	Ser	Val	Phe 245	Leu	Phe	Pro	Pro	Lys 250	Pro	Lys	Asp	Thr	Leu 255	Met
Ile	Ser	Arg	Thr 260	Pro	Glu	Val	Thr	Cys 265	Val	Val	Val	Asp	Val	Ser	Gln
Glu	Asp 275	Pro	Glu	Val	Gln	Phe	Asn 280	Trp	Tyr	Val	Asp	Gly 285	Val	Glu	Val
His 290	Asn	Ala	Lys	Thr	Lys	Pro 295	Arg	Glu	Glu	Gln	Phe 300	Asn	Ser	Thr	Tyr
Arg 305	Val	Val	Ser	Val	Leu 310	Thr	Val	Leu	His	Gln 315	Asp	Trp	Leu	Asn	Gly 320

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

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

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

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
370 375 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385 390 395 400

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

Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met
420 425 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
435 440 445

Leu Gly Lys
450

<210> 34

<211> 446

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 34

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

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser
20 25 30

Tyr Ser Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
35 40 45

Val Ser Val Ile Ser Gly Gly Gly Ser Phe Thr Ser Tyr Ala Asp Ser
50 55 60

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Asn Asn Thr Leu
65 70 75 80

Tyr Leu Gln Met Ser Ser Leu Arg Ala Glu Asp Thr Ala Phe Tyr Tyr
85 90 95

Cys Ala Arg Met Pro Leu Asn Ser Pro His Asp Cys Trp Gly Gln Gly
100 105 110

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

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

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

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

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

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

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

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

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro

	245		250		255
Glu Val Thr	Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val				
	260		265		270
Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr					
	275		280		285
Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val					
	290		295		300
Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys					
305		310		315	320
Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser					
	325		330		335
Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro					
	340		345		350
Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val					
	355		360		365
Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly					
	370		375		380
Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp					
385		390		395	400
Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp					
	405		410		415
Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His					
	420		425		430
Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys					
	435		440		445

<210> 35
 <211> 214
 <212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 35

Ala Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
20 25 30

Leu Gly 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 Leu Gln Asp Tyr Asn Tyr Ala Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

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

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
 195 200 205

Phe Asn Arg Gly Glu Cys
 210

<210> 36
 <211> 215
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic polypeptide

<400> 36

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 Thr Tyr
 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 Tyr 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 His Ser Pro
 85 90 95

Ile Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
 100 105 110

Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
 115 120 125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
 130 135 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
 145 150 155 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
 165 170 175

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
 180 185 190

Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
 195 200 205

Ser Phe Asn Arg Gly Glu Cys
 210 215

<210> 37
 <211> 214
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic polypeptide

<400> 37

Ala Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
 20 25 30

Leu Gly 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 Leu Gln Asp Tyr Asn Tyr Ser Leu
 85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Arg Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

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

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 38

<211> 215

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 38

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 Ala Thr Tyr
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 Tyr Asn Pro
85 90 95

Ile Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
100 105 110

Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
115 120 125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
130 135 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145 150 155 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
165 170 175

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
180 185 190

Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
195 200 205

Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 39

<211> 354

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 39

gaggtgcagc tgctggaaaag cggcggaggc ctggtgcaga gaggaggaag cctgagaccc	60
agctgtgccg ccagcggcctt caccttcagc agctacagca tgagctgggt caggcaggcc	120
cctggcaaag gactggagtg ggtgagcgtg attagcggca gcggcggcctt caccgattac	180
gccgacagcg tgaagggcag gttcaccatc agcagggaca atagcaagaa caccctgtac	240
ctgcacatga acagcctgag ggccgaggac accgccgtgt actactgcgc caggatgccc	300
ctgaacagcc ctcacgacta ctggggccag ggaaccctgg tgaccgtgtc cagc	354

<210> 40
 <211> 372
 <212> DNA
 <213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 40	
caggtgcagc tggtgcagag cggcgcggaa gtgaaaaaac cgggcagcag cgtgaaagt	60
agctgcaaag cgagcggcgg caccttcagc tcctattaca ttagctgggt gcgccaggcg	120
ccgggccagg gcctggaatg gatgggtggc attatcccaa tcagtgggcg tgctaattat	180
gcgcagaaat ttcagggccg cgtgaccatt accgctgatg aaagcaccag caccgcgtat	240
atggaactga gcagcctgcg cagcgaagat accgcggtgt attattgcgc gcgcgacggc	300
tacagtagtg gacgtagcac aacatacgca tttgactatt ggggccaggg caccctggtg	360
accgtgtcga gt	372

<210> 41
 <211> 357
 <212> DNA
 <213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 41	
gaagtgcagc tgctggagag cggaggagga ctggtgcagc ctcctggcgg aagcctgaga	60
ctgagctgcg ccgctagcgg cttcaccttc agcagctaca gcatgagctg ggtgagacag	120
gctcctggca agggcctgga gtgggtgagc gtgatcagcg gcggaggcag ctttaccagc	180
tacgccgaca gcgtgaaggg caggttcacc atcagcaggg acaacagcaa caacaccctg	240

tacctgcaga tgagcagcct gagggccgag gacaccgcct tctactactg cgccaggatg	300
cccctgaaca gcccccatga ctgctgggga cagggcaccc tggtgaccgt gagcagc	357

<210> 42
 <211> 321
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 42	
gccatccaga tgaccagag ccctagcagc ctgagcgcta gcgtgggcga cagggtgacc	60
atcacctgca gggccagcca gggcatcaga aacgacctgg gctggtacca gcagaagccc	120
ggcaaggccc ccaagctgct gatctacgcc gccagcagcc tgcagagcgg agtgcctagc	180
aggttcagcg gaagcggcag cggcaccgac ttcaccctga ccatcagcag cctgcagccc	240
gaggacttcg ccacctacta ctgcctgcag gactacaact acgccctgac attcggcggc	300
ggcaccaagg tggagatcaa g	321

<210> 43
 <211> 324
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 43	
gaaattgtgc tgaccagag cccgggcacc ctgagcctga gcccgggcga acgcgcgacc	60
ctgagctgcc gcgcgagcca gagcgtttcc acatactacc tggcgtggta tcagcagaaa	120
ccggggccagg cgccgcgcct gctgatttac ggtgcctcct atcgcgcgac cggcattccg	180
gatcgcttta gcggcagcgg ttccggcacc gattttaccc tgaccattag ccgcctggaa	240
ccggaagatt ttgcggtgta ttattgccag cagtacggtc acagcccgat tacttttggc	300
cagggcacca aagtggaaat caaa	324

<210> 44
 <211> 321
 <212> DNA
 <213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 44

gccatccaga tgacccagag ccctagcagc ctgagcgcta gcgtgggcga cagggtgacc	60
atcacctgca gggccagcca gggcatcagg aacgacctgg gctggtacca gcagaagccc	120
ggcaaggccc ccaagctgct gatctacgcc gccagcagcc tgcagagcgg agtgcctagc	180
aggttcagcg gcagcggaag cggcaccgac ttcaccctga ccatctccag cctgcagccc	240
gaggacttcg ccacctacta ctgcctgcag gactacaact acagcctgac cttcggcggc	300
ggcaccaagg tggagatcag g	321

<210> 45

<211> 324

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 45

gaaattgtgc tgacccagag cccgggcacc ctgagcctga gcccgggcga acgcgcgacc	60
ctgagctgcc gcgcgagcca gagcggtgcc acctattatc ttgcgtggta tcagcagaaa	120
ccggggccagg cgccgcgcct gctgatttac ggtgcatcct cccgtgcgac cggcattccg	180
gatcgcttta gcggcagcgg ttccggcacc gattttaccc tgaccattag ccgcctggaa	240
ccggaagatt ttgcggtgta ttattgccag cagtacggct ataaccaat tacctttggc	300
cagggcacca aagtggaaat caaa	324

<210> 46

<211> 1335

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 46

gaggtgcagc tgctggaaag cggcggaggc ctggtgcaga gaggaggaag cctgagaccc	60
agctgtgccg ccagcggctt caccttcagc agctacagca tgagctgggt caggcaggcc	120
cctggcaaag gactggagtg ggtgagcgtg attagcggca gcggcggctt caccgattac	180

gccgacagcg tgaagggcag gttcaccatc agcagggaca atagcaagaa caccctgtac	240
ctgcacatga acagcctgag ggccgaggac accgccgtgt actactgcgc caggatgccc	300
ctgaacagcc ctcacgacta ctggggccag ggaaccctgg tgaccgtgtc cagcgcttcc	360
accaagggcc catccgtctt ccccttggcg ccctgctcca ggagcacctc cgagagcaca	420
gccgccctgg gctgcctggg caaggactac ttccccgaac cggtgacggg gtcgtggaac	480
tcaggcgccc tgaccagcgg cgtgcacacc ttcccggctg tcctacagtc ctcaggactc	540
tactccctca gcagcgtggg gaccgtgccc tccagcagct tgggcacgaa aacctacacc	600
tgcaacgtag atcacaagcc cagcaacacc aagggtggaca agagagttga gtccaaatat	660
ggccccccat gcccaccatg cccagcacct gaggccgccg ggggaccatc agtcttcctg	720
ttccccccaa aacccaagga cactctcatg atctcccga cccctgaggt cacgtgcgtg	780
gtggtggacg tgagccagga agaccccgag gtccagttca actggtacgt ggatggcgtg	840
gaggtgcata atgccaagac aaagccgcgg gaggagcagt tcaacagcac gtaccgtgtg	900
gtcagcgtcc tcaccgtcct gcaccaggac tggctgaacg gcaaggagta caagtgaag	960
gtctccaaca aaggcctccc gtcctccatc gagaaaacca tctccaaagc caaagggcag	1020
ccccgagagc cacaggtgta caccctgccc ccatcccagg aggagatgac caagaaccag	1080
gtcagcctga cctgcctggg caaaggcttc taccacagcg acatcgccgt ggagtgggag	1140
agcaatgggc agccggagaa caactacaag accacgcctc ccgtgctgga ctccgacggc	1200
tccttcttcc tctacagcag gctaaccgtg gacaagagca ggtggcagga ggggaatgtc	1260
ttctcatgct ccgtgatgca tgaggctctg cacaaccact acacacagaa gagcctctcc	1320
ctgtctctgg gtaaa	1335

<210> 47

<211> 1353

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 47

caggtgcagc tggtgcagag cggcgcggaa gtgaaaaaac cgggcagcag cgtgaaagt	60

agctgcaaag cgagcggcgg caccttcagc tcctattaca ttagctgggt gcgccaggcg	120

ccgggccagg gcctggaatg gatgggtggc attatcccaa tcagtgggcg tgctaattat	180
gcgcagaaat ttcagggccg cgtgaccatt accgctgatg aaagcaccag caccgcgtat	240
atggaactga gcagcctgcg cagcgaagat accgcggtgt attattgcgc gcgcgacggc	300
tacagtagtg gacgtagcac aacatacgca ttgactatt ggggccaggg caccctggtg	360
accgtgtcga gtgcttcac caagggccca tccgtcttcc ccctggcgcc ctgctccagg	420
agcacctccg agagcacagc cgccctgggc tgcctggtca aggactactt ccccgaaccg	480
gtgacggtgt cgtggaactc aggcgcctg accagcggcg tgcacacctt cccggctgtc	540
ctacagtcct caggactcta ctccctcagc agcgtggtga ccgtgccctc cagcagcttg	600
ggcacgaaaa cctacacctg caacgtagat cacaagccca gcaacaccaa ggtggacaag	660
agagttgagt ccaaatatgg tccccatgc ccaccatgcc cagcacctga ggccgccggg	720
ggaccatcag tcttcctgtt cccccaaaa cccaaggaca ctctcatgat ctcccggacc	780
cctgaggtca cgtgcgtggt ggtggacgtg agccaggaag accccgaggt ccagttcaac	840
tggtacgtgg atggcgtgga ggtgcataat gccaaagaca agccgcggga ggagcagttc	900
aacagcacgt accgtgtggt cagcgtcctc accgtcctgc accaggactg gctgaacggc	960
aaggagtaca agtgcaaggt ctccaacaaa ggcctcccgt cctccatcga gaaaaccatc	1020
tccaaagcca aagggcagcc ccgagagcca caggtgtaca ccctgcccc atcccaggag	1080
gagatgacca agaaccaggt cagcctgacc tgcctggtca aaggcttcta cccagcgac	1140
atcgccgtgg agtgggagag caatgggcag ccggagaaca actacaagac cacgcctccc	1200
gtgctggact ccgacggctc cttcttcctc tacagcaggc taaccgtgga caagagcagg	1260
tggcaggagg ggaatgtctt ctcatgctcc gtgatgcatg aggctctgca caaccactac	1320
acacagaaga gcctctccct gtctctgggt aaa	1353

<210> 48

<211> 1338

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 48

gaagtgcagc tgctggagag cggaggagga ctggtgcagc ctccctggcgg aagcctgaga	60

ctgagctgcg ccgctagcgg cttcaccttc agcagctaca gcatgagctg ggtgagacag	120
gctcctggca agggcctgga gtgggtgagc gtgatcagcg gcggaggcag ctttaccagc	180
tacgccgaca gcgtgaaggg caggttcacc atcagcaggg acaacagcaa caacaccctg	240
tacctgcaga tgagcagcct gagggccgag gacaccgcct tctactactg cgccaggatg	300
cccctgaaca gccccatga ctgctgggga cagggcaccc tggtgaccgt gagcagcgct	360
tccaccaagg gcccatccgt cttccccctg gcgccctgct ccaggagcac ctccgagagc	420
acagccgccc tgggctgcct ggtcaaggac tacttccccg aaccggtgac ggtgtcgtgg	480
aactcaggcg ccctgaccag cggcgtgcac accttcccgg ctgtcctaca gtcctcagga	540
cttactctcc tcagcagcgt ggtgaccgtg cctccagca gcttgggcac gaaaacctac	600
acctgcaacg tagatcacia gcccagcaac accaaggtgg acaagagagt tgagtccaaa	660
tatggtcccc catgcccacc atgccagca cctgaggccg ccgggggacc atcagtcttc	720
ctgttcccc caaaaccaa ggacactctc atgatctccc ggaccctga ggtcacgtgc	780
gtggtggtgg acgtgagcca ggaagacccc gaggtccagt tcaactggta cgtggatggc	840
gtggaggtgc ataatgcaa gacaaagccg cgggaggagc agttcaacag cacgtaccgt	900
gtggtcagcg tcctcaccgt cctgcaccag gactggctga acggcaagga gtacaagtgc	960
aaggtctcca acaaaggcct cccgtcctcc atcgagaaaa ccatctcaa agccaaaggg	1020
cagccccgag agccacaggt gtacaccctg cccccatccc aggaggagat gaccaagaac	1080
caggtcagcc tgacctgcct ggtcaaaggc ttctaccca gcgacatcgc cgtggagtgg	1140
gagagcaatg ggcagccgga gaacaactac aagaccacgc ctcccgtgct ggactccgac	1200
ggctccttct tcctctacag caggctaacc gtggacaaga gcaggtggca ggaggggaat	1260
gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacaca gaagagcctc	1320
tccctgtctc tgggtaaa	1338

<210> 49

<211> 642

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 49

gccatccaga tgaccagag ccctagcagc ctgagcgcta gcgtgggcga cagggtgacc	60
atcacctgca gggccagcca gggcatcaga aacgacctgg gctggtacca gcagaagccc	120
ggcaaggccc ccaagctgct gatctacgcc gccagcagcc tgcagagcgg agtgcctagc	180
aggttcagcg gaagcggcag cggcaccgac ttcaccctga ccatcagcag cctgcagccc	240
gaggacttcg ccacctaata ctgcctgcag gactacaact acgccctgac attcggcggc	300
ggcaccaagg tggagatcaa gcgtacggtg gctgcacat ctgtcttcat cttcccgcca	360
tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat	420
cccagagagg ccaaagtaca gtggaagggtg gataacgccc tccaatcggg taactcccag	480
gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg	540
ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc	600
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<210> 50

<211> 645

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 50

gaaattgtgc tgaccagag cccgggcacc ctgagcctga gcccgggcga acgcgcgacc	60
ctgagctgcc gcgcgagcca gagcggttcc acatactacc tggcgtggta tcagcagaaa	120
ccgggccagg cgccgcgcct gctgatttac ggtgcctcct atcgcgcgac cggcattccg	180
gatcgcttta gcggcagcgg ttccggcacc gattttaccc tgaccattag ccgcctggaa	240
ccggaagatt ttgcggtgta ttattgccag cagtacggtc acagcccgat tacttttggc	300
cagggcacca aagtggaaat caaacgtacg gtggctgcac catctgtctt catcttcccg	360
ccatctgatg agcagttgaa atctggaact gcctctgttg tgtgcctgct gaataacttc	420
tatcccagag aggccaaagt acagtggaag gtggataacg ccctccaatc gggtaactcc	480
caggagagtg tcacagagca ggacagcaag gacagcacct acagcctcag cagcacctg	540
acgctgagca aagcagacta cgagaaacac aaagtctacg cctgcgaagt caccatcag	600
ggcctgagct cgcccgtcac aaagagcttc aacaggggag agtgt	645

<210> 51
 <211> 642
 <212> DNA
 <213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 51
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 atcacctgca gggccagcca gggcatcagg aacgacctgg gctggtacca gcagaagccc 120
 ggcaaggccc ccaagctgct gatctacgcc gccagcagcc tgcagagcgg agtgcctagc 180
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 ggcaccaagg tggagatcag gcgtacggtg gctgcaccat ctgtcttcat cttcccgcca 360
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 cccagagagg ccaaagtaca gtggaagggtg gataacgccc tccaatcggg taactcccag 480
 gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg 540
 ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc 600
 ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt 642

<210> 52
 <211> 110
 <212> PRT
 <213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 52

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 Asn Ile Gly Thr Tyr
 20 25 30

Lys Phe Val Ser Trp Tyr Gln Gln His Pro Asp Lys Ala Pro Lys Val
 35 40 45

Leu Leu Tyr Glu Val Ser Lys Arg Pro Ser Gly Val Ser Ser 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 Gln Ala Asp Tyr His Cys Val Ser Tyr Ala Gly Ser
85 90 95

Gly Thr Leu Leu Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 53

<211> 109

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 53

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

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

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

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

Ala Lys Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
100 105

<210> 54
<211> 98
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 54

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 Glu 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

<210> 55
<211> 95
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 55

Ala Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp

20

25

30

Leu Gly 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 Leu Gln Asp Tyr Asn Tyr Pro
 85 90 95

<210> 56

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 56

Ser Tyr Trp Ile Ser
 1 5

<210> 57

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 57

Ile Ile Tyr Pro Gly Asp Ser Tyr Thr Arg Tyr Ser Pro Ser Phe Gln
 1 5 10 15

Gly

<210> 58

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 58

Asp Tyr Glu Trp Glu Leu Phe Asp Ser Arg Leu Asp Tyr
1 5 10

<210> 59

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 59

Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn
1 5 10

<210> 60

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 60

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> 61

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 61

Gln Gln Ser Tyr Ser Thr Pro
1 5

<210> 62

<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 62

Asn Ala Trp Ile Ser
1 5

<210> 63
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 63

Trp Ile Asn Pro Glu Ser Gly Arg Ala Asn Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 64
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 64

Glu Leu Tyr Tyr Leu Val Tyr Ser Thr Tyr Tyr Tyr Ala Phe Asp Tyr
1 5 10 15

<210> 65
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 65

Arg Ala Ser Gln Ser Ile Asp Arg Trp Leu Asn
1 5 10

<210> 66
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 66

Gln Gln Ser Pro Arg Tyr Pro Leu Thr
1 5

<210> 67
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 67

Ser Tyr Asp Ile Ser
1 5

<210> 68
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 68

Gly Ile Ile Pro Ile Glu Gly Thr Ala Asn Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 69
<211> 10
<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 69

Asp Tyr Pro Ala Gly Tyr Gly Phe Asp Tyr
1 5 10

<210> 70

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 70

Arg Ala Ser Gln Ser Val Ser Ser Ser Tyr Leu Ala
1 5 10

<210> 71

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 71

Gly Ala Ser Ser Arg Ala Thr
1 5

<210> 72

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 72

Gln Gln Tyr Gly Ser Ser Pro Leu Thr
1 5

<210> 73

<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 73

Ser Asp Trp Met Ser
1 5

<210> 74
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 74

Ala Ile Ser Gly Asn Gly Gly Ser Thr Glu Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 75
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 75

Asp Pro Tyr Tyr Tyr Tyr Asp Gly Asp Ser Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> 76
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 76

Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn
 1 5 10

<210> 77
 <211> 374
 <212> PRT
 <213> Homo sapiens

<400> 77

Met Val Leu Trp Glu Ser Pro Arg Gln Cys Ser Ser Trp Thr Leu Cys
 1 5 10 15

Glu Gly Phe Cys Trp Leu Leu Leu Leu Pro Val Met Leu Leu Ile Val
 20 25 30

Ala Arg Pro Val Lys Leu Ala Ala Phe Pro Thr Ser Leu Ser Asp Cys
 35 40 45

Gln Thr Pro Thr Gly Trp Asn Cys Ser Gly Tyr Asp Asp Arg Glu Asn
 50 55 60

Asp Leu Phe Leu Cys Asp Thr Asn Thr Cys Lys Phe Asp Gly Glu Cys
 65 70 75 80

Leu Arg Ile Gly Asp Thr Val Thr Cys Val Cys Gln Phe Lys Cys Asn
 85 90 95

Asn Asp Tyr Val Pro Val Cys Gly Ser Asn Gly Glu Ser Tyr Gln Asn
 100 105 110

Glu Cys Tyr Leu Arg Gln Ala Ala Cys Lys Gln Gln Ser Glu Ile Leu
 115 120 125

Val Val Ser Glu Gly Ser Cys Ala Thr Asp Ala Gly Ser Gly Ser Gly
 130 135 140

Asp Gly Val His Glu Gly Ser Gly Glu Thr Ser Gln Lys Glu Thr Ser
 145 150 155 160

Thr Cys Asp Ile Cys Gln Phe Gly Ala Glu Cys Asp Glu Asp Ala Glu
 165 170 175

Asp Val Trp Cys Val Cys Asn Ile Asp Cys Ser Gln Thr Asn Phe Asn
180 185 190

Pro Leu Cys Ala Ser Asp Gly Lys Ser Tyr Asp Asn Ala Cys Gln Ile
195 200 205

Lys Glu Ala Ser Cys Gln Lys Gln Glu Lys Ile Glu Val Met Ser Leu
210 215 220

Gly Arg Cys Gln Asp Asn Thr Thr Thr Thr Thr Lys Ser Glu Asp Gly
225 230 235 240

His Tyr Ala Arg Thr Asp Tyr Ala Glu Asn Ala Asn Lys Leu Glu Glu
245 250 255

Ser Ala Arg Glu His His Ile Pro Cys Pro Glu His Tyr Asn Gly Phe
260 265 270

Cys Met His Gly Lys Cys Glu His Ser Ile Asn Met Gln Glu Pro Ser
275 280 285

Cys Arg Cys Asp Ala Gly Tyr Thr Gly Gln His Cys Glu Lys Lys Asp
290 295 300

Tyr Ser Val Leu Tyr Val Val Pro Gly Pro Val Arg Phe Gln Tyr Val
305 310 315 320

Leu Ile Ala Ala Val Ile Gly Thr Ile Gln Ile Ala Val Ile Cys Val
325 330 335

Val Val Leu Cys Ile Thr Arg Lys Cys Pro Arg Ser Asn Arg Ile His
340 345 350

Arg Gln Lys Gln Asn Thr Gly His Tyr Ser Ser Asp Asn Thr Thr Arg
355 360 365

Ala Ser Thr Arg Leu Ile
370

<210> 78
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 78

Ser Asp Ala Met His
1 5

<210> 79
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 79

Glu Ile Ser Gly Ser Gly Gly Tyr Thr Asn Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 80
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 80

Asp Ser Tyr Asp Ser Ser Leu Tyr Val Gly Asp Tyr Phe Asp Tyr
1 5 10 15

<210> 81
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 81

Arg Ala Ser Gln Ser Val Ser Ser Tyr Leu Ala
1 5 10

<210> 82

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 82

Asp Ala Ser Asn Arg Ala Thr
1 5

<210> 83

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 83

Gln Gln Arg Ser Asn Trp Pro Leu Thr
1 5

<210> 84

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 84

Ser Tyr Ala Ile Ser
1 5

<210> 85

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 85

Trp Ile Ser Pro Tyr Asn Gly Asn Ala Asn Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 86

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 86

Asp Ser Asp Arg Ser Tyr Asn Leu Asp Tyr
1 5 10

<210> 87

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 87

Arg Ala Ser Gln Ser Ile Ser Gly Trp Leu Asn
1 5 10

<210> 88

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 88

Gln Gln Ser Tyr Ser Thr Pro Leu Thr
1 5

<210> 89
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 89

Ser Tyr Trp Ile Gly
1 5

<210> 90
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 90

Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe Gln
1 5 10 15

Gly

<210> 91
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 91

Gly Leu Pro Ile Trp Tyr Leu Asp Tyr
1 5

<210> 92
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 92

Arg Ala Ser Gln Ser Val Ala Ser Asp Leu Ala
1 5 10

<210> 93

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 93

Phe Ala Ser Asn Arg Ala Thr
1 5

<210> 94

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 94

Gln Gln Ser Ile Thr Trp Pro Phe Thr
1 5

<210> 95

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 95

Ser Tyr Ala Ile Ser
1 5

<210> 96

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 96

Trp	Ile	Ile	Pro	Tyr	Asn	Gly	Asn	Ala	Asn	Tyr	Ala	Gln	Lys	Phe	Gln
1				5					10					15	

Gly

<210> 97

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 97

Val	Asn	Ser	Ala	Ala	Leu	Val	Trp	Glu	Arg	Leu	Asp	Tyr
1				5					10			

<210> 98

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 98

Gly	Ile	Ile	Pro	Ile	Phe	Gly	Thr	Ala	Asn	Tyr	Ala	Gln	Lys	Phe	Gln
1				5					10					15	

Gly

<210> 99

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 99

Ala Ser Arg Val Trp His Ala Ser Tyr Gly Tyr Leu Asp Tyr
1 5 10

<210> 100
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 100

Arg Ala Ser Gln Ser Val Ser Lys Trp Leu Ala
1 5 10

<210> 101
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 101

Gln Gln Arg Phe Thr Ala Pro Trp Thr
1 5

<210> 102
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 102

Gly Trp Ala Tyr Asp Arg Gly Leu Asp Tyr
1 5 10

<210> 103
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 103

Lys Ser Ser Gln Ser Val Leu Tyr Ser Ser Asn Asn Lys Asn Tyr Leu
1 5 10 15

Ala

<210> 104

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 104

Trp Ala Ser Thr Arg Glu Ser
1 5

<210> 105

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 105

Gln Gln Tyr Tyr Ser Thr Pro Leu Thr
1 5

<210> 106

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 106

Ala Tyr His Tyr Ser Lys Gly Leu Asp Tyr
1 5 10

<210> 107

<211> 5

<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 107

Asp Tyr Ala Ile Ser
1 5

<210> 108
<211> 17
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 108

Arg Ile Asp Pro Ile Glu Gly Thr Ala Asn Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 109
<211> 17
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 109

Asp Arg Tyr Tyr Tyr Asp Gly Val Tyr Trp Tyr Ser Asp Tyr Phe Asp
1 5 10 15

Tyr

<210> 110
<211> 122
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 110

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 Trp Ile Ser Pro Tyr Asn Gly Asn Ala Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu 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 Val Asn Ser Ala Ala Leu Val Trp Glu Arg Leu Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 111

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 111

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Asp Arg Trp
20 25 30

Leu Asn 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 Ser Pro Arg Tyr Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 112

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 112

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 Lys Ser Tyr
20 25 30

Asp Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Gly Ile Ile Pro Ile Glu Gly Thr Ala Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu 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 Asp Tyr Pro Ala Gly Tyr Gly Phe Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 113
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 113

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

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 114
<211> 125
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 114

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Ser Asp
20 25 30

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

Ser Ala Ile Ser Gly Asn Gly Gly Ser Thr Glu Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

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

Ala Arg Asp Pro Tyr Tyr Tyr Tyr Asp Gly Asp Ser Tyr Tyr Gly Met
100 105 110

Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 115

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 115

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20 25 30

Leu Asn 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 Ser Tyr Ser Thr Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 116
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 116

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Lys Ser Asp
20 25 30

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

Ser Glu Ile Ser Gly Ser Gly Gly Tyr Thr Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

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

Ala Arg Asp Ser Tyr Asp Ser Ser Leu Tyr Val Gly Asp Tyr Phe Asp
100 105 110

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 117
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 117

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 Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 118
<211> 125
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 118

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 Asp Asp Tyr
20 25 30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Arg Ile Asp Pro Ile Glu Gly Thr Ala Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu 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 Asp Arg Tyr Tyr Tyr Asp Gly Val Tyr Trp Tyr Ser Asp Tyr
100 105 110

Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
115 120 125

<210> 119

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 119

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20 25 30

Leu Asn 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 Ser Tyr Ser Thr Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 120

<211> 122

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 120

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 Ser Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Tyr 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 Asp Tyr Glu Trp Glu Leu Phe Asp Ser Arg Leu Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 121
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 121

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 Trp Ile Ser Pro Tyr Asn Gly Asn Ala Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu 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 Asp Ser Asp Arg Ser Tyr Asn Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 122
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 122

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Gly Trp
20 25 30

Leu Asn 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 Ser Tyr Ser Thr Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 123

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 123

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 Gly Leu Pro Ile Trp Tyr Leu Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser Ala
115

<210> 124

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 124

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 Asp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Phe 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 Ser Ile Thr Trp Pro Phe
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 125
 <211> 122
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> Description of Artificial Sequence: Synthetic polypeptide

 <400> 125

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 Trp Ile Ile Pro Tyr Asn Gly Asn Ala Asn Tyr Ala Gln Lys Phe
 50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu 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 Val Asn Ser Ala Ala Leu Val Trp Glu Arg Leu Asp Tyr Trp
 100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 126
 <211> 123
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> Description of Artificial Sequence: Synthetic polypeptide

 <400> 126

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 Glu 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 Ala Ser Arg Val Trp His Ala Ser Tyr Gly Tyr Leu Asp Tyr
 100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 127

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 127

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 Trp
 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 Phe Thr Ala Pro Trp
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 128

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 128

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 Gly Trp Ala Tyr Asp Arg Gly Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 129
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 129

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
20 25 30

Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
85 90 95

Tyr Tyr Ser Thr Pro Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
100 105 110

Lys

<210> 130
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 130

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 Tyr His Tyr Ser Lys Gly Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 131

<211> 113

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 131

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
20 25 30

Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
85 90 95

Tyr Tyr Ser Thr Pro Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
100 105 110

Lys

<210> 132
<211> 449
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 132

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 Trp Ile Ser Pro Tyr Asn Gly Asn Ala Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu 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 Val Asn Ser Ala Ala Leu Val Trp Glu Arg Leu Asp Tyr Trp
100 105 110

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

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

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

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

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

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

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

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
225 230 235 240

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

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

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

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

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

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

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

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

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

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

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

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

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

Lys

<210> 133

<211> 214

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 133

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Asp Arg Trp
20 25 30

Leu Asn 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 Ser Pro Arg Tyr Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

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

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 134

<211> 446

<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 134

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 Lys Ser Tyr
20 25 30

Asp Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Gly Ile Ile Pro Ile Glu Gly Thr Ala Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu 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 Asp Tyr Pro Ala Gly Tyr Gly Phe Asp Tyr Trp Gly Gln Gly
100 105 110

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

<210> 135

<211> 215

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 135

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

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
100 105 110

Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
115 120 125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
 130 135 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
 145 150 155 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
 165 170 175

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
 180 185 190

Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
 195 200 205

Ser Phe Asn Arg Gly Glu Cys
 210 215

<210> 136

<211> 452

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 136

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Ser Asp
 20 25 30

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

Ser Ala Ile Ser Gly Asn Gly Gly Ser Thr Glu Tyr Ala Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80

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

Ala Arg Asp Pro Tyr Tyr Tyr Tyr Asp Gly Asp Ser Tyr Tyr Gly Met
100 105 110

Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr
115 120 125

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser
130 135 140

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

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

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

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys
195 200 205

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

Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala
225 230 235 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
245 250 255

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
260 265 270

Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu
275 280 285

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

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
 305 310 315 320

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

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
 340 345 350

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

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
 370 375 380

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
 385 390 395 400

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

Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val
 420 425 430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
 435 440 445

Ser Leu Gly Lys
 450

<210> 137
 <211> 214
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic polypeptide

<400> 137

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20 25 30

Leu Asn 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 Ser Tyr Ser Thr Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

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

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 138
 <211> 451
 <212> PRT
 <213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 138

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Lys Ser Asp
 20 25 30

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

Ser Glu Ile Ser Gly Ser Gly Gly Tyr Thr Asn Tyr Ala Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80

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

Ala Arg Asp Ser Tyr Asp Ser Ser Leu Tyr Val Gly Asp Tyr Phe Asp
 100 105 110

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys
 115 120 125

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

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

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

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
180 185 190

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

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

Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
225 230 235 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
245 250 255

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

Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val
275 280 285

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

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305 310 315 320

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

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

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

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
370 375 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385 390 395 400

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

Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met
420 425 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
435 440 445

Leu Gly Lys
450

<210> 139

<211> 214

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 139

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 Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
 115 120 125

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

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
 145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
 165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
 180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
 195 200 205

Phe Asn Arg Gly Glu Cys
 210

<210> 140
 <211> 453
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic polypeptide

<400> 140

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 Asp Asp Tyr
 20 25 30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45

Gly Arg Ile Asp Pro Ile Glu Gly Thr Ala Asn Tyr Ala Gln Lys Phe
 50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu 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 Asp Arg Tyr Tyr Tyr Asp Gly Val Tyr Trp Tyr Ser Asp Tyr
100 105 110

Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120 125

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr
130 135 140

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

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

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
180 185 190

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr
195 200 205

Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val
210 215 220

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala
225 230 235 240

Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
245 250 255

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
260 265 270

Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
275 280 285

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

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
305 310 315 320

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

Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
340 345 350

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

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
370 375 380

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

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
405 410 415

Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
420 425 430

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
435 440 445

Leu Ser Leu Gly Lys
450

<210> 141

<211> 446

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 141

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 Trp Ile Ser Pro Tyr Asn Gly Asn Ala Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu 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 Asp Ser Asp Arg Ser Tyr Asn Leu Asp Tyr Trp Gly Gln Gly
100 105 110

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

<210> 142
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 142

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Gly Trp
20 25 30

Leu Asn 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 Ser Tyr Ser Thr Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

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

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
 145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
 165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
 180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
 195 200 205

Phe Asn Arg Gly Glu Cys
 210

<210> 143
 <211> 445
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic polypeptide

<400> 143

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 Gly Leu Pro Ile Trp Tyr Leu Asp Tyr Trp Gly Gln Gly Thr
 100 105 110

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

<210> 144

<211> 214

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 144

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 Asp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Phe 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 Ser Ile Thr Trp Pro Phe
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

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

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 145

<211> 449

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 145

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 Trp Ile Ile Pro Tyr Asn Gly Asn Ala Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu 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 Val Asn Ser Ala Ala Leu Val Trp Glu Arg Leu Asp Tyr Trp
100 105 110

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

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

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

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

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

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

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

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
 225 230 235 240

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

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

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

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

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

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

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

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

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

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

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

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

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

Lys

<210> 146
<211> 450
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 146

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 Glu 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 Ala Ser Arg Val Trp His Ala Ser Tyr Gly Tyr Leu Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly
115 120 125

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

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

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

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

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

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

Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
 225 230 235 240

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

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

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

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

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

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

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

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

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

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

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

Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu
435 440 445

Gly Lys
450

<210> 147

<211> 214

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 147

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 Trp
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 Phe Thr Ala Pro Trp
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

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

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 148

<211> 446

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 148

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 Gly Trp Ala Tyr Asp Arg Gly Leu Asp Tyr Trp Gly Gln Gly
100 105 110

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

<210> 149
 <211> 220
 <212> PRT
 <213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 149

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
 1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
 20 25 30

Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
 35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
 50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
 65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
 85 90 95

Tyr Tyr Ser Thr Pro Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
 100 105 110

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
 115 120 125

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
 130 135 140

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
 145 150 155 160

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
 165 170 175

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
180 185 190

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
195 200 205

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215 220

<210> 150
<211> 446
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 150

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 Tyr His Tyr Ser Lys Gly Leu Asp Tyr Trp Gly Gln Gly
100 105 110

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

<210> 151

<211> 449

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 151

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 Ser Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
 35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Tyr 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 Asp Tyr Glu Trp Glu Leu Phe Asp Ser Arg Leu Asp Tyr Trp
100 105 110

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

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

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

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

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

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

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

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
225 230 235 240

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

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

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

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

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

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

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

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

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

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

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

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

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

Lys

<210> 152
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 152

Gly Tyr Ser Phe Thr Ser Tyr Trp
1 5

<210> 153
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 153

Ile Tyr Pro Ser Asp Ser Tyr Thr
1 5

<210> 154
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 154

Ala Arg Arg Asn Ser Ala Glu Asn Tyr Ala Asp Leu Asp Tyr
1 5 10

<210> 155
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 155

Gln Ser Ile Ser Asn Asp
1 5

<210> 156
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 156

Tyr Ala Ser
1

<210> 157

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 157

Gln Gln Ser Phe Thr Ala Pro Leu Thr
1 5

<210> 158

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 158

Gly Phe Thr Phe Ser Asn Tyr Ala
1 5

<210> 159

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 159

Ile Asn Tyr Gly Gly Gly Ser Lys
1 5

<210> 160

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 160

Ala Lys Asp Tyr Gly Pro Phe Ala Leu Asp Tyr
1 5 10

<210> 161

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 161

Gln Ser Val Asp Asp Trp
1 5

<210> 162

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 162

Thr Ala Ser
1

<210> 163

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 163

Gln Gln Tyr His His Trp Pro Leu Thr
1 5

<210> 164

<211> 10

<212> PRT

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 164

Gly Gly Ser Ile Ser Ser Ser Thr Tyr Tyr
1 5 10

<210> 165
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 165

Ile Tyr Phe Thr Gly Ser Thr
1 5

<210> 166
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 166

Ala Lys Glu Asp Asp Ser Ser Gly Tyr Tyr Ser Phe Asp Tyr
1 5 10

<210> 167
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 167

Gln Gly Ile Ser Ser Tyr
1 5

<210> 168
<211> 3

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 168

Ala Ala Ser
1

<210> 169
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 169

Gln Gln Val Asn Ser Tyr Pro Leu Thr
1 5

<210> 170
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 170

Gly Val Ser Ile Ser Ser Ser Thr Tyr Tyr
1 5 10

<210> 171
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 171

Ile Tyr Phe Thr Gly Asn Thr
1 5

<210> 172
<211> 12
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 172

Gly Ser Leu Phe Gly Asp Tyr Gly Tyr Phe Asp Tyr
1 5 10

<210> 173
<211> 6
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 173

Gln Phe Ile Ser Ser Asn
1 5

<210> 174
<211> 3
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 174

Gly Ala Ser
1

<210> 175
<211> 9
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 175

Gln Gln Tyr Asn Asn Trp Pro Ser Thr
1 5

<210> 176
 <211> 8
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> Description of Artificial Sequence: Synthetic peptide

 <400> 176

Gly Tyr Thr Phe Asn Thr Tyr Ala
 1 5

<210> 177
 <211> 8
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> Description of Artificial Sequence: Synthetic peptide

 <400> 177

Ile Asn Thr Asn Thr Gly Asn Pro
 1 5

<210> 178
 <211> 14
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> Description of Artificial Sequence: Synthetic peptide

 <400> 178

Ala Arg Arg Tyr Phe Asp Trp Leu Leu Gly Ala Phe Asp Ile
 1 5 10

<210> 179
 <211> 6
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> Description of Artificial Sequence: Synthetic peptide

