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(54) Title: ANTI-IL-5 ANTIBODIES

FIG. 13A

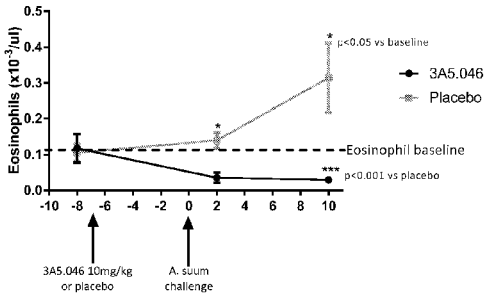
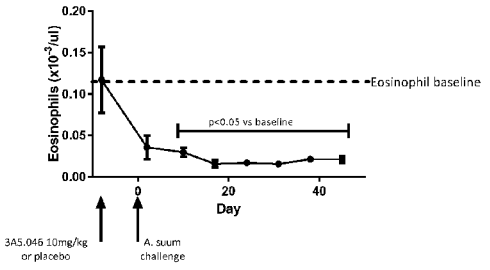


FIG. 13B



(57) Abstract: Disclosed herein are fully human antibody molecules that immunospecifically bind to human IL-5. The antibody molecules can bind to human IL-5 with an equilibrium affinity constant (KD) of at least about 40 pM as determined by surface plasmon resonance.

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[Continued on next page]

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ANTI-IL-5 ANTIBODIES

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 62/438,502, filed December 23, 2016, the disclosure of which is hereby incorporated by reference in its entirety.

SEQUENCE LISTING

[0002] 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 ASCII copy, created on November 30, 2017, is named 102085.000906_sl.txt and is 93,529 bytes in size.

TECHNICAL FIELD

[0003] Disclosed herein are novel antibody molecules that immunospecifically bind IL-5, and uses of the disclosed antibodies.

BACKGROUND

[0004] Interleukin-5 (IL-5) is a T-helper 2 (Th2) cytokine which causes the proliferation and differentiation of both B cells and eosinophils. In B cells, IL-5 also increases immunoglobulin secretion. IL-5 is a key modulator of eosinophils, where it also regulates maturation, migration to tissues, survival, and the prevention of apoptosis.

[0005] Through two separate motifs, IL-5 binds to its specific receptor (IL5-Rα) and a signaling receptor, a common β-chain (βc) shared between Interleukin-3 (IL-3) and granulocyte-macrophage colony stimulating factor (GMCSF). The affinity of IL-5 for IL5-Rα has been reported to be in the mid-low nM range (0.2-100 nM); this shifts into the mid-pM range (~100 pM) in the presence of βc. IL5-Rα binds to IL-5 specifically, which then recruits βc to IL-5R.

[0006] The therapeutic potential of targeting interleukin-5 (IL-5) has been demonstrated by extensive validation in the literature and recent positive Phase III clinical data for both reslizumab and mepolizumab.

SUMMARY

[0007] Disclosed herein are human antibody molecules that immunospecifically bind to human IL-5 with an equilibrium affinity constant (K_D) of at least about 40 pM as determined by surface plasmon resonance.

[0008] Also provided are antibody molecules comprising a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 4, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 6, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 8, a light chain CDR1 comprising the amino acid sequence of SEQ ID NOs: 5, 21, 24, 27, 30, 33, 36, 39, or 66, a light chain CDR2 comprising the amino acid sequence of SEQ ID NOs: 7, 42, or 45, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NOs: 15, 48, 51, 54, 57, 60, or 63.

[0009] The disclosed antibody molecules can comprise a heavy chain variable region comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 16 and a light chain variable region comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 17, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, 52, 55, 58, 61, 64, or 67, wherein the variability (i.e. the at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity) occurs outside of the CDR sequence.

[0010] The disclosed antibody molecules can comprise a heavy chain comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NOs: 18 or 20 and a light chain comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 19, 23, 26, 29, 32, 35, 38, 41, 44, 47, 50, 53, 56, 59, 62, 65, or 68, wherein the variability (i.e. the at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity) occurs outside of the CDR sequence.

[0011] Nucleic acid molecules encoding the disclosed antibody molecules, vectors comprising the nucleic acid molecules, and cells transformed to express the disclosed antibody molecules are also provided.

[0012] Also disclosed are pharmaceutical compositions comprising any of the antibody molecules disclosed herein.