 <400> 179

Gln Gly Ile Ser Ser Trp
1 5

<210> 180
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 180

Gln Gln Ala Asn Ser Phe Pro Leu Thr
1 5

<210> 181
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 181

Gly Gly Thr Phe Ser Ser Tyr Ala
1 5

<210> 182
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 182

Ile Ser Ala Ile Phe Gly Thr Ala
1 5

<210> 183
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 183

Ala Arg Gly Asn Ser Phe His Ala Leu Trp Asp Tyr Ala Phe Asp Tyr
1 5 10 15

<210> 184

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 184

Gln Ser Val Leu Tyr Ser Ser Asn Asn Lys Asn Tyr
1 5 10

<210> 185

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 185

Trp Ala Ser

1

<210> 186

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 186

Gln Gln Tyr Tyr Ser Thr Pro Leu Thr
1 5

<210> 187

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 187

Ile Ile Pro Ile Phe Gly Asn Ala
1 5

<210> 188

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 188

Ala Arg Thr Ile Ile Tyr Leu Asp Tyr Val His Ile Leu Asp Tyr
1 5 10 15

<210> 189

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 189

Gly Phe Thr Phe Ser Asn Tyr Trp
1 5

<210> 190

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 190

Ile Arg Tyr Asp Gly Gly Ser Lys
1 5

<210> 191

<211> 12

<212> PRT

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 191

Ala Lys Asp Ala Tyr Pro Pro Tyr Ser Phe Asp Tyr
1 5 10

<210> 192
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 192

Gln Ser Val Ser Ser Tyr
1 5

<210> 193
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 193

Asp Ala Ser
1

<210> 194
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 194

Gln Gln Arg Ser Asn Trp Pro Leu Thr
1 5

<210> 195
<211> 8

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 195

Gly Phe Thr Phe Ser Ser Tyr Ala
1 5

<210> 196
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 196

Ile Ser Gly Ser Gly Gly Ser Thr
1 5

<210> 197
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 197

Ala Lys Gly Asp Glu Tyr Tyr Tyr Pro Asp Pro Leu Asp Tyr
1 5 10

<210> 198
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 198

Gln Ser Ile Ser Ser Tyr
1 5

<210> 199
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 199

Gln Gln Ser Tyr Ser Thr Pro Leu Thr
1 5

<210> 200
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 200

Ala Lys Glu Trp Ser Ser Tyr Phe Gly Leu Asp Tyr
1 5 10

<210> 201
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 201

Ile Ser Pro Ile Phe Gly Thr Ala
1 5

<210> 202
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 202

Ala Arg Arg Tyr Asp Asn Phe Ala Arg Ser Gly Asp Leu Asp Tyr
1 5 10 15

<210> 203
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 203

Gln Gln Tyr Asn Asn Trp Pro Phe Thr
1 5

<210> 204
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 204

Ser Ser Asp Val Gly Asp Tyr Asn Tyr
1 5

<210> 205
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 205

Asp Val Ser
1

<210> 206
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 206

Ala Ser Tyr Ala Gly Asn Tyr Asn Val Val
1 5 10

<210> 207
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 207

Ser Ser Tyr Ala Gly Asn Tyr Asn Val Val
1 5 10

<210> 208
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 208

Ala Arg His Leu His Asn Ala Ile His Leu Asp Tyr
1 5 10

<210> 209
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 209

Gln Ser Val Ser Asn Phe
1 5

<210> 210
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 210

Gln Gln Gly Lys His Trp Pro Trp Thr
1 5

<210> 211

<211> 448

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 211

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 Ser Asp Ser Tyr 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 Asn Ser Ala Glu Asn Tyr Ala Asp Leu Asp Tyr Trp Gly
100 105 110

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

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

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

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

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

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

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

Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
225 230 235 240

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

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

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

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

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

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

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

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

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

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

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

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

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

<210> 212
 <211> 214
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic polypeptide

<400> 212

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 Ile Ser Asn Asp
 20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45

Tyr Tyr 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 Asn Ser Leu Gln Pro
 65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Phe Thr Ala Pro Leu
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

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

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 213
<211> 445
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 213

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

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

Ser Gly Ile Asn Tyr Gly Gly Gly Ser Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

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

Ala Lys Asp Tyr Gly Pro Phe Ala Leu Asp Tyr Trp Gly Gln Gly Thr
100 105 110

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

<210> 214

<211> 214

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 214

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 Asp Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Thr 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 Tyr His His Trp Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

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

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 215
<211> 449
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 215

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Ser
20 25 30

Thr Tyr Tyr Trp Gly Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu
35 40 45

Trp Ile Gly Ser Ile Tyr Phe Thr Gly Ser Thr Asp Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Arg Val Ser 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 Lys Glu Asp Asp Ser Ser Gly Tyr Tyr Ser Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Asn Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
115 120 125

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

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

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

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

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

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

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
225 230 235 240

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

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

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

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

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

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

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

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

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

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

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

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

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

Lys

<210> 216
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 216

Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Tyr
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 Thr Leu Gln 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

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Val Asn Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

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

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 217
<211> 448
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 217

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Ile Ser Ser Ser
20 25 30

Thr Tyr Tyr Trp Gly Trp Leu Arg Gln Pro Pro Gly Met Gly Leu Glu
35 40 45

Trp Thr Gly Ser Ile Tyr Phe Thr Gly Asn Thr Tyr Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Arg 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 Gly Ser Leu Phe Gly Asp Tyr Gly Tyr Phe Asp Tyr Trp Gly Gln
100 105 110

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

<210> 218

<211> 214

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 218

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Pro Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Phe Ile 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 Asp 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 Ser
85 90 95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

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

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 219
<211> 448
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 219

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Asn Thr Tyr
20 25 30

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

Gly Trp Ile Asn Thr Asn Thr Gly Asn Pro Thr Tyr Ala Gln Gly Phe
50 55 60

Thr Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr
65 70 75 80

Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Tyr Phe Asp Trp Leu Leu Gly Ala Phe Asp Ile Trp Gly
100 105 110

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

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

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

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

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

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

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

Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
225 230 235 240

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

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

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

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

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

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

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

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

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

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

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

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

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

<210> 220
 <211> 214
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic polypeptide

<400> 220

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 Leu
 85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

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

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 221

<211> 450

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 221

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 Ser Ala Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu 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 Asn Ser Phe His Ala Leu Trp Asp Tyr Ala Phe Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly
115 120 125

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

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

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

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

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

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

Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
225 230 235 240

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

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

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

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

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

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

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

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

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
 370 375 380

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

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

Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His
 420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu
 435 440 445

Gly Lys
 450

<210> 222
 <211> 220
 <212> PRT
 <213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 222

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
20 25 30

Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
85 90 95

Tyr Tyr Ser Thr Pro Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
100 105 110

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
115 120 125

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
130 135 140

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
145 150 155 160

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
165 170 175

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
180 185 190

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
195 200 205

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215 220

<210> 223
<211> 449
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 223

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 Asn Ala Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu 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 Thr Ile Ile Tyr Leu Asp Tyr Val His Ile Leu Asp Tyr Trp
100 105 110

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

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

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

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

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

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

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

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
 225 230 235 240

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

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

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

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

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

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

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

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

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

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

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

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

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

Lys

<210> 224

<211> 446

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 224

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
 20 25 30

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

Ser Ala Ile Arg Tyr Asp Gly Gly Ser Lys Tyr Tyr Ala Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80

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

Ala Lys Asp Ala Tyr Pro Pro Tyr Ser Phe Asp Tyr Trp Gly Gln Gly
100 105 110

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

<210> 225

<211> 214

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 225

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 Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

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

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 226

<211> 448

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 226

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

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

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

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

Ala Lys Gly Asp Glu Tyr Tyr Tyr Pro Asp Pro Leu Asp Tyr Trp Gly
100 105 110

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

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

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

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

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

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

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

Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
 225 230 235 240

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

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

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

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

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

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

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

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

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

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

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

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

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

<210> 227
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 227

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20 25 30

Leu Asn 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 Ser Tyr Ser Thr Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

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

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
 145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
 165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
 180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
 195 200 205

Phe Asn Arg Gly Glu Cys
 210

<210> 228

<211> 446

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 228

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
 20 25 30

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

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80

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

Ala Lys Glu Trp Ser Ser Tyr Phe Gly Leu Asp Tyr Trp Gly Gln Gly
100 105 110

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

<210> 229

<211> 449

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 229

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 Trp Ile Ser Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu 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 Arg Tyr Asp Asn Phe Ala Arg Ser Gly Asp Leu Asp Tyr Trp
100 105 110

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

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

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

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

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

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

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

Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
225 230 235 240

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

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

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

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

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

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

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

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

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

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

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

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

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

Lys

<210> 230
 <211> 214
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> Description of Artificial Sequence: Synthetic polypeptide

 <400> 230

 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 Phe Ile 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 Asp 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 Phe
 85 90 95

 Thr Phe Gly Pro Gly His Cys Val Asp Ile Lys Arg Thr Val Ala Ala
 100 105 110

 Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
 115 120 125

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

 Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
 145 150 155 160

 Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
 165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 231
<211> 216
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 231

Gln Ser Ala Leu Thr Gln Pro Arg Ser Val Ser Gly Ser Pro Gly His
1 5 10 15

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

Asn Tyr Val Ser Trp Tyr Gln Gln Arg Pro Gly Lys Val Pro Lys Leu
35 40 45

Leu Ile Tyr Asp Val Ser Lys Arg Pro Ser Gly Val Pro Asp 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 Ile Tyr Phe Cys Ala Ser Tyr Ala Gly Asn
85 90 95

Tyr Asn Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105 110

Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
115 120 125

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
 130 135 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
 145 150 155 160

Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
 165 170 175

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
 180 185 190

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
 195 200 205

Thr Val Ala Pro Thr Glu Cys Ser
 210 215

<210> 232

<211> 216

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 232

Gln Ser Ala Leu Thr Gln Pro Arg Ser Val Ser Gly Ser Pro Gly His
 1 5 10 15

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

Asn Tyr Val Ser Trp Tyr Gln Gln Arg Pro Gly Lys Val Pro Lys Leu
 35 40 45

Leu Ile Tyr Asp Val Ser Lys Arg Pro Ser Gly Val Pro Asp 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 Ile Tyr Phe Cys Ser Ser Tyr Ala Gly Asn
85 90 95

Tyr Asn Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105 110

Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
115 120 125

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
130 135 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145 150 155 160

Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
165 170 175

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
180 185 190

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
195 200 205

Thr Val Ala Pro Thr Glu Cys Ser
210 215

<210> 233

<211> 446

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 233

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 Ser Ala Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu 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 His Leu His Asn Ala Ile His Leu Asp Tyr Trp Gly Gln Gly
100 105 110

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

<210> 234

<211> 214

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 234

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 Phe
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 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 Lys His Trp Pro Trp
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

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

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser	Pro	Val	Thr	Lys	Ser
		195					200					205			

Phe	Asn	Arg	Gly	Glu	Cys
	210				

<210> 235

<400> 235
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<210> 245

<400> 245
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<210> 246

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 246

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

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ser
20 25 30

Gly Met Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
35 40 45

Trp Leu Ala His Ile Tyr Trp Asp Asp Asp Lys Arg Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Arg Leu Thr Ile Thr Lys Asp Thr Ser Lys Asn Gln Val
65 70 75 80

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

Cys Ala Arg Leu Tyr Gly Phe Thr Tyr Gly Phe Ala Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 247

<211> 125
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 247

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Thr Tyr
20 25 30

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

Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Ala
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Ala Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Phe
100 105 110

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 248
<211> 125
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 248

Gln Leu Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Asn Pro Ser Glu
1 5 10 15

Thr Leu Ser His Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Ser
20 25 30

Ser His Tyr Trp Gly Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu
35 40 45

Trp Ile Gly Lys Ile Tyr Tyr Ser Gly Asn Thr Tyr Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Arg Val Thr Ile Ser Ile Asp Thr Ser Lys Asn Gln Phe
65 70 75 80

Ser Leu Lys Met Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95

Cys Ala Arg Leu Ala Asp Val Val Val Val Pro Ala Ala Arg Tyr Phe
100 105 110

Asp Ser Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 249

<211> 122

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 249

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 Arg 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 His Cys Ala Arg Glu Thr Met Phe Arg Gly Leu Met Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 250

<211> 129

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 250

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Cys Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Ser Thr Leu Tyr
65 70 75 80

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

Ala Lys Asp Phe Arg Ser Leu Asp Trp Leu Pro Pro Asp Ser Thr Ser
100 105 110

Tyr Asp Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
115 120 125

Ser

<210> 251
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 251

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

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

Gly Trp Ile Asn Thr Asn Thr Gly Asn Pro Thr Tyr Ala Gln Ala Phe
50 55 60

Thr Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr
65 70 75 80

Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Arg Glu Val Arg Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> 252
<211> 125
<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 252

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Arg Ser Thr
20 25 30

Asn Tyr Tyr Trp Gly Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu
35 40 45

Trp Ile Gly Thr Ile Tyr Tyr Ser Gly Asn 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 Leu Ala Asp Val Val Val Val Pro Ala Ala Arg Tyr Phe
100 105 110

Asp Tyr Trp Gly Gln Gly Ile Leu Val Thr Val Ser Ser
115 120 125

<210> 253

<211> 125

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 253

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Arg Ser Ser

20 25 30
 Gly Phe Tyr Trp Gly Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu
 35 40 45
 Trp Ile Gly Thr Ile Tyr Tyr Ser Gly Asn 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 Phe
 85 90 95
 Cys Ala Arg Leu Ala Asp Val Val Val Val Pro Ala Ala Arg Tyr Phe
 100 105 110
 Asp Asn Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120 125
 <210> 254
 <211> 125
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence: Synthetic polypeptide
 <400> 254
 Gln Leu Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
 1 5 10 15
 Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Thr Gly
 20 25 30
 Arg Tyr Tyr Trp Gly Trp Ile Arg Gln Pro Pro Gly Lys Gly Val Ile
 35 40 45
 Trp Ile Gly Asn Ile Tyr Tyr Ser Gly Asn 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	Asn	Ser	Val	Thr	Ala	Ala	Asp	Thr	Ala	Val	Tyr	Tyr
				85					90					95	
Cys	Ala	Arg	Leu	Gly	Ser	Leu	Val	Val	Val	Pro	Ala	Ala	Met	Ser	Phe
			100					105					110		
Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser			
		115					120					125			
<210> 255															
<211> 125															
<212> PRT															
<213> Artificial Sequence															
<220>															
<223> Description of Artificial Sequence: Synthetic polypeptide															
<400> 255															
Gln	Leu	Gln	Leu	Gln	Glu	Ser	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Glu
1				5					10					15	
Thr	Leu	Ser	Leu	Thr	Cys	Thr	Val	Ser	Gly	Gly	Ser	Ile	Arg	Gly	Ser
			20					25					30		
Ser	Tyr	Tyr	Trp	Gly	Trp	Val	Arg	Gln	Pro	Pro	Gly	Lys	Gly	Leu	Glu
		35					40					45			
Trp	Ile	Gly	Ser	Ile	Tyr	Ser	Ser	Gly	Asn	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	Leu	Tyr	Tyr
				85					90					95	
Cys	Ala	Arg	Leu	Gly	Ser	Leu	Val	Val	Val	Pro	Ala	Ala	Met	Ser	Phe
			100					105					110		
Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser			

115

120

125

<210> 256
 <211> 119
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic polypeptide

<400> 256

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

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
 20 25 30

Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Arg Gly Leu Glu Trp
 35 40 45

Ile Gly Glu Ile Tyr His Ser Gly Asn Thr Asn Asn Ser Pro Ser Leu
 50 55 60

Lys Ser Arg Val Thr Ile Ser Ala Asp Lys Ser Lys Asn Gln Phe Ser
 65 70 75 80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Phe Cys
 85 90 95

Ala Arg Ile Ile Ala Val Ala Arg Tyr Phe Asp Ser Trp Gly Gln Gly
 100 105 110

Thr Leu Val Thr Val Ser Ser
 115

<210> 257
 <211> 129
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic polypeptide

<400> 257

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

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

Val Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

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

Ala Lys Asp Phe Arg Asp Phe Asp Trp Leu Pro Pro Asp Ser Thr Ser
100 105 110

Tyr His Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
115 120 125

Ser

<210> 258

<211> 129

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 258

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

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

Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Gly Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Phe Arg Ser Phe Asp Trp Leu Pro Pro Asp Ser Ala Ser
100 105 110

Tyr His Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
115 120 125

Ser

<210> 259

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 259

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

Ser Leu Gly Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Gly Tyr
20 25 30

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

Ser Ala Ile Asp Tyr Ser Gly Asn Asp Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

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

Ala Lys Glu Ser Gln Leu Leu His Gly Leu Phe Glu His Trp Gly Gln
100 105 110

Gly Ile Leu Val Thr Val Ser Ser
115 120

<210> 260

<400> 260
000

<210> 261
<211> 125
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 261

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Arg Gly Ser
20 25 30

Ser Tyr Tyr Trp Gly Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu
35 40 45

Trp Ile Gly Ser Ile Tyr Ser Ser Gly Asn 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 Leu Gly Ser Leu Val Val Val Pro Ala Ala Met Ser Phe
100 105 110

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 262
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 262

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

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

Ala Asn Ile Lys Gln His Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

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

Ala Arg Asp Arg Asp Leu Gly Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 263
<211> 119

<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 263

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Arg Phe Thr Phe Ser Ser Tyr
20 25 30

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

Ser Thr Ile Asn Ile Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

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

Thr Lys Gly Gly Tyr Ser Ser Gly Pro Phe Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Ser Val Ser Ser
115

<210> 264
<211> 129
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 264

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Arg Phe Thr Phe Ser Ser Tyr
20 25 30

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

Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

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

Ala Lys Asp Phe Arg Ser Phe Asp Trp Leu Pro Pro Asp Ser Ala Ser
100 105 110

Tyr His Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
115 120 125

Ser

<210> 265
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 265

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Tyr Ala
20 25 30

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

Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Ile Ser Lys Asn Thr Leu Tyr Leu
65 70 75 80

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

Arg Thr Tyr Asn Ser Gly Tyr Tyr Asp Gly Asp Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 266

<211> 129

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 266

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

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

Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe
65 70 75 80

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

Ala Lys Asp Phe Arg Tyr Phe Asp Trp Leu Pro Pro Asp Ser Ser Ser
100 105 110

Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
115 120 125

Ser

<210> 267
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 267

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

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

Gly Trp Ile Asn Thr Asn Thr Gly Asn Pro Thr Tyr Ala Gln Gly Phe
50 55 60

Thr Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Val Ser Ser Ala Tyr
65 70 75 80

Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Thr Asp Arg Asp Arg Gly Thr Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 268
<211> 129
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 268

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ala Tyr
20 25 30

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

Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Gly Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Phe Arg Ser Phe Asp Trp Leu Pro Pro Asp Ser Ala Ser
100 105 110

Tyr His Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
115 120 125

Ser

<210> 269
<211> 129
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 269

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

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

Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

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

Ala Lys Asp Phe Arg Ser Phe Asp Trp Leu Pro Pro Asp Ser Thr Ser
100 105 110

Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
115 120 125

Ser

<210> 270

<211> 118

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 270

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

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

Ala Asn Ile Lys Gln His Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Val Lys Asn Ser Leu Tyr
65 70 75 80

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

Ala Arg Asp Arg Asp Leu Gly Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 271

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 271

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Leu Thr Arg Ser
20 25 30

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

Gly Trp Ile Asn Thr Asn Thr Gly Asn Pro Thr Tyr Ala Gln Gly Phe
50 55 60

Thr Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Val Asn Thr Ala Tyr
65 70 75 80

Leu Leu Ile Ser Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Ser Asp Ile Leu Pro Gly Tyr His Glu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 272
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 272

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

Leu Ser Val Gln 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 Val Ala Val Ala Ala Ser Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 273
 <211> 125
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> Description of Artificial Sequence: Synthetic polypeptide

<400> 273

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Arg
 20 25 30

Ser His Tyr Trp Gly Trp Ile Arg Gln Pro Pro Gly Val Gly Leu Glu
 35 40 45

Trp Ile Gly Ser Ile Tyr Tyr Thr 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 Leu Ala Asp Ile Val Val Val Pro Ala Ala Arg Tyr Phe
 100 105 110

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120 125

<210> 274
 <211> 125
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> Description of Artificial Sequence: Synthetic polypeptide

<400> 274

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Arg Ser Ser
20 25 30

Ser Tyr Tyr Trp Gly Trp Ile Arg Gln Pro Pro Gly Lys Gly Pro Glu
35 40 45

Trp Ile Gly Ser Ile Tyr Ser Ser Gly Asn 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 Ile Ser Met Thr Ala Ala Asp Thr Ala Val Phe Tyr
85 90 95

Cys Ala Arg Leu Ala Ala Thr Ile Val Val Pro Ala Ala Arg Tyr Phe
100 105 110

Asp Cys Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 275

<211> 118

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 275

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Phe Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

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

Ala Asn Ile Lys Gln His Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

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

Ala Arg Asp Arg Asp Leu Gly Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 276
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 276

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Trp Met Thr Trp Val Arg Pro Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Lys Arg Asp Gly Gly Glu Lys Tyr Tyr Val Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Ala Asn Ser Leu Tyr
65 70 75 80

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

Ala Arg Pro Phe Tyr Asp His Phe Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 277
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 277

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ser Thr Tyr
20 25 30

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

Gly Trp Ile Asn Thr Asn Thr Gly Asn Pro Thr Tyr Ala Gln Gly Phe
50 55 60

Thr Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr
65 70 75 80

Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Arg Asp Arg Gly Thr Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 278
<211> 119
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 278

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30

Ala Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Leu Ser Trp Asn Gly Gly Asn Ile Gly Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Phe Tyr Tyr Cys
85 90 95

Thr Lys Asp Thr Pro Tyr Gly Asp Tyr Phe Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 279

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 279

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Gly Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30

Ala Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Leu Ser Trp Asn Gly Gly Asn Ile Gly Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

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

Ala Lys Asp Ser Pro Tyr Gly Asp Tyr Phe Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 280

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 280

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30

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

Ser Gly Ile Gly Trp Ser Gly Gly Ser Ile Val Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Lys Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

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

Ala Lys Asp Ser Pro Tyr Gly Asp Phe Phe Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 281

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 281

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30

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

Ser Gly Ile Gly Trp Ser Gly Gly Ser Ile Val Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

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

Ala Lys Asp Ser Pro Tyr Gly Asp Phe Phe Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 282
 <211> 120
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> Description of Artificial Sequence: Synthetic polypeptide

<400> 282

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

 Ser Leu Lys Leu Ser Cys Thr Ala Ser Gly Phe Thr Phe Arg Ser Tyr
 20 25 30

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

 Ser Ala Ile Asn Gly Tyr Gly Asp Gly Arg Tyr Tyr Ala Asp Ser Val
 50 55 60

 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80

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

 Ala Lys Asp Gln Gly Phe Gly Glu Leu Phe Phe Asp Tyr Trp Gly Gln
 100 105 110

 Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 283
 <211> 117
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> Description of Artificial Sequence: Synthetic polypeptide

 <400> 283

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Tyr Tyr
 20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Asp Lys Gly Leu Glu Trp Val
 35 40 45

Ala Val Ile Trp Phe Asp Gly Asn Asn Lys Tyr Tyr Ala Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80

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

Ala Arg Asp Arg Glu Leu Leu Phe Asp Tyr Trp Gly Gln Gly Thr Leu
 100 105 110

Val Thr Val Ser Ser
 115

<210> 284

<211> 129

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 284

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
 20 25 30

Ala Met His Trp Val Arg Gln Val Pro Gly Glu Gly Leu Glu Trp Val
 35 40 45

Ser Gly Ile Ser Trp Asn Gly Gly Asp Met Val Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Val Lys Asp Met Pro Tyr Phe Asp Phe Leu Thr Gly Ser Asp Tyr Tyr
100 105 110

Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
115 120 125

Ser

<210> 285

<211> 117

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 285

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Thr Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

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

Ala Val Ile Trp Tyr Val Gly Ser His Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

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

Ala Arg Asp Gly Ser Leu Cys Phe Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 286
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 286

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Arg Ala Ser Gln Ser Val Asp Tyr Asn
20 25 30

Gly Ile Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Pro Glu Ser Gly Val Pro Asp
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Ile Ile
85 90 95

Glu Asp Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 287
<211> 109
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 287

Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser
20 25 30

Asn Tyr Ala Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
35 40 45

Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Gly Thr Pro Ala Arg Phe
50 55 60

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val
65 70 75 80

Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
85 90 95

Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 288

<211> 106

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 288

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

Thr Ala Ser Ile Ile Cys Ser Gly Asp Lys Leu Gly Asn Lys Tyr Ala
20 25 30

Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
35 40 45

Gln Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
 50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Val
 65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Thr Tyr Val
 85 90 95

Phe Gly Thr Gly Thr Lys Val Thr Val Leu
 100 105

<210> 289

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 289

Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
 1 5 10 15

Thr Ala Arg Ile Thr Cys Gly Gly Ser Asn Ile Gly Ser Lys Ser Val
 20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Met Val Val Tyr
 35 40 45

Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
 50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly
 65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Ser Ser Asp Val
 85 90 95

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
 100 105

<210> 290
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 290

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

Thr Ala Ser Ile Thr Cys Ser Gly His Lys Leu Gly Asp Lys Tyr Ala
20 25 30

Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Val Val Ile Tyr
35 40 45

Lys Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Phe Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Thr Val Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 291
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 291

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala
20 25 30

Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
35 40 45

Gln Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Thr Val Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 292

<211> 106

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 292

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala
20 25 30

Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
35 40 45

Gln Asp Tyr Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Thr Tyr Val
85 90 95

Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105

<210> 293
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 293

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala
20 25 30

Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
35 40 45

Gln Asp Tyr Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Thr Met
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ile Ser Thr Tyr Val
85 90 95

Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105

<210> 294
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 294

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala
20 25 30

Cys Trp Tyr Gln Leu Arg Pro Gly Gln Ser Pro Ile Leu Val Ile Tyr
35 40 45

Gln Asp Ser Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Thr Trp Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 295

<211> 106

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 295

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala
20 25 30

Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
35 40 45

Gln Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Thr Trp Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 296

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 296

Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1 5 10 15

Thr Ala Arg Ile Thr Cys Gly Gly Asn Asn Ile Gly Ile Lys Ser Val
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val Tyr
35 40 45

Asp Asp Ser Asp Arg Pro Pro Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Thr Arg Val Glu Ala Gly
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Ser Ser Asp His
85 90 95

Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 297

<211> 106

<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 297

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala
20 25 30

Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Val Val Ile Tyr
35 40 45

Gln Asp Arg Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Phe Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Thr Val Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 298
<211> 106
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 298

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala
20 25 30

Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
35 40 45

Gln Asp Gly Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Phe Gly Asn Lys Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Arg Asn Thr Val Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 299
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 299

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
20 25 30

Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Ala Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Ile Leu Ile
65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
85 90 95

Tyr Tyr Gly Thr Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
100 105 110

Lys

<210> 300
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 300

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 Phe
85 90 95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

<210> 301
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 301

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

Thr Ala Ser Ile Thr Cys Ser Gly Asn Lys Leu Gly Ala Lys Phe Ala
20 25 30

Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
35 40 45

Gln Asp Asn Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Val
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Thr Val Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 302

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 302

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

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

Arg Trp Tyr Gln Gln Lys Thr Gly Gln Ser Pro Val Leu Val Met Tyr
35 40 45

Gln Asp Ser Lys Arg Pro Ser Gly Ile Arg Glu Arg Phe Tyr Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Pro Thr Ile Ser Gly Thr Gln Ala Val
65 70 75 80

Asp Glu Ala Glu Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Thr Gly Val
85 90 95

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 303
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 303

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Pro Pro Gly Gln
1 5 10 15

Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala
20 25 30

Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
35 40 45

Gln Asp Asn Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Gly Arg Asn Thr Val Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 304
<211> 111

<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 304

Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

Ser Ile Pro Ile Ser Ser Thr Gly Thr Ser Ser Asp Asp Gly Lys Asn
20 25 30

Asn Ile Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Lys Asp Ser Lys 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 Asp Asp Glu Ala Asp Tyr His Cys Cys Ser Tyr Ala Gly Ala
85 90 95

Ser Asn His Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 305
<211> 106
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 305

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

Thr Ala Ser Ile Thr Cys Ser Gly Asp Glu Leu Gly Asn Lys Tyr Ala
20 25 30

Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Val Val Val Tyr
35 40 45

Gln Asp Arg Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Phe Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Thr Val Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 306
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 306

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 Asp Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Val Pro Lys Leu
35 40 45

Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Met 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 Ser Ser Ser
85 90 95

Ser Ala Leu Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 307
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 307

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala
20 25 30

Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
35 40 45

Gln Asp Asn Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Asn Thr Val Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 308
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 308

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

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

Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Val Val Ile His
35 40 45

Gln Asp Arg Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Phe Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Thr Val Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 309

<211> 106

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 309

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asn Lys Tyr Ala
20 25 30

Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
35 40 45

Gln Asp Thr Lys Arg Pro Ser Gly Ile Pro Glu Arg Val Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80

Asp Glu Ala Asp Tyr His Cys Gln Ala Trp Asp Ser Ser Thr Val Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 310
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 310

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 Ile Asn Ser Asp Val Gly Ser Tyr
20 25 30

Asp Leu Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Leu Ile Tyr Asp Gly Ser Glu Arg Pro Ser Gly Val Phe Gly Arg Phe
50 55 60

Ser Gly Ser Lys Ser Asp Asn Thr Thr Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Ala Tyr Tyr Cys Cys Ser Tyr Glu Val Thr
85 90 95

Thr Thr Tyr Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 311
<211> 108
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 311

Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1 5 10 15

Thr Ala Arg Ile Thr Cys Gly Gly Asn Asn Ile Gly Ser Lys Ser Val
20 25 30

His Trp Ser Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val Tyr
35 40 45

Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Asn Ser Asp His
85 90 95

Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 312

<211> 106

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 312

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala
20 25 30

Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
35 40 45

Gln Asp Ser Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Glu Thr Gln Ala Met
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Thr Tyr Val
85 90 95

Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105

<210> 313

<211> 106

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 313

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

Thr Val Ser Ile Ser Cys Ser Gly Asp Arg Leu Gly Asp Lys Tyr Ala
20 25 30

Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
35 40 45

Gln Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Ser Tyr Val
85 90 95

Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105

<210> 314
<211> 106
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 314

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Ser Lys Phe Ala
20 25 30

Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
35 40 45

Gln Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Thr Val Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 315
<211> 108
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 315

Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ala Val Ala Pro Gly Gln
1 5 10 15

Thr Ala Arg Ile Thr Cys Gly Gly Ser Asn Ile Gly Lys Ile Ser Val
20 25 30

His Trp Tyr Gln Gln Lys Ala Gly Gln Ala Pro Val Leu Val Val His
35 40 45

Asp Asp Arg Ala Arg Pro Ser Gly Ile Pro Glu Arg Leu Ser Gly Ser
50 55 60

Asn Ser Gly Thr Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Val Gly
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asn Ser Ser Ser Val His
85 90 95

Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 316
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 316

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 Asp Asp
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 Asp 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 Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Ser Ser Ser
85 90 95

Thr Thr Leu Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 317
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 317

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Trp 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 Gln Pro Gly Lys Ala Pro Asn Leu Leu Ile
35 40 45

Tyr Arg Ser 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 Asp Asn Ser Phe Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 318
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 318

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Glu Trp 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 Gly Ala Ser Ser Trp 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 Asp Asn Ser Phe Pro Tyr
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
 100 105

<210> 319

<211> 113

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 319

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
 1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Thr Val Leu Tyr Ser
 20 25 30

Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
 35 40 45

Pro Pro Lys Leu Leu Ile Ser Trp Ala Ser Thr Arg Lys Ser Gly Val
 50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Val Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln His
85 90 95

Tyr Tyr Ser Thr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
100 105 110

Lys

<210> 320

<211> 113

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 320

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Thr Val Phe Tyr Ser
20 25 30

Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Ser Trp Ala Ser Thr Arg Lys Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Val Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln His
85 90 95

Tyr Tyr Ser Thr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
100 105 110

Lys

<210> 321
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 321

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 Lys 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 Cys Cys Gln Gln Tyr Asn Ser Tyr Pro Trp
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 322
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 322

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

Thr Ala Ser Ile Thr Cys Ser Gly Asp Glu Leu Gly Asp Met Tyr Ala
20 25 30

Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Leu Val Val Ile Tyr
35 40 45

Gln Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80

Asp Glu Ala Ala Tyr Tyr Cys Gln Thr Trp Asp Thr Arg Ile Ala Val
85 90 95

Phe Gly Gly Gly Thr Asn Leu Thr Val Leu
100 105

<210> 323

<211> 106

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 323

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

Thr Ala Ser Ile Thr Cys Ser Gly Asp Asn Leu Gly Asn Glu His Val
20 25 30

Cys Trp Tyr His Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
35 40 45

Gln Asn Asn Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Ser Ile Ser Gly Thr Gln Ala Thr
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Thr Thr Ala Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 324
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 324

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

Thr Ala Asn Ile Ser Cys Ser Gly Val Thr Leu Gly Tyr Asn Tyr Ala
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Ile Leu Val Ile Ser
35 40 45

Gln Asp Thr Gln Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80

Asp Glu Ala Ala Tyr Tyr Cys Gln Ala Trp Asp Ile Thr Thr Val Leu
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 325
<211> 106
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 325

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Ala
20 25 30

Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
35 40 45

Gln Asp Gly Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Phe Gly Asn Lys Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Arg Asn Thr Val Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 326

<211> 106

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 326

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1 5 10 15

Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asn Lys Tyr Ala
20 25 30

Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
35 40 45

Gln Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
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Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Thr Val Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

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Gly Phe Ser Leu Ser Thr Ser Gly Met Gly
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<210> 328
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<213> Artificial Sequence

<220>
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<400> 328

Gly Phe Thr Phe Asn Thr Tyr Ala
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Gly Asp Ser Val Phe Asn Asn Asn Ala Ala
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Gly Gly Ser Ile Ser Ser Ser Ser His Tyr
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Gly Asp Ser Val Ser Ser Asn Ser Ala Ala
1 5 10

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Gly Phe Thr Phe Ser Ser Tyr Gly
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Gly Tyr Thr Phe Thr Asn Tyr Ala
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Gly Gly Ser Ile Arg Ser Thr Asn Tyr Tyr
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<210> 335

<211> 10

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Gly Gly Ser Ile Arg Ser Ser Gly Phe Tyr
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Gly Gly Ser Ile Ser Thr Gly Arg Tyr Tyr
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Gly Gly Ser Ile Arg Gly Ser Ser Tyr Tyr
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Gly Gly Ser Ile Ser Ser Ser Asn Trp
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Gly Phe Thr Phe Ser Ser Tyr Gly
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<210> 340

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Gly Phe Thr Phe Ser Ser Tyr Gly
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<400> 342

Gly Gly Ser Ile Ser Ser Ser Ser Tyr Tyr
1 5 10

<210> 343
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<400> 343

Gly Gly Ser Ile Arg Gly Ser Ser Tyr Tyr
1 5 10

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Gly Phe Thr Phe Ser Ser Tyr Trp
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Arg Phe Thr Phe Ser Ser Tyr Ala
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Arg Phe Thr Phe Ser Ser Tyr Gly
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Gly Phe Thr Phe Ser Ser Tyr Gly
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Gly Tyr Thr Leu Thr Arg Ser Ala
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Gly Asp Ser Val Ser Ser Asn Ser Ala Ala
1 5 10

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Gly Gly Ser Ile Ser Ser Arg Ser His Tyr
1 5 10

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<400> 356

Gly Gly Ser Ile Arg Ser Ser Ser Tyr Tyr
1 5 10

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Gly Phe Thr Phe Ser Ser Tyr Trp
1 5

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<400> 358

Gly Phe Thr Phe Ser Ser Tyr Trp
1 5

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Gly Tyr Thr Phe Ser Thr Tyr Ala
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Gly Phe Thr Phe Asp Asp Tyr Ala
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Gly Phe Thr Phe Asp Asp Tyr Ala
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Gly Phe Thr Phe Arg Ser Tyr Ala
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<210> 366

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Gly Phe Thr Phe Asp Asp Tyr Ala
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<210> 367

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Gly Phe Thr Phe Ser Asn Tyr Gly
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Ile Tyr Trp Asp Asp Asp Lys
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1 5 10

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<212> PRT
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Thr Tyr Tyr Arg Ser Lys Trp Leu Tyr
1 5

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<400> 371

Ile Tyr Tyr Ser Gly Asn Thr
1 5

<210> 372
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<400> 372

Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn
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<210> 373

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Ile Ser Tyr Asp Gly Ser Asn Lys
1 5

<210> 374

<211> 8

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<400> 375

Ile Tyr Tyr Ser Gly Asn Thr
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<400> 376

Ile Tyr Tyr Ser Gly Asn Thr
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<210> 377
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<400> 377

Ile Tyr Tyr Ser Gly Asn Thr
1 5

<210> 378
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<400> 378

Ile Tyr Ser Ser Gly Asn Thr
1 5

<210> 379
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<400> 379

Ile Tyr His Ser Gly Asn Thr
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<210> 380
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<400> 380

Ile Ser Tyr Asp Gly Ser Asn Lys
1 5

<210> 381
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<400> 381

Ile Ser Tyr Asp Gly Ser Asn Lys
1 5

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Ile Asp Tyr Ser Gly Asn Asp Thr
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<210> 383
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<400> 383

Ile Asn Tyr Ser Gly Ser Thr
1 5

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<400> 384

Ile Tyr Ser Ser Gly Asn Thr
1 5

<210> 385
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<220>
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<400> 385

Ile Lys Gln His Gly Ser Glu Lys
1 5

<210> 386
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<400> 386

Ile Asn Ile Ser Gly Gly Ser Thr
1 5

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<400> 387

Ile Ser Tyr Asp Gly Ser Asn Lys
1 5

<210> 388

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Ile Ser Gly Ser Gly Gly Ser Thr
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<210> 389

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Ile Ser Tyr Asp Gly Ser Asn Lys
1 5

<210> 390

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Ile Asn Thr Asn Thr Gly Asn Pro
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<210> 391

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<400> 391

Ile Ser Tyr Asp Gly Ser Asn Lys
1 5

<210> 392

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 392

Ile Ser Tyr Asp Gly Ser Asn Lys
1 5

<210> 393

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<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 393

Ile Lys Gln His Gly Ser Glu Lys
1 5

<210> 394

<211> 8

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<400> 394

Ile Asn Thr Asn Thr Gly Asn Pro
1 5

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<211> 9

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<400> 395

Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn
1 5

<210> 396
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<400> 396

Ile Tyr Tyr Thr Gly Ser Thr
1 5

<210> 397
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<400> 397

Ile Tyr Ser Ser Gly Asn Thr
1 5

<210> 398
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<400> 398

Ile Lys Gln His Gly Ser Glu Lys
1 5

<210> 399
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<210> 400
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Leu Ser Trp Asn Gly Gly Asn Ile
1 5

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Leu Ser Trp Asn Gly Gly Asn Ile
1 5

<210> 403
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Ile Gly Trp Ser Gly Gly Ser Ile
1 5

<210> 404
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1 5

<210> 405
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Ile Asn Gly Tyr Gly Asp Gly Arg
1 5

<210> 406
<211> 8
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Ile Trp Phe Asp Gly Asn Asn Lys
1 5

<210> 407
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Ile Ser Trp Asn Gly Gly Asp Met
1 5

<210> 408
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<220>
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<400> 408

Ile Trp Tyr Val Gly Ser His Lys
1 5

<210> 409
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<212> PRT
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<220>
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Ala Arg Leu Tyr Gly Phe Thr Tyr Gly Phe Ala Tyr
1 5 10

<210> 410
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<210> 411
<211> 10
<212> PRT
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Ala Arg Gly Tyr Ser Ser Ser Phe Asp Tyr
1 5 10

<210> 412
<211> 17
<212> PRT
<213> Artificial Sequence

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<400> 412

Ala Arg Leu Ala Asp Val Val Val Val Pro Ala Ala Arg Tyr Phe Asp
1 5 10 15

Ser

<210> 413
<211> 12
<212> PRT
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<400> 413

Ala Arg Glu Thr Met Phe Arg Gly Leu Met Asp Tyr
1 5 10

<210> 414
<211> 22
<212> PRT
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<220>

<223> Description of Artificial Sequence: Synthetic peptide

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Ala Lys Asp Phe Arg Ser Leu Asp Trp Leu Pro Pro Asp Ser Thr Ser
1 5 10 15

Tyr Asp Gly Met Asp Val
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<210> 415

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

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Ala Arg Asp Arg Glu Val Arg Asp Tyr
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<210> 416

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 416

Ala Arg Leu Ala Asp Val Val Val Val Pro Ala Ala Arg Tyr Phe Asp
1 5 10 15

Tyr

<210> 417

<211> 17

<212> PRT

<213> Artificial Sequence

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<400> 417

Ala Arg Leu Ala Asp Val Val Val Val Pro Ala Ala Arg Tyr Phe Asp
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Asn

<210> 418

<211> 17

<212> PRT

<213> Artificial Sequence

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<400> 418

Ala Arg Leu Gly Ser Leu Val Val Val Pro Ala Ala Met Ser Phe Asp
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Tyr

<210> 419

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<400> 419

Ala Arg Leu Gly Ser Leu Val Val Val Pro Ala Ala Met Ser Phe Asp
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Tyr

<210> 420

<211> 12

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<400> 420

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<400> 421

Ala Lys Asp Phe Arg Asp Phe Asp Trp Leu Pro Pro Asp Ser Thr Ser
1 5 10 15

Tyr His Gly Met Asp Val
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<210> 422

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<400> 422

Ala Lys Asp Phe Arg Ser Phe Asp Trp Leu Pro Pro Asp Ser Ala Ser
1 5 10 15

Tyr His Gly Met Asp Val
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<210> 423

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 423

Ala Lys Glu Ser Gln Leu Leu His Gly Leu Phe Glu His
1 5 10

<210> 424
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<400> 424

Ala Arg Leu Asp Gly Tyr Glu Ser Pro Phe Asp Tyr
1 5 10

<210> 425
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<400> 425

Ala Arg Leu Gly Ser Leu Val Val Val Pro Ala Ala Met Ser Phe Asp
1 5 10 15

Tyr

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<400> 426

Ala Arg Asp Arg Asp Leu Gly Tyr Phe Asp Tyr
1 5 10

<210> 427
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<400> 427

Thr Lys Gly Gly Tyr Ser Ser Gly Pro Phe Asp Tyr
1 5 10

<210> 428

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Ala Lys Asp Phe Arg Ser Phe Asp Trp Leu Pro Pro Asp Ser Ala Ser
1 5 10 15

Tyr His Gly Met Asp Val
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<210> 429

<211> 15

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Ala Arg Thr Tyr Asn Ser Gly Tyr Tyr Asp Gly Asp Phe Asp Tyr
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<210> 430