[0013] Also provided are methods of treating a subject having eosinophilic asthma, hypereosinophilic syndrome, nasal polyposis with eosinophilic involvement, eosinophilic granulomatosis with polyangiitis, atopic dermatitis or eosinophilic esophagitis comprising administering to the subject a therapeutically effective amount of any of the herein disclosed

antibody molecules, or pharmaceutical compositions comprising the same, to treat the eosinophilic asthma, hypereosinophilic syndrome, nasal polyposis with eosinophilic involvement, eosinophilic granulomatosis with polyangiitis, atopic dermatitis or eosinophilic esophagitis.

[0014] Use of an effective amount of any of the herein disclosed antibody molecules, or pharmaceutical compositions comprising the same, in the treatment of eosinophilic asthma, hypereosinophilic syndrome, nasal polyposis with eosinophilic involvement, eosinophilic granulomatosis with polyangiitis, atopic dermatitis, or eosinophilic esophagitis are also provided.

[0015] Further provided is the use of any of the herein disclosed antibody molecules, or pharmaceutical compositions comprising the same, in the manufacture of a medicament for the treatment of eosinophilic asthma, hypereosinophilic syndrome, nasal polyposis with eosinophilic involvement, eosinophilic granulomatosis with polyangiitis, atopic dermatitis or eosinophilic esophagitis.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] 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 antibody molecules, methods, and uses, there are shown in the drawings exemplary embodiments of the antibody molecules, methods, and uses; however, the antibody molecules, methods, and uses are not limited to the specific embodiments disclosed. In the drawings:

[0017] **FIG. 1** illustrates a TF-1.6G4 assay showing that antibody variant 3A5.001 (in IgG4 format) retained an equivalent potency to the original antibody 3A5 (in IgG1 format).

[0018] **FIG. 2** illustrates a TF-1.6G4 assay showing that antibody variant 3A5.040 retained an equivalent potency to the parent antibody 3A5.001.

[0019] **FIG. 3** is a graphical matrix showing the position and identity of the different single amino acid substitutions that were generated on the 3A5.040 VH CDRs, aligned to the original 3A5.040 VH sequence (top sequence). The boxes contain the residues which were designated CDR residues according to the AbM nomenclature. In addition to the CDR residues, variants were made to Kabat residue numbers 93 and 94 (adjacent to HC CDR3) as described in the Example "Functional testing and characterization of antibodies." The various sequences recited in this figure are provided in SEQ ID NO:73.

[0020] **FIG. 4** is graphical matrix showing the position and identity of the different single amino acid substitutions that were generated to the 3A5.040 VL CDRs, aligned to the original 3A5.040 VL sequence (top sequence). The boxes contain the residues which were designated CDR residues according to the AbM nomenclature. The various sequences recited in this figure are provided in SEQ ID NO:74.

[0021] **FIG. 5** illustrates exemplary light chain CDR consensus sequences aligned to the 3A5.040 VL sequence (top sequence). 3A5.040 VL CDR single amino acid substitution variants which showed potential improvements according to the inclusion criteria described in the Examples of (the ratio of variant kd to 3A5.040 kd $\geq$ 1.5) and (the ratio of variant expression level to 3A5.040 expression level $\geq$0.5) were included in the consensus sequences. CDR definitions and numbering are according to AbM and Kabat nomenclature, respectively. The boxes identify the positions of CDR residues. The various sequences recited in this figure are provided in SEQ ID NO:75.

[0022] **FIG. 6** illustrates a multi-concentration Biacore kinetic analysis of 3A5.046 antibody binding to recombinant human IL-5 at 2.5, 1.25, 0.625, 0.313 and 0.156 µg/mL. Sensorgrams show decreasing concentrations of IL-5 in order from 2.5 µg/mL IL-5 in the top trace to 0.156 µg/mL IL-5 in the bottom trace.

[0023] **FIG. 7A** and **FIG. 7B** illustrate the proliferation of TF-1.6G4 cells in response to IL-5, and the potency of inhibition of IL-5 driven proliferation by 3A5.046. 3A5.046 was a more potent inhibitor of human IL-5 (FIG. 7A) and cynomolgus monkey IL-5 (FIG. 7B) than mepolizumab.

[0024] **FIG. 8A** and **FIG. 8B** illustrate an exemplary ELISA developed using the 3A5 antibody and a control capture antibody (R&D Systems). The ELISA was able to detect recombinant IL-5 (FIG. 8A) and IL-5 produced from CD3/CD28/IL-33 activated primary human T-cells from 3 donors (FIG. 8B). FIG. 8B top panel: Donor 1, FIG. 8B middle panel: Donor 3; FIG. 8B bottom panel: Donor 4.

[0025] **FIG. 9** illustrates the results of an experiment in which CD34+ cord blood cells differentiated into phenotypically mature eosinophils using IL-5 and other cytokines as described in the Examples. Antibody 3A5.046 was more potent than mepolizumab at inhibiting IL-5 induced eosinophil differentiation.

[0026] **FIG. 10A**, **FIG. 10B**, **FIG. 10C**, **FIG. 10D**, and **FIG. 10E** illustrate the results of the Biacore crossreactivity analysis of antibody 3A5.046 binding to human IL-5 (FIG. 10A), cynomolgus monkey IL-5 (FIG. 10B), mouse IL-5 (FIG. 10C), rat IL-5 (FIG.

10D), and guinea pig IL-5 (FIG. 10E). Double-referenced sensorgrams are shown for binding to cytokines at 1 μg/ml or 10 μg/ml.

[0027] **FIG. 11A**, **FIG. 11B**, **FIG. 11C**, and **FIG. 11D** illustrate the results of a Biacore specificity analysis of antibody 3A5.046. Double-referenced sensorgrams are shown for binding to cytokines at 10 μg/ml (FIG. 11A and FIG. 11B) or 1 μg/ml (FIG. 11C and FIG. 11D).

[0028] **FIG. 12** illustrates the results of *Ascaris suum* (*A. suum*) challenge in a cynomolgus monkey model of airway eosinophilia. At day 2 there was a substantial difference in lung (BALF) eosinophil numbers when comparing 3A5.046-treated and vehicle (placebo)-treated animals ($p<0.01$; Mann-Whitney test).

[0029] **FIG 13A** and **FIG. 13B** illustrate the blood eosinophil response over 10 days following an *A. suum* challenge in cynomolgus monkeys which were pre-treated with 3A5.046 or a isotype-matched control antibody ("placebo") one week before *A. suum* challenge (FIG. 13A). Figure 13B illustrates further details of the blood eosinophil counts for animals treated with 3A5.046 antibody, up to 45 days post-challenge (52 days post-dose). Eosinophil counts remained below baseline for at least 45 days post-challenge following a single dose of 3A5.046 one week before challenge.

[0030] **FIG. 14** illustrates BALF eosinophil levels in a human IL-5 knock-in (KI) rat model in response to a challenge with *Alternaria alternata*. This model may be used to test the potency of an anti-IL-5 antibody to modulate the numbers of BALF eosinophils following *Alternaria* challenge.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

[0031] The disclosed antibody molecules, methods, and uses may be understood more readily by reference to the following detailed description taken in connection with the accompanying figures, which form a part of this disclosure. It is to be understood that the disclosed antibody molecules, methods, and uses are not limited to the specific antibody molecules, methods, and uses described and/or shown herein, and that the terminology used herein is for the purpose of describing particular embodiments by way of example only and is not intended to be limiting of the claimed antibody molecules, methods, and uses.

[0032] Unless specifically stated otherwise, any description as to a possible mechanism or mode of action or reason for improvement is meant to be illustrative only, and the disclosed antibody molecules, methods, and uses are not to be constrained by the

correctness or incorrectness of any such suggested mechanism or mode of action or reason for improvement.

[0033] Throughout this text, the descriptions refer to antibody molecules and methods of using said antibody molecules. Where the disclosure describes or claims a feature or embodiment associated with an antibody molecule, such a feature or embodiment is equally applicable to the methods of using said antibody molecule. Likewise, where the disclosure describes or claims a feature or embodiment associated with a method of using an antibody molecule, such a feature or embodiment is equally applicable to the antibody molecule.

[0034] Where a range of numerical values is recited or established herein, the range includes the endpoints thereof and all the individual integers and fractions within the range, and also includes each of the narrower ranges therein formed by all the various possible combinations of those endpoints and internal integers and fractions to form subgroups of the larger group of values within the stated range to the same extent as if each of those narrower ranges was explicitly recited. Where a range of numerical values is stated herein as being greater than a stated value, the range is nevertheless finite and is bounded on its upper end by a value that is operable within the context of the invention as described herein. Where a range of numerical values is stated herein as being less than a stated value, the range is nevertheless bounded on its lower end by a non-zero value. It is not intended that the scope of the invention be limited to the specific values recited when defining a range. All ranges are inclusive and combinable.