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<223> Description of Artificial Sequence: Synthetic peptide

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Ala Lys Asp Phe Arg Tyr Phe Asp Trp Leu Pro Pro Asp Ser Ser Ser
1 5 10 15

Tyr Tyr Gly Met Asp Val
20

<210> 431
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<400> 431

Ala Thr Asp Arg Asp Arg Gly Thr Asp Tyr
1 5 10

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<400> 432

Ala Lys Asp Phe Arg Ser Phe Asp Trp Leu Pro Pro Asp Ser Ala Ser
1 5 10 15

Tyr His Gly Met Asp Val
20

<210> 433
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<400> 433

Ala Lys Asp Phe Arg Ser Phe Asp Trp Leu Pro Pro Asp Ser Thr Ser
1 5 10 15

Tyr Tyr Gly Met Asp Val
20

<210> 434
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Ala Arg Asp Arg Asp Leu Gly Tyr Phe Asp Tyr
1 5 10

<210> 435
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<223> Description of Artificial Sequence: Synthetic peptide

<400> 435

Ala Ser Asp Ile Leu Pro Gly Tyr His Glu Asp Tyr
1 5 10

<210> 436
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<223> Description of Artificial Sequence: Synthetic peptide

<400> 436

Ala Arg Glu Val Ala Val Ala Ala Ser Phe Asp Tyr
1 5 10

<210> 437
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<400> 437

Ala Arg Leu Ala Asp Ile Val Val Val Pro Ala Ala Arg Tyr Phe Asp
1 5 10 15

Tyr

<210> 438
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<400> 438

Ala Arg Leu Ala Ala Thr Ile Val Val Pro Ala Ala Arg Tyr Phe Asp
1 5 10 15

Cys

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<400> 439

Ala Arg Asp Arg Asp Leu Gly Tyr Phe Asp Tyr
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Ala Arg Pro Phe Tyr Asp His Phe Asp Tyr
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Ala	Arg	Asp	Arg	Asp	Arg	Gly	Thr	Asp	Tyr
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Ala Lys Asp Ser Pro Tyr Gly Asp Phe Phe Asp Tyr
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Ala Lys Asp Gln Gly Phe Gly Glu Leu Phe Phe Asp Tyr
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Ala Arg Asp Arg Glu Leu Leu Phe Asp Tyr
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Val Lys Asp Met Pro Tyr Phe Asp Phe Leu Thr Gly Ser Asp Tyr Tyr
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Tyr Tyr Gly Met Asp Val
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Thr Gly Ala Val Thr Thr Ser Asn Tyr
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Ser Ser Asn Ile Gly Thr Tyr Lys Phe
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Asn Ile Gly Ser Lys Ser
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Thr Leu Gly Tyr Asn Tyr
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Gln Asp Gly
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Ala Ala Ser
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Gln Asp Asn
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Lys Asp Ser
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Asp Val Ser
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Gln Asp Asn
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Gln Asp Arg
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Asp Asp Arg
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Asp Val Ser
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Gly Ala Ser
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Trp Ala Ser
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Trp Ala Ser
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Lys Ala Ser
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Gln Asp Ser
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1 5

<210> 562

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 562

Gln Ala Trp Asp Ser Ser Ser Tyr Val
1 5

<210> 563

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 563

Gln Ala Trp Asp Ser Ser Thr Val Val
1 5

<210> 564

<211> 11

<212> PRT

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 564

Gln Val Trp Asn Ser Ser Ser Val His Pro Val
1 5 10

<210> 565
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 565

Ser Ser Tyr Ser Ser Ser Thr Thr Leu Glu Val
1 5 10

<210> 566
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 566

Gln Gln Asp Asn Ser Phe Pro Tyr Thr
1 5

<210> 567
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 567

Gln Gln Asp Asn Ser Phe Pro Tyr Thr
1 5

<210> 568
<211> 9

<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 568

Gln His Tyr Tyr Ser Thr Pro Tyr Thr
1 5

<210> 569

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 569

Gln His Tyr Tyr Ser Thr Pro Tyr Thr
1 5

<210> 570

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 570

Gln Gln Tyr Asn Ser Tyr Pro Trp Thr
1 5

<210> 571

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 571

Gln Thr Trp Asp Thr Arg Ile Ala Val
1 5

<210> 572
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 572

Gln Ala Trp Asp Ser Thr Thr Ala Val
1 5

<210> 573
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 573

Gln Ala Trp Asp Ile Thr Thr Val Leu
1 5

<210> 574
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 574

Gln Ala Trp Asp Arg Asn Thr Val Val
1 5

<210> 575
<211> 334
<212> PRT
<213> Homo sapiens

<400> 575

Phe Pro Thr Ser Leu Ser Asp Cys Gln Thr Pro Thr Gly Trp Asn Cys
1 5 10 15

Ser Gly Tyr Asp Asp Arg Glu Asn Asp Leu Phe Leu Cys Asp Thr Asn

20

25

30

Thr Cys Lys Phe Asp Gly Glu Cys Leu Arg Ile Gly Asp Thr Val Thr
 35 40 45

Cys Val Cys Gln Phe Lys Cys Asn Asn Asp Tyr Val Pro Val Cys Gly
 50 55 60

Ser Asn Gly Glu Ser Tyr Gln Asn Glu Cys Tyr Leu Arg Gln Ala Ala
 65 70 75 80

Cys Lys Gln Gln Ser Glu Ile Leu Val Val Ser Glu Gly Ser Cys Ala
 85 90 95

Thr Asp Ala Gly Ser Gly Ser Gly Asp Gly Val His Glu Gly Ser Gly
 100 105 110

Glu Thr Ser Gln Lys Glu Thr Ser Thr Cys Asp Ile Cys Gln Phe Gly
 115 120 125

Ala Glu Cys Asp Glu Asp Ala Glu Asp Val Trp Cys Val Cys Asn Ile
 130 135 140

Asp Cys Ser Gln Thr Asn Phe Asn Pro Leu Cys Ala Ser Asp Gly Lys
 145 150 155 160

Ser Tyr Asp Asn Ala Cys Gln Ile Lys Glu Ala Ser Cys Gln Lys Gln
 165 170 175

Glu Lys Ile Glu Val Met Ser Leu Gly Arg Cys Gln Asp Asn Thr Thr
 180 185 190

Thr Thr Thr Lys Ser Glu Asp Gly His Tyr Ala Arg Thr Asp Tyr Ala
 195 200 205

Glu Asn Ala Asn Lys Leu Glu Glu Ser Ala Arg Glu His His Ile Pro
 210 215 220

Cys Pro Glu His Tyr Asn Gly Phe Cys Met His Gly Lys Cys Glu His
 225 230 235 240

Ser Ile Asn Met Gln Glu Pro Ser Cys Arg Cys Asp Ala Gly Tyr Thr
245 250 255

Gly Gln His Cys Glu Lys Lys Asp Tyr Ser Val Leu Tyr Val Val Pro
260 265 270

Gly Pro Val Arg Phe Gln Tyr Val Leu Ile Ala Ala Val Ile Gly Thr
275 280 285

Ile Gln Ile Ala Val Ile Cys Val Val Val Leu Cys Ile Thr Arg Lys
290 295 300

Cys Pro Arg Ser Asn Arg Ile His Arg Gln Lys Gln Asn Thr Gly His
305 310 315 320

Tyr Ser Ser Asp Asn Thr Thr Arg Ala Ser Thr Arg Leu Ile
325 330

<210> 576

<400> 576
000

<210> 577
<211> 41
<212> PRT
<213> Unknown

<220>
<223> Description of Unknown: TMEFF2 sequence

<400> 577

His His Ile Pro Cys Pro Glu His Tyr Asn Gly Phe Cys Met His Gly
1 5 10 15

Lys Cys Glu His Ser Ile Asn Met Gln Glu Pro Ser Cys Arg Cys Asp
20 25 30

Ala Gly Tyr Thr Gly Gln His Cys Glu
35 40

<210> 578
<211> 304

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 578

Phe Pro Thr Ser Leu Ser Asp Cys Gln Thr Pro Thr Gly Trp Asn Cys
1 5 10 15

Ser Gly Tyr Asp Asp Arg Glu Asn Asp Leu Phe Leu Cys Asp Thr Asn
20 25 30

Thr Cys Lys Phe Asp Gly Glu Cys Leu Arg Ile Gly Asp Thr Val Thr
35 40 45

Cys Val Cys Gln Phe Lys Cys Asn Asn Asp Tyr Val Pro Val Cys Gly
50 55 60

Ser Asn Gly Glu Ser Tyr Gln Asn Glu Cys Tyr Leu Arg Gln Ala Ala
65 70 75 80

Cys Lys Gln Gln Ser Glu Ile Leu Val Val Ser Glu Gly Ser Cys Ala
85 90 95

Thr Asp Ala Gly Ser Gly Ser Gly Asp Gly Val His Glu Gly Ser Gly
100 105 110

Glu Thr Ser Gln Lys Glu Thr Ser Thr Cys Asp Ile Cys Gln Phe Gly
115 120 125

Ala Glu Cys Asp Glu Asp Ala Glu Asp Val Trp Cys Val Cys Asn Ile
130 135 140

Asp Cys Ser Gln Thr Asn Phe Asn Pro Leu Cys Ala Ser Asp Gly Lys
145 150 155 160

Ser Tyr Asp Asn Ala Cys Gln Ile Lys Glu Ala Ser Cys Gln Lys Gln
165 170 175

Glu Lys Ile Glu Val Met Ser Leu Gly Arg Cys Gln Asp Asn Thr Thr
180 185 190

Thr Thr Thr Lys Ser Glu Asp Gly His Tyr Ala Arg Thr Asp Tyr Ala
195 200 205

Glu Asn Ala Asn Lys Leu Glu Glu Ser Ala Arg Glu His His Ile Pro
210 215 220

Cys Pro Glu His Tyr Asn Gly Phe Cys Met His Gly Lys Cys Glu His
225 230 235 240

Ser Ile Asn Met Gln Glu Pro Ser Cys Arg Cys Asp Ala Gly Tyr Thr
245 250 255

Gly Gln His Cys Glu Lys Lys Asp Tyr Ser Val Leu Tyr Val Val Pro
260 265 270

Gly Pro Val Arg Phe Gln Tyr Val Gly Gly Gly Ser His His His His
275 280 285

His His Leu Asn Asp Ile Phe Glu Ala Gln Lys Ile Glu Trp His Glu
290 295 300

<210> 579
<211> 797
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 579

Ser Gly Glu Thr Ser Gln Lys Glu Thr Ser Thr Cys Asp Ile Cys Gln
1 5 10 15

Phe Gly Ala Glu Cys Asp Glu Asp Ala Glu Asp Val Trp Cys Val Cys
20 25 30

Asn Ile Asp Cys Ser Gln Thr Asn Phe Asn Pro Leu Cys Ala Ser Asp
35 40 45

Gly Lys Ser Tyr Asp Asn Ala Cys Gln Ile Lys Glu Ala Ser Cys Gln
50 55 60

Lys Gln Glu Lys Ile Glu Val Met Ser Leu Gly Arg Cys Gln Asp Asn
65 70 75 80

Thr Thr Thr Thr Thr Lys Ser Glu Asp Gly His Tyr Ala Arg Thr Asp
85 90 95

Tyr Ala Glu Asn Ala Asn Lys Leu Glu Glu Ser Ala Arg Glu His His
100 105 110

Ile Pro Cys Pro Glu His Tyr Asn Gly Phe Cys Met His Gly Lys Cys
115 120 125

Glu His Ser Ile Asn Met Gln Glu Pro Ser Cys Arg Cys Asp Ala Gly
130 135 140

Tyr Thr Gly Gln His Cys Glu Lys Lys Asp Tyr Ser Val Leu Tyr Val
145 150 155 160

Val Pro Gly Pro Val Arg Phe Gln Tyr Val Gly Ser Gly Ser Gly Ser
165 170 175

Glu Asn Leu Tyr Phe Gln Gly Val Arg Ser Ser Ser Asp Ala His Lys
180 185 190

Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys
195 200 205

Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Ser Pro Phe
210 215 220

Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr
225 230 235 240

Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr
245 250 255

Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr
260 265 270

Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu
275 280 285

Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val
290 295 300

Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu
305 310 315 320

Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr
325 330 335

Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala
340 345 350

Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro
355 360 365

Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln
370 375 380

Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys
385 390 395 400

Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe
405 410 415

Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu
420 425 430

Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu
435 440 445

Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys
450 455 460

Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu
465 470 475 480

Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp
485 490 495

Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp
500 505 510

Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp
515 520 525

Tyr Ser Val Val Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr
530 535 540

Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys
545 550 555 560

Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile
565 570 575

Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln
580 585 590

Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr
595 600 605

Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys
610 615 620

Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr
625 630 635 640

Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro
645 650 655

Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg
660 665 670

Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys
675 680 685

Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu
690 695 700

Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu
705 710 715 720

Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met
725 730 735

Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys
740 745 750

Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln
755 760 765

Ala Ala Leu Gly Leu Gly Gly Gly Ser His His His His His His Leu
770 775 780

Asn Asp Ile Phe Glu Ala Gln Lys Ile Glu Trp His Glu
785 790 795

<210> 580

<211> 101

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 580

Asn Thr Thr Thr Thr Thr Lys Ser Glu Asp Gly His Tyr Ala Arg Thr
1 5 10 15

Asp Tyr Ala Glu Asn Ala Asn Lys Leu Glu Glu Ser Ala Arg Glu His
20 25 30

His Ile Pro Cys Pro Glu His Tyr Asn Gly Phe Cys Met His Gly Lys
35 40 45

Cys Glu His Ser Ile Asn Met Gln Glu Pro Ser Cys Arg Cys Asp Ala
50 55 60

Gly Tyr Thr Gly Gln His Cys Glu Lys Lys Asp Tyr Ser Val Leu Tyr
65 70 75 80

Val Val Pro Gly Pro Val Arg Phe Gln Tyr Val Gly Gly Gly Ser His
85 90 95

His His His His His
100

<210> 581
<211> 333
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 581

Asn Thr Thr Thr Thr Thr Lys Ser Glu Asp Gly His Tyr Ala Arg Thr
1 5 10 15

Asp Tyr Ala Glu Asn Ala Asn Lys Leu Glu Glu Ser Ala Arg Glu His
20 25 30

His Ile Pro Cys Pro Glu His Tyr Asn Gly Phe Cys Met His Gly Lys
35 40 45

Cys Glu His Ser Ile Asn Met Gln Glu Pro Ser Cys Arg Cys Asp Ala
50 55 60

Gly Tyr Thr Gly Gln His Cys Glu Lys Lys Asp Tyr Ser Val Leu Tyr
65 70 75 80

Val Val Pro Gly Pro Val Arg Phe Gln Tyr Val Gly Gly Gly Ser Pro
85 90 95

Arg Asn Cys Gly Gly Asp Cys Lys Pro Cys Ile Cys Thr Gly Ser Glu
100 105 110

Val Ser Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr
115 120 125

Ile Thr Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Gln
130 135 140

Asp Asp Pro Glu Val His Phe Ser Trp Phe Val Asp Asp Val Glu Val
 145 150 155 160

His Thr Ala Gln Thr Arg Pro Pro Glu Glu Gln Phe Asn Ser Thr Phe
 165 170 175

Arg Ser Val Ser Glu Leu Pro Ile Leu His Gln Asp Trp Leu Asn Gly
 180 185 190

Arg Thr Phe Arg Cys Lys Val Thr Ser Ala Ala Phe Pro Ser Pro Ile
 195 200 205

Glu Lys Thr Ile Ser Lys Pro Glu Gly Arg Thr Gln Val Pro His Val
 210 215 220

Tyr Thr Met Ser Pro Thr Lys Glu Glu Met Thr Gln Asn Glu Val Ser
 225 230 235 240

Ile Thr Cys Met Val Lys Gly Phe Tyr Pro Pro Asp Ile Tyr Val Glu
 245 250 255

Trp Gln Met Asn Gly Gln Pro Gln Glu Asn Tyr Lys Asn Thr Pro Pro
 260 265 270

Thr Met Asp Thr Asp Gly Ser Tyr Phe Leu Tyr Ser Lys Leu Asn Val
 275 280 285

Lys Lys Glu Lys Trp Gln Gln Gly Asn Thr Phe Thr Cys Ser Val Leu
 290 295 300

His Glu Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His Ser
 305 310 315 320

Pro Gly Lys Gly Gly Gly Ser His His His His His His
 325 330

<210> 582

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 582

Ser Tyr Ser Met Ser
1 5

<210> 583

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 583

Ser Tyr Tyr Ile Ser
1 5

<210> 584

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 584

Val Ile Ser Gly Ser Gly Gly Phe Thr Asp Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 585

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 585

Gly Ile Ile Pro Ile Ser Gly Arg Ala Asn Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 586
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 586

Val Ile Ser Gly Gly Gly Ser Phe Thr Ser Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 587
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 587

Met Pro Leu Asn Ser Pro His Asp Tyr
1 5

<210> 588
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 588

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> 589
<211> 124
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 589

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

Tyr Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Gly Ile Ile Pro Ile Ser Gly Arg Ala Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu 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 Asp Gly Tyr Ser Ser Gly Arg Ser Thr Thr Tyr Ala Phe Asp
100 105 110

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 590

<211> 645

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 590

gaaattgtgc tgaccagag cccgggcacc ctgagcctga gcccgggcga acgcgcgacc 60

ctgagctgcc gcgcgagcca gagcgttgcc acctattatc ttgcgtggta tcagcagaaa 120

ccgggccagg cgccgcgcct gctgatttac ggtgcatcct cccgtgcgac cggcattccg 180

gatcgcttta gcggcagcgg ttccggcacc gattttaccc tgaccattag ccgcctggaa 240

ccggaagatt ttgcggtgta ttattgccag cagtacggct ataaccaat tacctttggc 300
cagggcacca aagtggaaat caaacgtacg gtggctgcac catctgtctt catcttcccg 360
ccatctgatg agcagttgaa atctggaact gcctctgttg tgtgcctgct gaataacttc 420
tatcccagag aggccaaagt acagtggaag gtggataacg ccctccaatc gggtaactcc 480
caggagagtg tcacagagca ggacagcaag gacagcacct acagcctcag cagcaccttg 540
acgctgagca aagcagacta cgagaaacac aaagtctacg cctgcgaagt caccatcag 600
ggcctgagct cgcccgtcac aaagagcttc aacaggggag agtgt 645

<210> 591
<211> 96
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 591

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

<210> 592
<211> 15
<212> PRT
<213> Unknown

<220>

<223> Description of Unknown: TMEFF2 sequence

<400> 592

His	Gly	Lys	Cys	Glu	His	Ser	Ile	Asn	Met	Gln	Glu	Pro	Ser	Cys
1				5					10					15

<210> 593

<400> 593
000

<210> 594

<400> 594
000

<210> 595

<400> 595
000

<210> 596

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic 6xHis tag

<400> 596

His	His	His	His	His	His
1				5	

<210> 597

<400> 597
000

<210> 598

<400> 598
000

<210> 599

<400> 599
000

<210> 600
<211> 17
<212> PRT
<213> Unknown

<220>

<223> Description of Unknown: TMEFF2 sequence

<400> 600

Asp Ala Gly Tyr Thr Gly Gln His Cys Glu Lys Lys Asp Tyr Ser Val
1 5 10 15

Leu

<210> 601
<211> 330
<212> PRT
<213> Homo sapiens

<400> 601

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> 602
 <211> 327
 <212> PRT
 <213> Homo sapiens

<400> 602

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
 1 5 10 15

Ser Thr Ser Glu Ser 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 Lys Thr
 65 70 75 80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro
 100 105 110

Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
 115 120 125

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
 130 135 140

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
 145 150 155 160

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
 165 170 175

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
 180 185 190

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
195 200 205

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
210 215 220

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225 230 235 240

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
245 250 255

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
260 265 270

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
275 280 285

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
290 295 300

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305 310 315 320

Leu Ser Leu Ser Leu Gly Lys
325

<210> 603

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 603

Leu Gln Asp Tyr Asn Tyr Pro Leu Thr
1 5

<210> 604

<211> 118

<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 604

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

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

Ser Val Ile Ser Gly Ser Gly Gly Phe Thr Asp Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

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

Ala Arg Met Pro Leu Asn Ser Pro His Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 605

<400> 605
000

<210> 606

<400> 606
000

<210> 607

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 607

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
20 25 30

Leu Gly 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 Leu Gln Asp Tyr Asn Tyr Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 608

<400> 608
000

<210> 609

<400> 609
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<210> 610

<400> 610
000

<210> 611

<400> 611
000

<210> 612
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 612

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

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

Ser Val Ile Ser Gly Ser Gly Gly Phe Thr Asp Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

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

Ala Arg Met Pro Leu Asn Ser Pro His Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 613
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 613