[0035] Reference to a particular numerical value includes at least that particular value, unless the context clearly dictates otherwise.

[0036] When values are expressed as approximations, by use of the antecedent "about," it will be understood that the particular value forms another embodiment. The term "about" when used in reference to numerical ranges, cutoffs, or specific values is used to indicate that the recited values may vary by up to as much as 10% from the listed value. Thus, the term "about" is used to encompass variations of ± 10% or less, variations of ± 5% or less, variations of ± 1% or less, variations of ± 0.5% or less, or variations of ± 0.1% or less from the specified value.

[0037] It is to be appreciated that certain features of the disclosed antibody molecules, methods, and uses which are, for clarity, described herein in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the disclosed antibody molecules, methods, and uses that are,

for brevity, described in the context of a single embodiment, may also be provided separately or in any subcombination.

[0038] As used herein, the singular forms "a," "an," and "the" include the plural.

[0039] Various terms relating to aspects of the description are used throughout the specification and claims. Such terms are to be given their ordinary meaning in the art unless otherwise indicated. Other specifically defined terms are to be construed in a manner consistent with the definitions provided herein.

[0040] The term "comprising" is intended to include, but is not necessarily limited to, examples encompassed by the terms "consisting essentially of" and "consisting of"; similarly, the term "consisting essentially of" is intended to include, but is not necessarily limited to, examples encompassed by the term "consisting of."

[0041] The term "antibody molecule" is meant in a broad sense and includes full length immunoglobulin molecules and antigen binding fragments thereof.

[0042] Immunoglobulins can be assigned to five major classes, namely IgA, IgD, IgE, IgG, and IgM, depending on the heavy chain constant domain amino acid sequence. IgA and IgG are further sub-classified as the isotypes IgA1, IgA2, IgG1, IgG2, IgG3, and IgG4. Antibody light chains of any vertebrate species can be assigned to one of two clearly distinct types, namely kappa (κ) and lambda (λ), based on the amino acid sequences of their constant domains.

[0043] "Antigen binding fragment" refers to a portion of an immunoglobulin molecule that retains the antigen binding properties of the parental full length antibody (i.e. "antigen binding fragment thereof"). Exemplary antigen binding fragments can have: heavy chain complementarity determining regions (HCDR) 1, 2, and/or 3; light chain complementarity determining regions (LCDR) 1, 2, and/or 3; a heavy chain variable region (VH); a light chain variable region (VL); and combinations thereof. Antigen binding fragments include: a Fab fragment, a monovalent fragment consisting of the VL, VH, constant light (CL), and constant heavy 1 (CH1) domains; a $F(ab)_2$ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; a Fd fragment consisting of the VH and CH1 domains; a Fv fragment consisting of the VL and VH domains of a single arm of an antibody; and a domain antibody (dAb) fragment (Ward *et al.*, Nature 341:544- 546, 1989), which consists of a VH domain or a VL domain. VH and VL domains can be engineered and linked together via a synthetic linker to form various types of single chain antibody designs where the VH/VL domains pair intramolecularly, or intermolecularly in those cases when the VH and VL domains are expressed by separate

single chain antibody constructs, to form a monovalent antigen binding site, such as single chain Fv (scFv) or diabody, described for example in Int'l Pat. Pub. Nos. WO1998/44001, WO1988/01649, WO1994/13804, and WO1992/01047. These antibody fragments are obtained using techniques well known to those of skill in the art, and the fragments are screened for utility in the same manner as are full length antibodies.

[0044] The phrase "immunospecifically binds" refers to the ability of the disclosed antibody molecules to preferentially bind to its target (IL-5 in the case of anti-IL-5 antibody molecules) without preferentially binding other molecules in a sample containing a mixed population of molecules. Antibody molecules that immunospecifically bind IL-5 are substantially free of other antibodies having different antigenic specificities (e.g., an anti-IL-5 antibody is substantially free of antibodies that specifically bind antigens other than IL-5). Antibody molecules that immunospecifically bind IL-5, however, can have cross-reactivity to other antigens, such as orthologs of human IL-5, including *Macaca fascicularis* (cynomolgus monkey) IL-5. The antibody molecules disclosed herein are able to immunospecifically bind both naturally-produced human IL-5 and to IL-5 which is recombinantly produced in mammalian or prokaryotic cells.