Ala Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
20 25 30

Leu Gly 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 Leu Gln Asp Tyr Asn Tyr Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 614

<211> 445

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 614

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

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

Ser Val Ile Ser Gly Ser Gly Gly Phe Thr Asp Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

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

Ala Arg Met Pro Leu Asn Ser Pro His Asp Tyr Trp Gly Gln Gly Thr
100 105 110

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

<210> 615

<211> 214

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 615

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
20 25 30

Leu Gly 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 Leu Gln Asp Tyr Asn Tyr Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

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

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 616

<211> 445

<212> PRT
 <213> Artificial Sequence

 <220>
 <223> Description of Artificial Sequence: Synthetic polypeptide

 <400> 616

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

 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30

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

 Ser Val Ile Ser Gly Ser Gly Gly Phe Thr Asp Tyr Ala Asp Ser Val
 50 55 60

 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80

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

 Ala Arg Met Pro Leu Asn Ser Pro His Asp Tyr Trp Gly Gln Gly Thr
 100 105 110

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

<210> 617
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 617

Ala Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
20 25 30

Leu Gly 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 Leu Gln Asp Tyr Asn Tyr Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

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

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
 145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
 165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
 180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
 195 200 205

Phe Asn Arg Gly Glu Cys
 210

<210> 618
 <211> 354
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 618
 gaggtgcagc tgctggaaag cggcggaggc ctggtgcagc ccggaggaag cctgagactc 60
 agctgtgccg ccagcggctt caccttcagc agctacagca tgagctgggt caggcaggcc 120
 cctggcaaag gactggagtg ggtgagcgtg attagcggca gcggcggctt caccgattac 180
 gccgacagcg tgaagggcag gttcaccatc agcagggaaca atagcaagaa caccctgtac 240
 ctgcagatga acagcctgag ggccgaggac accgccgtgt actactgcgc caggatgccc 300
 ctgaacagcc ctcacgacta ctggggccag ggaaccctgg tgaccgtgtc cagc 354

<210> 619
 <211> 321
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 619
gacatccaga tgacccagag ccctagcagc ctgagcgcta gcgtgggcga cagggtgacc 60
atcacctgca gggccagcca gggcatcaga aacgacctgg gctggtacca gcagaagccc 120
ggcaaggccc ccaagctgct gatctacgcc gccagcagcc tgcagagcgg agtgcctagc 180
aggttcagcg gaagcggcag cggcaccgac ttcaccctga ccatcagcag cctgcagccc 240
gaggacttcg ccacctacta ctgcctgcag gactacaact accccctgac attcggcggc 300
ggcaccaagg tggagatcaa g 321

<210> 620
<211> 1335
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 620
gaggtgcagc tgctggaaag cggcggaggc ctggtgcagc ccggagggaag cctgagactc 60
agctgtgccg ccagcggcctt caccttcagc agctacagca tgagctgggt caggcaggcc 120
cctggcaaag gactggagtg ggtgagcgtg attagcggca gcggcggcctt caccgattac 180
gccgacagcg tgaagggcag gttcaccatc agcagggaca atagcaagaa caccctgtac 240
ctgcagatga acagcctgag ggccgaggac accgccgtgt actactgcgc caggatgccc 300
ctgaacagcc ctcacgacta ctggggccag ggaaccctgg tgaccgtgtc cagcgcttcc 360
accaagggcc catccgtctt ccccctggcg ccctgctcca ggagcacctc cgagagcaca 420
gccgccctgg gctgcctggt caaggactac ttccccgaac cggtagcggg gtcgtggaac 480
tcaggcggcc tgaccagcgg cgtgcacacc ttcccggctg tcctacagtc ctcaggactc 540
tactccctca gcagcgtggt gaccgtgccc tccagcagct tgggcacgaa aacctacact 600
tgcaacgtag atcacaagcc cagcaacacc aaggtggaca agagagttga gtccaaatat 660
gggtcccccat gccaccatg cccagcacct gaggccgccg ggggaccatc agtcttcctg 720
ttcccccaa aaccaagga cactctcatg atctcccga cccctgaggt cacgtgcgtg 780
gtggtggacg tgagccagga agacccgag gtccagttca actggtacgt ggatggcgtg 840
gaggtgcata atgccaagac aaagccgcgg gaggagcagt tcaacagcac gtaccgtgtg 900
gtcagcgtcc tcaccgtcct gcaccaggac tggctgaacg gcaaggagta caagtgaag 960

gtctccaaca aaggcctccc gtctccatc gagaaaacca tctccaaagc caaagggcag	1020
ccccgagagc cacaggtgta caccctgccc ccatcccagg aggagatgac caagaaccag	1080
gtcagcctga cctgcctggt caaaggcttc taccacagcg acatcgccgt ggagtgggag	1140
agcaatgggc agccggagaa caactacaag accacgcctc ccgtgctgga ctccgacggc	1200
tccttcttcc tctacagcag gctaaccgtg gacaagagca gatggcagga ggggaatgtc	1260
ttctcatgct ccgtgatgca tgaggctctg cacaaccact acacacagaa gagcctctcc	1320
ctgtctctgg gtaaa	1335

<210> 621
 <211> 645
 <212> DNA
 <213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 621	
gacatccaga tgaccagag ccctagcagc ctgagcgcta gcgtgggcga cagggtgacc	60
atcacctgca gggccagcca gggcatcaga aacgacctgg gctggtacca gcagaagccc	120
ggcaaggccc ccaagctgct gatctacgcc gccagcagcc tgcagagcgg agtgcctagc	180
aggttcagcg gaagcggcag cggcaccgac ttcacctga ccatcagcag cctgcagccc	240
gaggacttcg ccacctacta ctgcctgcag gactacaact accccctgac attcggcggc	300
ggcaccaagg tggagatcaa gcgtacggtg gctgcaccat ctgtcttcat cttcccgcga	360
tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat	420
cccagagagg ccaaagtaca gtggaagggtg gataacgccc tccaatcggg taactcccag	480
gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg	540
ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc	600
ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gttag	645

<210> 622
 <211> 354
 <212> DNA
 <213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 622

gaggtgcagc tgctggaaag cggcggaggc ctggtgcagc ccggagggaag cctgagactc	60
agctgtgccg ccagcggctt caccttcagc agctacagca tgagctgggt caggcaggcc	120
cctggcaaag gactggagtg ggtgagcgtg attagcggca gcggcggctt caccgattac	180
gccgacagcg tgaagggcag gttcaccatc agcagggaaca atagcaagaa caccctgtac	240
ctgcacatga acagcctgag ggccgaggac accgccgtgt actactgcgc caggatgccc	300
ctgaacagcc ctcacgacta ctggggccag ggaaccctgg tgaccgtgtc cagc	354

<210> 623

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 623

gccatccaga tgaccagag ccctagcagc ctgagcgcta gcgtgggcga cagggtgacc	60
atcacctgca gggccagcca gggcatcaga aacgacctgg gctggtacca gcagaagccc	120
ggcaaggccc ccaagctgct gatctacgcc gccagcagcc tgcagagcgg agtgcctagc	180
aggttcagcg gaagcggcag cggcaccgac ttcacctga ccatcagcag cctgcagccc	240
gaggacttcg ccacctacta ctgcctgcag gactacaact accccctgac attcggcggc	300
ggcaccaagg tggagatcaa g	321

<210> 624

<211> 1335

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 624

gaggtgcagc tgctggaaag cggcggaggc ctggtgcagc ccggagggaag cctgagactc	60
agctgtgccg ccagcggctt caccttcagc agctacagca tgagctgggt caggcaggcc	120
cctggcaaag gactggagtg ggtgagcgtg attagcggca gcggcggctt caccgattac	180
gccgacagcg tgaagggcag gttcaccatc agcagggaaca atagcaagaa caccctgtac	240

ctgcacatga acagcctgag ggccgaggac accgccgtgt actactgcgc caggatgccc	300
ctgaacagcc ctcacgacta ctggggccag ggaaccctgg tgaccgtgtc cagcgcttcc	360
accaagggcc catccgtctt ccccctggcg ccctgctcca ggagcacctc cgagagcaca	420
gccgccctgg gctgcctggc caaggactac ttccccgaac cggtagcggg gtcgtggaac	480
tcaggcgccc tgaccagcgg cgtgcacacc ttcccggctg tcctacagtc ctcaggactc	540
tactccctca gcagcgtggg gaccgtgccc tccagcagct tgggcacgaa aacctacact	600
tgcaacgtag atcacaagcc cagcaacacc aagggtggaca agagagttga gtccaaatat	660
ggccccccat gccaccatg cccagcacct gaggccgccg ggggaccatc agtcttcctg	720
ttccccccaa aacccaagga cactctcatg atctcccga cccctgaggt cacgtgcgtg	780
gtgggtggacg tgagccagga agaccccgag gtccagttca actgggtacgt ggatggcgtg	840
gaggtgcata atgccaagac aaagccgcgg gaggagcagt tcaacagcac gtaccgtgtg	900
gtcagcgtcc tcaccgtcct gcaccaggac tggctgaacg gcaaggagta caagtgcaag	960
gtctccaaca aaggcctccc gtcctccatc gagaaaacca tctccaaagc caaagggcag	1020
ccccgagagc cacaggtgta caccctgccc ccatcccagg aggagatgac caagaaccag	1080
gtcagcctga cctgcctggc caaaggcttc taccacagcg acatcgccgt ggagtgggag	1140
agcaatgggc agccggagaa caactacaag accacgcctc ccgtgctgga ctccgacggc	1200
tccttcttcc tctacagcag gctaaccgtg gacaagagca gatggcagga ggggaatgtc	1260
ttctcatgct ccgtgatgca tgaggctctg cacaaccact acacacagaa gagcctctcc	1320
ctgtctctgg gtaaa	1335

<210> 625

<211> 645

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 625

gcatccaga tgaccagag ccctagcagc ctgagcgcta gcgtgggcga cagggtgacc	60

atcacctgca gggccagcca gggcatcaga aacgacctgg gctggtacca gcagaagccc	120

ggcaaggccc ccaagctgct gatctacgcc gccagcagcc tgcagagcgg agtgcctagc	180

aggttcagcg gaagcggcag cggcaccgac ttcaccctga ccatcagcag cctgcagccc	240
gaggacttcg ccacctacta ctgcctgcag gactacaact accccctgac attcggcggc	300
ggcaccaagg tggagatcaa gcgtacggtg gctgcaccat ctgtcttcat cttcccgcga	360
tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat	420
cccagagagg ccaaagtaca gtggaagggtg gataacgccc tccaatcggg taactcccag	480
gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg	540
ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc	600
ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gttag	645

<210> 626
 <211> 330
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic polypeptide

<400> 626

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 Leu
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> 627
<211> 327
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 627

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1 5 10 15

Ser Thr Ser Glu Ser 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 Lys Thr
65 70 75 80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro
100 105 110

Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
115 120 125

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
130 135 140

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145 150 155 160

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
165 170 175

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
180 185 190

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
195 200 205

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
210 215 220

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225 230 235 240

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
245 250 255

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
260 265 270

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Leu Leu Tyr Ser
275 280 285

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
290 295 300

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305 310 315 320

Leu Ser Leu Ser Leu Gly Lys
325

<210> 628

<211> 330

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 628

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 Arg 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> 629
<211> 91
<212> PRT
<213> Unknown

<220>
<223> Description of Unknown: TMEFF2 sequence

<400> 629

Asn Thr Thr Thr Thr Thr Lys Ser Glu Asp Gly His Tyr Ala Arg Thr
1 5 10 15

Asp Tyr Ala Glu Asn Ala Asn Lys Leu Glu Glu Ser Ala Arg Glu His
20 25 30

His Ile Pro Cys Pro Glu His Tyr Asn Gly Phe Cys Met His Gly Lys
35 40 45

Cys Glu His Ser Ile Asn Met Gln Glu Pro Ser Cys Arg Cys Asp Ala
50 55 60

Gly Tyr Thr Gly Gln His Cys Glu Lys Lys Asp Tyr Ser Val Leu Tyr
65 70 75 80

Val Val Pro Gly Pro Val Arg Phe Gln Tyr Val
85 90

<210> 630
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 630

Arg Ala Ser Gln Ser Val Ser Ser Tyr Leu Ala
1 5 10

<210> 631
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 631

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 Tyr 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 Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

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

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 632
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 632

Asp Ser Tyr Asp Ser Ser Leu Tyr Val Gly Asp Tyr Phe Asp Tyr
1 5 10 15

<210> 633
<211> 447
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 633

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Ile Ser Ser Ser
20 25 30

Thr Tyr Tyr Trp Gly Trp Leu Arg Gln Pro Pro Gly Met Gly Leu Glu
35 40 45

Trp Thr Gly Ser Ile Tyr Phe Thr Gly Asn Thr Tyr Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Arg 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 Gly Ser Leu Phe Gly Asp Tyr Gly Tyr Phe Asp Tyr Trp Gly Gln
100 105 110

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

<210> 634
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 634

Gln Ala Trp Asp Ser Ser Thr Val Val
1 5

<210> 635
<211> 207
<212> PRT
<213> Homo sapiens

<400> 635

Met Gln Ser Gly Thr His Trp Arg Val Leu Gly Leu Cys Leu Leu Ser
1 5 10 15

Val Gly Val Trp Gly Gln Asp Gly Asn Glu Glu Met Gly Gly Ile Thr
20 25 30

Gln Thr Pro Tyr Lys Val Ser Ile Ser Gly Thr Thr Val Ile Leu Thr
35 40 45

Cys Pro Gln Tyr Pro Gly Ser Glu Ile Leu Trp Gln His Asn Asp Lys
50 55 60

Asn Ile Gly Gly Asp Glu Asp Asp Lys Asn Ile Gly Ser Asp Glu Asp
65 70 75 80

His Leu Ser Leu Lys Glu Phe Ser Glu Leu Glu Gln Ser Gly Tyr Tyr
85 90 95

Val Cys Tyr Pro Arg Gly Ser Lys Pro Glu Asp Ala Asn Phe Tyr Leu
100 105 110

Tyr Leu Arg Ala Arg Val Cys Glu Asn Cys Met Glu Met Asp Val Met
115 120 125

Ser Val Ala Thr Ile Val Ile Val Asp Ile Cys Ile Thr Gly Gly Leu
130 135 140

Leu Leu Leu Val Tyr Tyr Trp Ser Lys Asn Arg Lys Ala Lys Ala Lys
145 150 155 160

Pro Val Thr Arg Gly Ala Gly Ala Gly Gly Arg Gln Arg Gly Gln Asn
165 170 175

Lys Glu Arg Pro Pro Pro Val Pro Asn Pro Asp Tyr Glu Pro Ile Arg
180 185 190

Lys Gly Gln Arg Asp Leu Tyr Ser Gly Leu Asn Gln Arg Arg Ile
195 200 205

<210> 636
<211> 104
<212> PRT
<213> Homo sapiens

<400> 636

Asp Gly Asn Glu Glu Met Gly Gly Ile Thr Gln Thr Pro Tyr Lys Val
1 5 10 15

Ser Ile Ser Gly Thr Thr Val Ile Leu Thr Cys Pro Gln Tyr Pro Gly
20 25 30

Ser Glu Ile Leu Trp Gln His Asn Asp Lys Asn Ile Gly Gly Asp Glu
35 40 45

Asp Asp Lys Asn Ile Gly Ser Asp Glu Asp His Leu Ser Leu Lys Glu
50 55 60

Phe Ser Glu Leu Glu Gln Ser Gly Tyr Tyr Val Cys Tyr Pro Arg Gly
65 70 75 80

Ser Lys Pro Glu Asp Ala Asn Phe Tyr Leu Tyr Leu Arg Ala Arg Val
85 90 95

Cys Glu Asn Cys Met Glu Met Asp
100

<210> 637

<211> 450

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 637

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 Phe Asn Asn
20 25 30

Asn Ala Ala Trp Thr 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 Leu Tyr Asp Tyr Ala
50 55 60

Val Ser Val Lys Ser Arg Ile Thr Val Asn Pro Asp Thr Ser Arg Asn
65 70 75 80

Gln Phe Thr Leu Gln Leu Lys Ser Val Thr Pro Glu Asp Thr Ala Leu
85 90 95

Tyr Tyr Cys Ser Arg Gly Tyr Ser Ser Ser Phe Asp Tyr Trp Gly Gln
100 105 110

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

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

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

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

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

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

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225 230 235 240

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

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
260 265 270

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

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

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

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

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

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

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
 370 375 380

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

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

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
 420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
 435 440 445

Gly Lys
 450

<210> 638

<211> 450

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 638

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 Phe Asn Asn
 20 25 30

Asn Gly Ala Trp Ser 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 Leu Tyr Asp Tyr Ala
 50 55 60

Val Ser Val Lys Ser Arg Ile Thr Val Asn Pro Asp Thr Ser Arg Asn
65 70 75 80

Gln Phe Thr Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Leu
85 90 95

Tyr Tyr Cys Ala Arg Gly Tyr Ser Ser Ser Phe Asp Tyr Trp Gly Gln
100 105 110

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

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

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

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

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

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

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225 230 235 240

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

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
260 265 270

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

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

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

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
 325 330 335

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

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

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
 370 375 380

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

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

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
 420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
 435 440 445

Gly Lys
 450

<210> 639

<211> 450

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 639

Gln Val Arg 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 Phe Asn Asn
20 25 30

Asn Ala Ala Trp Ser 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 Leu Tyr Asp Tyr Ala
50 55 60

Val Thr Val Lys Ser Arg Ile Thr Val Asn Pro Asp Thr Ser Arg Asn
65 70 75 80

Gln Phe Thr Leu Gln Leu Thr Ser Val Thr Pro Glu Asp Thr Ala Leu
85 90 95

Tyr Tyr Cys Ala Arg Gly Tyr Ser Ser Ser Phe Asp Tyr Trp Gly Gln
100 105 110

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

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

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

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

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

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

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
 210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
 225 230 235 240

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

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
 260 265 270

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

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

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

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
 325 330 335

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

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

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
 370 375 380

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

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

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
 420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly Lys
450

<210> 640
<211> 447
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 640

Gln Val Gln Leu Gln Gln Ser Gly Pro Arg Leu Val Arg Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Phe Asn Asn
20 25 30

Asn Ala Ala Trp Ser 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 Leu Tyr Asp Tyr Ala
50 55 60

Val Ser Val Lys Ser Arg Ile Thr Val Asn Pro Asp Thr Ser Arg Asn
65 70 75 80

Gln Phe Thr Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Leu
85 90 95

Tyr Tyr Cys Ala Arg Gly Tyr Ser Ser Ser Phe Asp Tyr Trp Gly Gln
100 105 110

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

<210> 641

<211> 450

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 641

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 Phe Asn Asn
20 25 30

Asn Ala Ala Trp Ser 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 Leu Tyr Asp Tyr Ala
50 55 60

Val Ser Val Lys Ser Arg Ile Thr Val Asn Pro Asp Thr Ser Arg Asn
65 70 75 80

Gln Phe Thr Leu Gln Leu Lys Ser Val Thr Pro Glu Asp Thr Ala Leu
 85 90 95

Tyr Tyr Cys Ser Arg Gly Tyr Ser Ser Ser Phe Asp Tyr Trp Gly Gln
 100 105 110

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

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
 130 135 140

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

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

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

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

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
 210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
 225 230 235 240

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

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
 260 265 270

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

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

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

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
 325 330 335

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

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

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
 370 375 380

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

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

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
 420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
 435 440 445

Gly Lys
 450

<210> 642

<211> 450

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 642

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 Phe Asn Asn
20 25 30

Asn Ala Ala Trp Ser 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 Leu Tyr Asp Tyr Ala
50 55 60

Val Ser Val Lys Ser Arg Ile Thr Val Asn Pro Asp Thr Ser Arg Asn
65 70 75 80

Gln Phe Thr Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Leu
85 90 95

Tyr Tyr Cys Val Arg Gly Tyr Ser Ser Ser Phe Asp Tyr Trp Gly Gln
100 105 110

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

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

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

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

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

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

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
 225 230 235 240

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

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
 260 265 270

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

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

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

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
 325 330 335

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

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

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
 370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
 385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
 405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
 420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
 435 440 445

Gly Lys
450

<210> 643
<211> 450
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 643

Gln Val Gln Leu Gln Gln Ser Gly Pro Arg Leu Val Arg Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Phe Asn Asn
20 25 30

Asn Ala Ala Trp Ser 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 Leu Tyr Asp Tyr Ala
50 55 60

Val Ser Val Lys Ser Arg Ile Thr Val Asn Pro Asp Thr Ser Arg Asn
65 70 75 80

Gln Phe Thr Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Leu
85 90 95

Tyr Tyr Cys Ala Arg Gly Tyr Ser Ser Ser Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
290 295 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
 370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
 385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
 405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
 420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
 435 440 445

Gly Lys
 450

<210> 644

<211> 450

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 644

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 Phe Asn Asn
 20 25 30

Asn Ala Ala Trp Ser 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 Leu Tyr Asp Tyr Ala
 50 55 60

Val Ser Val Lys Ser Arg Ile Thr Val Asn Pro Asp Thr Ser Arg Asn
 65 70 75 80

Gln Phe Thr Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Leu
85 90 95

Tyr Tyr Cys Val Arg Gly Tyr Ser Ser Ser Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
290 295 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly Lys
450

<210> 645

<211> 216

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 645

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 Asn Ile Gly Thr Tyr
20 25 30

Lys Phe Val Ser Trp Tyr Gln Gln His Pro Asp Lys Ala Pro Lys Val
35 40 45

Leu Leu Tyr Glu Val Ser Lys Arg Pro Ser Gly Val Ser Ser 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 Gln Ala Asp Tyr His Cys Cys Ser Tyr Ala Gly Ser
85 90 95

Gly Thr Leu Leu Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105 110

Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
115 120 125

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
130 135 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145 150 155 160

Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
165 170 175

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
180 185 190

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
195 200 205

Thr Val Ala Pro Thr Glu Cys Ser
210 215

<210> 646
 <211> 216
 <212> PRT
 <213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 646

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 Asn Ile Gly Thr Tyr
 20 25 30

Lys Phe Val Ser Trp Tyr Gln Gln His Pro Asp Lys Ala Pro Lys Val
 35 40 45

Leu Leu Tyr Glu Val Ser Lys Arg Pro Ser Gly Val Ser Ser 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 Gln Ala Asp Tyr His Cys Cys Ser Tyr Ala Gly Ser
 85 90 95

Gly Thr Leu Leu Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
 100 105 110

Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
 115 120 125

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
 130 135 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
 145 150 155 160

Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
 165 170 175

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
180 185 190

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
195 200 205

Thr Val Ala Pro Thr Glu Cys Ser
210 215

<210> 647

<211> 216

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 647

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 Arg Asp Ile Gly Thr Tyr
20 25 30

Lys Phe Val Ser Trp Tyr Gln Gln His Pro Asp Lys Ala Pro Lys Val
35 40 45

Leu Leu Tyr Glu Val Ser Lys Arg Pro Ser Gly Val Ser Ser 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 Gln Ala Asp Tyr His Cys Cys Ser Tyr Ala Gly Ser
85 90 95

Gly Thr Leu Leu Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105 110

Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
115 120 125

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
 130 135 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
 145 150 155 160

Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
 165 170 175

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
 180 185 190

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
 195 200 205

Thr Val Ala Pro Thr Glu Cys Ser
 210 215

<210> 648

<211> 216

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 648

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 Arg Asp Ile Gly Thr Tyr
 20 25 30

Lys Phe Val Ser Trp Tyr Gln Gln His Pro Asp Lys Ala Pro Lys Val
 35 40 45

Leu Leu Tyr Glu Val Asn Lys Arg Pro Ser Gly Val Ser Ser 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 Gln Ala Asp Tyr His Cys Cys Ser Tyr Ala Gly Ser
85 90 95

Gly Thr Leu Leu Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105 110

Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
115 120 125

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
130 135 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145 150 155 160

Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
165 170 175

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
180 185 190

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
195 200 205

Thr Val Ala Pro Thr Glu Cys Ser
210 215

<210> 649
<211> 216
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 649

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 Asn Ile Gly Thr Tyr
20 25 30

Lys Phe Val Ser Trp Tyr Gln Gln His Pro Asp Lys Ala Pro Lys Val
35 40 45

Leu Leu Tyr Glu Val Ser Lys Arg Pro Ser Gly Val Ser Ser 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 Gln Ala Asp Tyr His Cys Cys Ser Tyr Ala Gly Ser
85 90 95

Gly Thr Leu Leu Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105 110

Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
115 120 125

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
130 135 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145 150 155 160

Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
165 170 175

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
180 185 190

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
195 200 205

Thr Val Ala Pro Thr Glu Cys Ser
210 215

<210> 650

<211> 216

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 650

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 Ile Gly Thr Tyr
20 25 30

Lys Phe Val Ser Trp Tyr Gln Gln His Pro Asp Lys Ala Pro Lys Val
35 40 45

Leu Leu Tyr Glu Val Ser Lys Arg Pro Ser Gly Val Ser Ser Arg Phe
50 55 60

Ser Gly Ser Lys Ser Asp Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Gln Ala Asp Tyr His Cys Cys Ser Tyr Ala Gly Ser
85 90 95

Gly Thr Leu Leu Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105 110

Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
115 120 125

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
130 135 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145 150 155 160

Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
165 170 175

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
180 185 190

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
195 200 205

Thr Val Ala Pro Thr Glu Cys Ser
210 215

<210> 651
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 651

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 Phe Asn Asn
20 25 30

Asn Ala Ala Trp Ser 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 Leu Tyr Asp Tyr Ala
50 55 60

Val Ser Val Lys Ser Arg Ile Thr Val Asn Pro Asp Thr Ser Arg Asn
65 70 75 80

Gln Phe Thr Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Leu
85 90 95

Tyr Tyr Cys Val Arg Gly Tyr Ser Ser Ser Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 652
<211> 120
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 652

Gln Val Gln Leu Gln Gln Ser Gly Pro Arg Leu Val Arg Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Phe Asn Asn
20 25 30

Asn Ala Ala Trp Ser 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 Leu Tyr Asp Tyr Ala
50 55 60

Val Ser Val Lys Ser Arg Ile Thr Val Asn Pro Asp Thr Ser Arg Asn
65 70 75 80

Gln Phe Thr Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Leu
85 90 95

Tyr Tyr Cys Ala Arg Gly Tyr Ser Ser Ser Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 653

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 653

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 Phe Asn Asn
20 25 30

Asn Ala Ala Trp Ser 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 Leu Tyr Asp Tyr Ala
50 55 60

Val Ser Val Lys Ser Arg Ile Thr Val Asn Pro Asp Thr Ser Arg Asn
65 70 75 80

Gln Phe Thr Leu Gln Leu Lys Ser Val Thr Pro Glu Asp Thr Ala Leu
85 90 95

Tyr Tyr Cys Ser Arg Gly Tyr Ser Ser Ser Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 654

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 654

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 Phe Asn Asn
20 25 30

Asn Gly Ala Trp Ser 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 Leu Tyr Asp Tyr Ala
50 55 60

Val Ser Val Lys Ser Arg Ile Thr Val Asn Pro Asp Thr Ser Arg Asn
65 70 75 80

Gln Phe Thr Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Leu
85 90 95

Tyr Tyr Cys Ala Arg Gly Tyr Ser Ser Ser Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 655

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 655

Gln Val Arg 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 Phe Asn Asn
20 25 30

Asn Ala Ala Trp Ser 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 Leu Tyr Asp Tyr Ala
50 55 60

Val Thr Val Lys Ser Arg Ile Thr Val Asn Pro Asp Thr Ser Arg Asn
65 70 75 80

Gln Phe Thr Leu Gln Leu Thr Ser Val Thr Pro Glu Asp Thr Ala Leu
85 90 95

Tyr Tyr Cys Ala Arg Gly Tyr Ser Ser Ser Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 656
<211> 120
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 656

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 Phe Asn Asn
20 25 30

Asn Ala Ala Trp Thr 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 Leu Tyr Asp Tyr Ala
50 55 60

Val Ser Val Lys Ser Arg Ile Thr Val Asn Pro Asp Thr Ser Arg Asn
65 70 75 80

Gln Phe Thr Leu Gln Leu Lys Ser Val Thr Pro Glu Asp Thr Ala Leu
85 90 95

Tyr Tyr Cys Ser Arg Gly Tyr Ser Ser Ser Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 657
<211> 120
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 657

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 Phe Asn Asn
20 25 30

Asn Ala Ala Trp Ser 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 Leu Tyr 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 Gly Tyr Ser Ser Ser Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 658

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 658

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 Arg Asp Ile Gly Thr Tyr
20 25 30

Lys Phe Val Ser Trp Tyr Gln Gln His Pro Asp Lys Ala Pro Lys Val
35 40 45

Leu Leu Tyr Glu Val Asn Lys Arg Pro Ser Gly Val Ser Ser 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 Gln Ala Asp Tyr His Cys Cys Ser Tyr Ala Gly Ser
85 90 95

Gly Thr Leu Leu Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 659
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 659

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 Asn Ile Gly Thr Tyr
20 25 30

Lys Phe Val Ser Trp Tyr Gln Gln His Pro Asp Lys Ala Pro Lys Val
35 40 45

Leu Leu Tyr Glu Val Ser Lys Arg Pro Ser Gly Val Ser Ser 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 Gln Ala Asp Tyr His Cys Cys Ser Tyr Ala Gly Ser
85 90 95

Gly Thr Leu Leu Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 660
<211> 110

<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 660

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 Ile Gly Thr Tyr
20 25 30

Lys Phe Val Ser Trp Tyr Gln Gln His Pro Asp Lys Ala Pro Lys Val
35 40 45

Leu Leu Tyr Glu Val Ser Lys Arg Pro Ser Gly Val Ser Ser Arg Phe
50 55 60

Ser Gly Ser Lys Ser Asp Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Gln Ala Asp Tyr His Cys Cys Ser Tyr Ala Gly Ser
85 90 95

Gly Thr Leu Leu Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 661
<211> 110
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 661

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 Asn Ile Gly Thr Tyr
20 25 30

Lys Phe Val Ser Trp Tyr Gln Gln His Pro Asp Lys Ala Pro Lys Val
35 40 45

Leu Leu Tyr Glu Val Ser Lys Arg Pro Ser Gly Val Ser Ser 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 Gln Ala Asp Tyr His Cys Val Ser Tyr Ala Gly Ser
85 90 95

Gly Thr Leu Leu Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 662
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 662

Asn Asn Asn Ala Ala Trp Ser
1 5

<210> 663
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 663

Arg Thr Tyr Tyr Arg Ser Lys Trp Leu Tyr Asp Tyr Ala Val Ser Val
1 5 10 15

Lys Ser

<210> 664
<211> 8

<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 664

Gly Tyr Ser Ser Ser Phe Asp Tyr
1 5

<210> 665

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 665

Asn Asn Asn Gly Ala Trp Ser
1 5

<210> 666

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 666

Asn Asn Asn Ala Ala Trp Thr
1 5

<210> 667

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 667

Thr Gly Thr Ser Arg Asp Ile Gly Thr Tyr Lys Phe Val Ser
1 5 10

<210> 668
<211> 14
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 668

Thr Gly Thr Ser Ser Asn Ile Gly Thr Tyr Lys Phe Val Ser
1 5 10

<210> 669
<211> 7
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 669

Glu Val Asn Lys Arg Pro Ser
1 5

<210> 670
<211> 10
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 670

Cys Ser Tyr Ala Gly Ser Gly Thr Leu Leu
1 5 10

<210> 671
<211> 14
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 671

Thr Gly Thr Ser Ser Asn Ile Gly Thr Tyr Lys Phe Val Ser
1 5 10

<210> 672
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 672

Thr Gly Thr Ser Arg Asp Ile Gly Thr Tyr Lys Phe Val Ser
1 5 10

<210> 673
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 673

Glu Val Ser Lys Arg Pro Ser
1 5

<210> 674
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 674

Thr Gly Thr Ser Ser Asp Ile Gly Thr Tyr Lys Phe Val Ser
1 5 10

<210> 675
<211> 447
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 675

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 Phe Asn Asn
 20 25 30
 Asn Ala Ala Trp Ser 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 Leu Tyr 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 Gly Tyr Ser Ser Ser Phe Asp Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
 115 120 125
 Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
 130 135 140
 Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
 145 150 155 160
 Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
 165 170 175
 Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
 180 185 190
 Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys
 195 200 205
 Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro
 210 215 220

Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val
 225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
 245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
 260 265 270

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
 275 280 285

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
 290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
 305 310 315 320

Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
 325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
 340 345 350

Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
 355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
 370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
 385 390 395 400

Asp Gly Ser Phe Leu Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
 405 410 415

Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
 420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
435 440 445

<210> 676
<211> 216
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 676

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 Asn Ile Gly Thr Tyr
20 25 30

Lys Phe Val Ser Trp Tyr Gln Gln His Pro Asp Lys Ala Pro Lys Val
35 40 45

Leu Leu Tyr Glu Val Ser Lys Arg Pro Ser Gly Val Ser Ser 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 Gln Ala Asp Tyr His Cys Val Ser Tyr Ala Gly Ser
85 90 95

Gly Thr Leu Leu Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105 110

Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
115 120 125

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
130 135 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145 150 155 160

Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
165 170 175

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
180 185 190

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
195 200 205

Thr Val Ala Pro Thr Glu Cys Ser
210 215

<210> 677
<211> 216
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 677

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 Asn Ile Gly Thr Tyr
20 25 30

Lys Phe Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Val
35 40 45

Met Ile Tyr Glu Val Ser Lys 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 Val Ser Tyr Ala Gly Ser
85 90 95

Gly Thr Leu Leu Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105 110

Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
115 120 125

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
130 135 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145 150 155 160

Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
165 170 175

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
180 185 190

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
195 200 205

Thr Val Ala Pro Thr Glu Cys Ser
210 215

<210> 678

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 678

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 Asn Ile Gly Thr Tyr
20 25 30

Lys Phe Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Val
35 40 45

Met Ile Tyr Glu Val Ser Lys 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 Val Ser Tyr Ala Gly Ser
85 90 95

Gly Thr Leu Leu Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 679

<211> 451

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 679

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Lys Ser Asp
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Glu Ile Ser Gly Ser Gly Gly Tyr Thr Asn Tyr Ala Asp Ser Leu
50 55 60

Lys Ser Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Ser Tyr Asp Ser Ser Leu Tyr Val Gly Asp Tyr Phe Asp
100 105 110

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys
115 120 125

Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu
 130 135 140

Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
 145 150 155 160

Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
 165 170 175

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
 180 185 190

Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn
 195 200 205

Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser
 210 215 220

Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
 225 230 235 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
 245 250 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln
 260 265 270

Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val
 275 280 285

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr
 290 295 300

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
 305 310 315 320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile
 325 330 335

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
 340 345 350

Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser
355 360 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
370 375 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385 390 395 400

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val
405 410 415

Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met
420 425 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
435 440 445

Leu Gly Lys
450

<210> 680
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 680

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 Tyr 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 Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 681

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 681

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Lys Ser Asp
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Glu Ile Ser Gly Ser Gly Gly Tyr Thr Asn Tyr Ala Asp Ser Leu
50 55 60

Lys Ser Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Ser Tyr Asp Ser Ser Leu Tyr Val Gly Asp Tyr Phe Asp
100 105 110

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 682

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 682

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 Tyr 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 Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 683
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 683

Glu Ile Ser Gly Ser Gly Gly Tyr Thr Asn Tyr Ala Asp Ser Leu Lys
1 5 10 15

Ser

<210> 684
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 684

Asp Ala Ser Tyr Arg Ala Thr
1 5

<210> 685
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 685

Asp Ala Ser Asn Arg Ala Thr
1 5

<210> 686

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 686

Gln Gln Arg Arg Asn Trp Pro Leu Thr
1 5

<210> 687

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 687

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 Phe Asn Asn
20 25 30

Asn Ala Ala Trp Ser 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 Leu Tyr Asp Tyr Ala
50 55 60

Val Ser Val Lys Ser Arg Ile Thr Val Asn Pro Asp Thr Ser Arg Asn
65 70 75 80

Gln Phe Thr Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Leu
85 90 95

Tyr Tyr Cys Val Arg Gly Tyr Ser Ser Ser Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 688

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 688

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 Arg Asp Ile Gly Thr Tyr
20 25 30

Lys Phe Val Ser Trp Tyr Gln Gln His Pro Asp Lys Ala Pro Lys Val
35 40 45

Leu Leu Tyr Glu Val Ser Lys Arg Pro Ser Gly Val Ser Ser 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 Gln Ala Asp Tyr His Cys Cys Ser Tyr Ala Gly Ser
85 90 95

Gly Thr Leu Leu Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 689

<211> 18

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 689

Arg Thr Tyr Tyr Arg Ser Lys Trp Leu Tyr Asp Tyr Ala Val Thr Val
1 5 10 15

Lys Ser

<210> 690

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 690

Val Ser Tyr Ala Gly Ser Gly Thr Leu Leu
1 5 10

<210> 691

<400> 691

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<210> 692

<400> 692

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<210> 693

<400> 693

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<210> 694

<400> 694

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<210> 695

<400> 695

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<210> 696

<400> 696

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 <400> 697
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<210> 708

<400> 708
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<210> 709

<400> 709
000

<210> 710

<400> 710
000

<210> 711

<211> 326

<212> PRT

<213> Homo sapiens

<400> 711

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1 5 10 15

Ser Thr Ser Glu Ser 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 Asn Phe Gly Thr Gln Thr
65 70 75 80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
100 105 110

Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
115 120 125

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
130 135 140

Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly
145 150 155 160

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn
165 170 175

Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp
180 185 190

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
195 200 205

Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu
210 215 220

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
225 230 235 240

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
245 250 255

Ser Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
260 265 270

Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
275 280 285

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
290 295 300

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
305 310 315 320

Ser Leu Ser Pro Gly Lys
325

<210> 712

<211> 360
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 712
caggtgcagc tgcagcagtc tggccctaga ctcgtgcggc cttcccagac cctgtctctg 60
acctgtgcca tctccggcga ctccgtgttc aacaacaacg ccgcctggtc ctggatccgg 120
cagagccctt ctagaggcct ggaatggctg ggccggacct actaccggtc caagtggctg 180
tacgactacg ccgtgtccgt gaagtcccgg atcaccgtga accctgacac ctcccggaac 240
cagttcacc cagctgctgaa ctccgtgacc cctgaggaca ccgccctgta ctactgcgcc 300
agaggctact cctcctcctt cgactattgg ggccagggca ccctcgtgac cgtgtcctct 360

<210> 713
<211> 330
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 713
cagtctgctc tgaccagcc tgcctccgtg tctggctctc ccggccagtc catcaccatc 60
agctgtaccg gcacctctc caacatcggc acctacaagt tcgtgtcctg gtatcagcag 120
caccgagaca agggcccaaa agtgctgctg tacgagggtg ccaagcggcc ctctggcgtg 180
tcctccagat tctccggctc caagtctggc aacaccgcct ccctgaccat cagcggactg 240
caggctgagg accaggccga ctaccactgt gtgtcctacg ctggctctgg caccctgctg 300
tttggcggag gcaccaagct gaccgtgctg 330

<210> 714
<211> 360
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 714
caggtgcagc tgcagcagag cggccccggc ctggtcaagc ccagccagac cctgagcctg 60

acctgcgcca tcagcggcga cagcgtgttc aacaacaacg ccgcctggtc ctggatccgc	120
cagagcccca gccgcggcct ggagtggctg ggccgcacct actaccgcag caagtggctg	180
tacgactacg ccgtgtccgt gaagtccgc atcaccatca accccgacac cagcaagaac	240
cagttctccc tgcagctgaa cagcgtgacc cccgaggaca ccgccgtgta ctactgcgcc	300
cgcggtaca gcagcagctt cgactactgg ggccagggca ccctgggtcac cgtgtccagc	360

<210> 715
 <211> 330
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 715	
cagtctgctc tgaccagcc tgcctccgtg tctggctctc ccggccagtc catcaccatc	60
agctgtaccg gcacctctc caacatcggc acctacaagt tcgtgtcctg gtatcagcag	120
caccccgga aggccccaa agtgatgac tacgaggtgt ccaagcggcc ctccggcgtg	180
tccaacagat tctccggctc caagtccggc aacaccgcct ccctgacaat cagcggactg	240
caggccgagg acgaggccga ctactactgt gtgtcctacg ccggctctgg caccctgctg	300
tttgcgggcg gaacaaagct gaccgtgctg	330

<210> 716
 <211> 4
 <212> PRT
 <213> Unknown

<220>
 <223> Description of Unknown: ER retention signal sequence

<400> 716

Lys Asp Glu Leu
 1

<210> 717
 <211> 101
 <212> PRT
 <213> Homo sapiens

<400> 717

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
 100

<210> 718
 <211> 99
 <212> PRT
 <213> Homo sapiens

<400> 718

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 Ser Tyr
 20 25 30

Asn Leu Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
 35 40 45

Met Ile Tyr Glu Val Ser Lys 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 Cys Ser Tyr Ala Gly Ser
85 90 95

Ser Thr Phe

<210> 719
<211> 750
<212> PRT
<213> Homo sapiens

<400> 719

Met Trp Asn Leu Leu His Glu Thr Asp Ser Ala Val Ala Thr Ala Arg
1 5 10 15

Arg Pro Arg Trp Leu Cys Ala Gly Ala Leu Val Leu Ala Gly Gly Phe
20 25 30

Phe Leu Leu Gly Phe Leu Phe Gly Trp Phe Ile Lys Ser Ser Asn Glu
35 40 45

Ala Thr Asn Ile Thr Pro Lys His Asn Met Lys Ala Phe Leu Asp Glu
50 55 60

Leu Lys Ala Glu Asn Ile Lys Lys Phe Leu Tyr Asn Phe Thr Gln Ile
65 70 75 80

Pro His Leu Ala Gly Thr Glu Gln Asn Phe Gln Leu Ala Lys Gln Ile
85 90 95

Gln Ser Gln Trp Lys Glu Phe Gly Leu Asp Ser Val Glu Leu Ala His
100 105 110

Tyr Asp Val Leu Leu Ser Tyr Pro Asn Lys Thr His Pro Asn Tyr Ile
115 120 125

Ser Ile Ile Asn Glu Asp Gly Asn Glu Ile Phe Asn Thr Ser Leu Phe
130 135 140

Glu Pro Pro Pro Pro Gly Tyr Glu Asn Val Ser Asp Ile Val Pro Pro
145 150 155 160

Phe Ser Ala Phe Ser Pro Gln Gly Met Pro Glu Gly Asp Leu Val Tyr
165 170 175

Val Asn Tyr Ala Arg Thr Glu Asp Phe Phe Lys Leu Glu Arg Asp Met
180 185 190

Lys Ile Asn Cys Ser Gly Lys Ile Val Ile Ala Arg Tyr Gly Lys Val
195 200 205

Phe Arg Gly Asn Lys Val Lys Asn Ala Gln Leu Ala Gly Ala Lys Gly
210 215 220

Val Ile Leu Tyr Ser Asp Pro Ala Asp Tyr Phe Ala Pro Gly Val Lys
225 230 235 240

Ser Tyr Pro Asp Gly Trp Asn Leu Pro Gly Gly Gly Val Gln Arg Gly
245 250 255

Asn Ile Leu Asn Leu Asn Gly Ala Gly Asp Pro Leu Thr Pro Gly Tyr
260 265 270

Pro Ala Asn Glu Tyr Ala Tyr Arg Arg Gly Ile Ala Glu Ala Val Gly
275 280 285

Leu Pro Ser Ile Pro Val His Pro Ile Gly Tyr Tyr Asp Ala Gln Lys
290 295 300

Leu Leu Glu Lys Met Gly Gly Ser Ala Pro Pro Asp Ser Ser Trp Arg
305 310 315 320

Gly Ser Leu Lys Val Pro Tyr Asn Val Gly Pro Gly Phe Thr Gly Asn
325 330 335

Phe Ser Thr Gln Lys Val Lys Met His Ile His Ser Thr Asn Glu Val
340 345 350

Thr Arg Ile Tyr Asn Val Ile Gly Thr Leu Arg Gly Ala Val Glu Pro
355 360 365

Asp Arg Tyr Val Ile Leu Gly Gly His Arg Asp Ser Trp Val Phe Gly
370 375 380

Gly Ile Asp Pro Gln Ser Gly Ala Ala Val Val His Glu Ile Val Arg
385 390 395 400

Ser Phe Gly Thr Leu Lys Lys Glu Gly Trp Arg Pro Arg Arg Thr Ile
405 410 415

Leu Phe Ala Ser Trp Asp Ala Glu Glu Phe Gly Leu Leu Gly Ser Thr
420 425 430

Glu Trp Ala Glu Glu Asn Ser Arg Leu Leu Gln Glu Arg Gly Val Ala
435 440 445

Tyr Ile Asn Ala Asp Ser Ser Ile Glu Gly Asn Tyr Thr Leu Arg Val
450 455 460

Asp Cys Thr Pro Leu Met Tyr Ser Leu Val His Asn Leu Thr Lys Glu
465 470 475 480

Leu Lys Ser Pro Asp Glu Gly Phe Glu Gly Lys Ser Leu Tyr Glu Ser
485 490 495

Trp Thr Lys Lys Ser Pro Ser Pro Glu Phe Ser Gly Met Pro Arg Ile
500 505 510

Ser Lys Leu Gly Ser Gly Asn Asp Phe Glu Val Phe Phe Gln Arg Leu
515 520 525

Gly Ile Ala Ser Gly Arg Ala Arg Tyr Thr Lys Asn Trp Glu Thr Asn
530 535 540

Lys Phe Ser Gly Tyr Pro Leu Tyr His Ser Val Tyr Glu Thr Tyr Glu
545 550 555 560

Leu Val Glu Lys Phe Tyr Asp Pro Met Phe Lys Tyr His Leu Thr Val
565 570 575

Ala Gln Val Arg Gly Gly Met Val Phe Glu Leu Ala Asn Ser Ile Val
580 585 590

Leu Pro Phe Asp Cys Arg Asp Tyr Ala Val Val Leu Arg Lys Tyr Ala
595 600 605

Asp Lys Ile Tyr Ser Ile Ser Met Lys His Pro Gln Glu Met Lys Thr
610 615 620

Tyr Ser Val Ser Phe Asp Ser Leu Phe Ser Ala Val Lys Asn Phe Thr
625 630 635 640

Glu Ile Ala Ser Lys Phe Ser Glu Arg Leu Gln Asp Phe Asp Lys Ser
645 650 655

Asn Pro Ile Val Leu Arg Met Met Asn Asp Gln Leu Met Phe Leu Glu
660 665 670

Arg Ala Phe Ile Asp Pro Leu Gly Leu Pro Asp Arg Pro Phe Tyr Arg
675 680 685

His Val Ile Tyr Ala Pro Ser Ser His Asn Lys Tyr Ala Gly Glu Ser
690 695 700

Phe Pro Gly Ile Tyr Asp Ala Leu Phe Asp Ile Glu Ser Lys Val Asp
705 710 715 720

Pro Ser Lys Ala Trp Gly Glu Val Lys Arg Gln Ile Tyr Val Ala Ala
725 730 735

Phe Thr Val Gln Ala Ala Ala Glu Thr Leu Ser Glu Val Ala
740 745 750

<210> 720
<211> 752
<212> PRT
<213> Mus sp.

<400> 720

Met Trp Asn Ala Leu Gln Asp Arg Asp Ser Ala Glu Val Leu Gly His
1 5 10 15

Arg Gln Arg Trp Leu Arg Val Gly Thr Leu Val Leu Ala Leu Thr Gly

20

25

30

Thr Phe Leu Ile Gly Phe Leu Phe Gly Trp Phe Ile Lys Pro Ser Asn
 35 40 45

Glu Ala Thr Gly Asn Val Ser His Ser Gly Met Lys Lys Glu Phe Leu
 50 55 60

His Glu Leu Lys Ala Glu Asn Ile Lys Lys Phe Leu Tyr Asn Phe Thr
 65 70 75 80

Arg Thr Pro His Leu Ala Gly Thr Gln Asn Asn Phe Glu Leu Ala Lys
 85 90 95

Gln Ile His Asp Gln Trp Lys Glu Phe Gly Leu Asp Leu Val Glu Leu
 100 105 110

Ser His Tyr Asp Val Leu Leu Ser Tyr Pro Asn Lys Thr His Pro Asn
 115 120 125

Tyr Ile Ser Ile Ile Asn Glu Asp Gly Asn Glu Ile Phe Lys Thr Ser
 130 135 140

Leu Ser Glu Gln Pro Pro Pro Gly Tyr Glu Asn Ile Ser Asp Val Val
 145 150 155 160

Pro Pro Tyr Ser Ala Phe Ser Pro Gln Gly Thr Pro Glu Gly Asp Leu
 165 170 175

Val Tyr Val Asn Tyr Ala Arg Thr Glu Asp Phe Phe Lys Leu Glu Arg
 180 185 190

Glu Met Lys Ile Ser Cys Ser Gly Lys Ile Val Ile Ala Arg Tyr Gly
 195 200 205

Lys Val Phe Arg Gly Asn Met Val Lys Asn Ala Gln Leu Ala Gly Ala
 210 215 220

Lys Gly Met Ile Leu Tyr Ser Asp Pro Ala Asp Tyr Phe Val Pro Ala
 225 230 235 240

Val Lys Ser Tyr Pro Asp Gly Trp Asn Leu Pro Gly Gly Gly Val Gln
245 250 255

Arg Gly Asn Val Leu Asn Leu Asn Gly Ala Gly Asp Pro Leu Thr Pro
260 265 270

Gly Tyr Pro Ala Asn Glu His Ala Tyr Arg His Glu Leu Thr Asn Ala
275 280 285

Val Gly Leu Pro Ser Ile Pro Val His Pro Ile Gly Tyr Asp Asp Ala
290 295 300

Gln Lys Leu Leu Glu His Met Gly Gly Pro Ala Pro Pro Asp Ser Ser
305 310 315 320

Trp Lys Gly Gly Leu Lys Val Pro Tyr Asn Val Gly Pro Gly Phe Ala
325 330 335

Gly Asn Phe Ser Thr Gln Lys Val Lys Met His Ile His Ser Tyr Thr
340 345 350

Lys Val Thr Arg Ile Tyr Asn Val Ile Gly Thr Leu Lys Gly Ala Leu
355 360 365

Glu Pro Asp Arg Tyr Val Ile Leu Gly Gly His Arg Asp Ala Trp Val
370 375 380

Phe Gly Gly Ile Asp Pro Gln Ser Gly Ala Ala Val Val His Glu Ile
385 390 395 400

Val Arg Ser Phe Gly Thr Leu Lys Lys Lys Gly Arg Arg Pro Arg Arg
405 410 415

Thr Ile Leu Phe Ala Ser Trp Asp Ala Glu Glu Phe Gly Leu Leu Gly
420 425 430

Ser Thr Glu Trp Ala Glu Glu His Ser Arg Leu Leu Gln Glu Arg Gly
435 440 445

Val Ala Tyr Ile Asn Ala Asp Ser Ser Ile Glu Gly Asn Tyr Thr Leu

450

455

460

Arg Val Asp Cys Thr Pro Leu Met Tyr Ser Leu Val Tyr Asn Leu Thr
 465 470 475 480

Lys Glu Leu Gln Ser Pro Asp Glu Gly Phe Glu Gly Lys Ser Leu Tyr
 485 490 495

Asp Ser Trp Lys Glu Lys Ser Pro Ser Pro Glu Phe Ile Gly Met Pro
 500 505 510

Arg Ile Ser Lys Leu Gly Ser Gly Asn Asp Phe Glu Val Phe Phe Gln
 515 520 525

Arg Leu Gly Ile Ala Ser Gly Arg Ala Arg Tyr Thr Lys Asn Trp Lys
 530 535 540

Thr Asn Lys Val Ser Ser Tyr Pro Leu Tyr His Ser Val Tyr Glu Thr
 545 550 555 560

Tyr Glu Leu Val Val Lys Phe Tyr Asp Pro Thr Phe Lys Tyr His Leu
 565 570 575

Thr Val Ala Gln Val Arg Gly Ala Met Val Phe Glu Leu Ala Asn Ser
 580 585 590

Ile Val Leu Pro Phe Asp Cys Gln Ser Tyr Ala Val Ala Leu Lys Lys
 595 600 605

Tyr Ala Asp Thr Ile Tyr Asn Ile Ser Met Lys His Pro Gln Glu Met
 610 615 620

Lys Ala Tyr Met Ile Ser Phe Asp Ser Leu Phe Ser Ala Val Asn Asn
 625 630 635 640

Phe Thr Asp Val Ala Ser Lys Phe Asn Gln Arg Leu Gln Glu Leu Asp
 645 650 655

Lys Ser Asn Pro Ile Leu Leu Arg Ile Met Asn Asp Gln Leu Met Tyr
 660 665 670

Leu Glu Arg Ala Phe Ile Asp Pro Leu Gly Leu Pro Gly Arg Pro Phe
675 680 685

Tyr Arg His Ile Ile Tyr Ala Pro Ser Ser His Asn Lys Tyr Ala Gly
690 695 700

Glu Ser Phe Pro Gly Ile Tyr Asp Ala Leu Phe Asp Ile Ser Ser Lys
705 710 715 720

Val Asn Ala Ser Lys Ala Trp Asn Glu Val Lys Arg Gln Ile Ser Ile
725 730 735

Ala Thr Phe Thr Val Gln Ala Ala Ala Glu Thr Leu Arg Glu Val Ala
740 745 750

<210> 721
<211> 750
<212> PRT
<213> Macaca fascicularis

<400> 721

Met Trp Asn Leu Leu His Glu Thr Asp Ser Ala Val Ala Thr Ala Arg
1 5 10 15

Arg Pro Arg Trp Leu Cys Ala Gly Ala Leu Val Leu Ala Gly Gly Phe
20 25 30

Phe Leu Leu Gly Phe Leu Phe Gly Trp Phe Ile Lys Ser Ser Ser Glu
35 40 45

Ala Thr Asn Ile Thr Pro Lys His Asn Met Lys Ala Phe Leu Asp Glu
50 55 60

Leu Lys Ala Glu Asn Ile Lys Lys Phe Leu His Asn Phe Thr Gln Ile
65 70 75 80

Pro His Leu Ala Gly Thr Glu Gln Asn Phe Gln Leu Ala Lys Gln Ile
85 90 95

Gln Ser Gln Trp Lys Glu Phe Gly Leu Asp Ser Val Glu Leu Thr His
100 105 110

Tyr Asp Val Leu Leu Ser Tyr Pro Asn Lys Thr His Pro Asn Tyr Ile
115 120 125

Ser Ile Ile Asn Glu Asp Gly Asn Glu Ile Phe Asn Thr Ser Leu Phe
130 135 140

Glu Pro Pro Pro Ala Gly Tyr Glu Asn Val Ser Asp Ile Val Pro Pro
145 150 155 160

Phe Ser Ala Phe Ser Pro Gln Gly Met Pro Glu Gly Asp Leu Val Tyr
165 170 175

Val Asn Tyr Ala Arg Thr Glu Asp Phe Phe Lys Leu Glu Arg Asp Met
180 185 190

Lys Ile Asn Cys Ser Gly Lys Ile Val Ile Ala Arg Tyr Gly Lys Val
195 200 205

Phe Arg Gly Asn Lys Val Lys Asn Ala Gln Leu Ala Gly Ala Thr Gly
210 215 220

Val Ile Leu Tyr Ser Asp Pro Asp Asp Tyr Phe Ala Pro Gly Val Lys
225 230 235 240

Ser Tyr Pro Asp Gly Trp Asn Leu Pro Gly Gly Gly Val Gln Arg Gly
245 250 255

Asn Ile Leu Asn Leu Asn Gly Ala Gly Asp Pro Leu Thr Pro Gly Tyr
260 265 270

Pro Ala Asn Glu Tyr Ala Tyr Arg Arg Gly Met Ala Glu Ala Val Gly
275 280 285

Leu Pro Ser Ile Pro Val His Pro Ile Gly Tyr Tyr Asp Ala Gln Lys
290 295 300

Leu Leu Glu Lys Met Gly Gly Ser Ala Ser Pro Asp Ser Ser Trp Arg
305 310 315 320

Gly Ser Leu Lys Val Pro Tyr Asn Val Gly Pro Gly Phe Thr Gly Asn
325 330 335

Phe Ser Thr Gln Lys Val Lys Met His Ile His Ser Thr Ser Glu Val
340 345 350

Thr Arg Ile Tyr Asn Val Ile Gly Thr Leu Arg Gly Ala Val Glu Pro
355 360 365

Asp Arg Tyr Val Ile Leu Gly Gly His Arg Asp Ser Trp Val Phe Gly
370 375 380

Gly Ile Asp Pro Gln Ser Gly Ala Ala Val Val His Glu Ile Val Arg
385 390 395 400

Ser Phe Gly Met Leu Lys Lys Glu Gly Trp Arg Pro Arg Arg Thr Ile
405 410 415

Leu Phe Ala Ser Trp Asp Ala Glu Glu Phe Gly Leu Leu Gly Ser Thr
420 425 430

Glu Trp Ala Glu Glu Asn Ser Arg Leu Leu Gln Glu Arg Gly Val Ala
435 440 445

Tyr Ile Asn Ala Asp Ser Ser Ile Glu Gly Asn Tyr Thr Leu Arg Val
450 455 460

Asp Cys Thr Pro Leu Met Tyr Ser Leu Val Tyr Asn Leu Thr Lys Glu
465 470 475 480

Leu Glu Ser Pro Asp Glu Gly Phe Glu Gly Lys Ser Leu Tyr Glu Ser
485 490 495

Trp Thr Lys Lys Ser Pro Ser Pro Glu Phe Ser Gly Met Pro Arg Ile
500 505 510

Ser Lys Leu Gly Ser Gly Asn Asp Phe Glu Val Phe Phe Gln Arg Leu
515 520 525

Gly Ile Ala Ser Gly Arg Ala Arg Tyr Thr Lys Asn Trp Glu Thr Asn
530 535 540

Lys Phe Ser Ser Tyr Pro Leu Tyr His Ser Val Tyr Glu Thr Tyr Glu
545 550 555 560

Leu Val Glu Lys Phe Tyr Asp Pro Met Phe Lys Tyr His Leu Thr Val
565 570 575

Ala Gln Val Arg Gly Gly Met Val Phe Glu Leu Ala Asn Ser Val Val
580 585 590

Leu Pro Phe Asp Cys Arg Asp Tyr Ala Val Val Leu Arg Lys Tyr Ala
595 600 605

Asp Lys Ile Tyr Asn Ile Ser Met Lys His Pro Gln Glu Met Lys Thr
610 615 620

Tyr Ser Val Ser Phe Asp Ser Leu Phe Ser Ala Val Lys Asn Phe Thr
625 630 635 640

Glu Ile Ala Ser Lys Phe Ser Glu Arg Leu Arg Asp Phe Asp Lys Ser
645 650 655

Asn Pro Ile Leu Leu Arg Met Met Asn Asp Gln Leu Met Phe Leu Glu
660 665 670

Arg Ala Phe Ile Asp Pro Leu Gly Leu Pro Asp Arg Pro Phe Tyr Arg
675 680 685

His Val Ile Tyr Ala Pro Ser Ser His Asn Lys Tyr Ala Gly Glu Ser
690 695 700

Phe Pro Gly Ile Tyr Asp Ala Leu Phe Asp Ile Glu Ser Lys Val Asp
705 710 715 720

Pro Ser Gln Ala Trp Gly Glu Val Lys Arg Gln Ile Ser Ile Ala Thr
725 730 735

Phe Thr Val Gln Ala Ala Ala Glu Thr Leu Ser Glu Val Ala
740 745 750

<210> 722
<211> 76
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 722

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Lys Ser Asp
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Glu Ile Ser Gly Ser Gly Gly Tyr Thr Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys
65 70 75

<210> 723
<211> 76
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 723

Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala
1 5 10 15

Val Tyr Tyr Cys Ala Arg Asp Ser Tyr Asp Ser Ser Leu Tyr Val Gly
20 25 30

Asp Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
35 40 45

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
50 55 60

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
65 70 75

<210> 724
<211> 75
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 724

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
1 5 10 15

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
20 25 30

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
35 40 45

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
50 55 60

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
65 70 75

<210> 725
<211> 72
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 725

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
65 70

<210> 726
<211> 72
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 726

Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys
1 5 10 15

Gln Gln Arg Ser Asn Trp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val
20 25 30

Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro
35 40 45

Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu
50 55 60

Asn Asn Phe Tyr Pro Arg Glu Ala
65 70

<210> 727
<211> 70
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 727

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
1 5 10 15

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
20 25 30

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
35 40 45

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
50 55 60

Phe Asn Arg Gly Glu Cys
65 70

<210> 728
<211> 450
<212> PRT
<213> artificial

<220>
<223> antibody

<400> 728

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 Phe Asn Asn
20 25 30

Asn Ala Ala Trp Ser 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 Leu Tyr 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 Gly Tyr Ser Ser Ser Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Ala
225 230 235 240

Ser Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Ala Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
290 295 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ser Ser Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Leu Leu Tyr Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly Lys
450

<210> 729
<211> 450
<212> PRT
<213> Artificial Sequence

<220>
<223> antibody fragment

<400> 729

Gln Val Gln Leu Gln Gln Ser Gly Pro Arg Leu Val Arg Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Phe Asn Asn
20 25 30

Asn Ala Ala Trp Ser 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 Leu Tyr Asp Tyr Ala
50 55 60

Val Ser Val Lys Ser Arg Ile Thr Val Asn Pro Asp Thr Ser Arg Asn
65 70 75 80

Gln Phe Thr Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Leu
85 90 95

Tyr Tyr Cys Ala Arg Gly Tyr Ser Ser Ser Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Ala
225 230 235 240

Ser Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Ala Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
290 295 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ser Ser Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Leu Leu Tyr Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly Lys
450