[0045] An antibody variable region consists of four "framework" regions interrupted by three "antigen binding sites." The antigen binding sites are defined using various terms: (i) Complementarity Determining Regions (CDRs), three in the VH (HCDR1, HCDR2, HCDR3), and three in the VL (LCDR1, LCDR2, LCDR3) are based on sequence variability (Wu and Kabat J Exp Med 132:211-50, 1970; Kabat et al. Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md., 1991); and (ii) "Hypervariable regions" ("HVR" or "HV"), three in the VH (H1, H2, H3) and three in the VL (L1, L2, L3) refer to the regions of the antibody variable domains which are hypervariable in structure as defined by Chothia and Lesk (Chothia and Lesk Mol Biol 196:901-17, 1987). The AbM definition of CDRs is also widely used; it is a compromise between Kabat and Chothia numbering schemes and is so-called because it was used by Oxford Molecular's AbM antibody modelling software (Rees, A.R., Searle, S.M.J., Henry, A.H.and Pedersen, J.T. (1996) In Sternberg M.J.E. (ed.), Protein Structure Prediction. Oxford University Press, Oxford, 141–172). Other terms include "IMGT-CDRs" (Lefranc *et al.*, Dev Comparat Immunol 27:55-77, 2003) and "Specificity Determining Residue Usage" (SDRU) (Almagro Mol Recognit 17:132-43, 2004). The International ImMunoGeneTics (IMGT) database (http://www_imgt_org) provides a standardized numbering and definition

of antigen-binding sites. The correspondence between CDRs, HVs and IMGT delineations is described in Lefranc *et al.,* Dev Comparat Immunol 27:55-77, 2003.

[0046] "Framework" or "framework sequences" are the remaining sequences of a variable region other than those defined to be antigen binding sites. Because the antigen binding sites can be defined by various terms as described above, the exact amino acid sequence of a framework depends on how the antigen-binding site was defined. "Human antibody," "fully human antibody," and like terms refers to an antibody having heavy and light chain variable regions in which both the framework and the antigen binding sites are derived from sequences of human origin. If the antibody contains a constant region, the constant region also is derived from sequences of human origin. A human antibody comprises heavy and/or light chain variable regions that are "derived from" sequences of human origin if the variable regions of the antibody are obtained from a system that uses human germline immunoglobulin or rearranged immunoglobulin genes. Such systems include human immunoglobulin gene libraries displayed on phage, and transgenic non-human animals such as mice carrying human immunoglobulin loci as described herein. "Human antibody" may contain amino acid differences when compared to the human germline or rearranged immunoglobulin sequences due to, for example, naturally occurring somatic mutations or intentional introduction of substitutions in the variable domain (framework and antigen binding sites), or constant domain. Typically, a "human antibody" is at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical in amino acid sequence to an amino acid sequence encoded by a human germline or rearranged immunoglobulin gene. In some cases, a "human antibody" may contain consensus framework sequences derived from human framework sequence analyses, for example as described in Knappik *et al.,* J Mol Biol 296:57-86, 2000, or synthetic HCDR3 incorporated into human immunoglobulin gene libraries displayed on phage, as described in, for example, Shi *et al.,* J Mol Biol 397:385-96, 2010 and Int'l Pat. Pub. No. WO2009/085462. Antibodies in which antigen binding sites are derived from a non-human species are not included in the definition of "human antibody."

[0047] Human antibodies, while derived from human immunoglobulin sequences, may be generated using systems such as phage display incorporating synthetic CDRs and/or synthetic frameworks, or can be subjected to *in vitro* mutagenesis to improve antibody properties in the variable regions or the constant regions or both, resulting in antibodies that do not naturally exist within the human antibody germline repertoire *in vivo.*

[0048] "Recombinant antibody" includes all antibodies that are prepared, expressed, created, or isolated by recombinant means, such as: antibodies isolated from an animal (e.g., a mouse) that is transgenic or transchromosomal for human immunoglobulin genes or a hybridoma prepared therefrom (described further below); antibodies isolated from a host cell transformed to express the antibody; antibodies isolated from a recombinant, combinatorial antibody library; and antibodies prepared, expressed, created, or isolated by any other means that involve splicing of human immunoglobulin gene sequences to other DNA sequences, or antibodies that are generated *in vitro* using Fab arm exchange.

[0049] "Monoclonal antibody" refers to a population of antibody molecules of a single molecular composition. A monoclonal antibody composition displays a single binding specificity and affinity for a particular epitope, or in a case of a bispecific monoclonal antibody, a dual binding specificity to two distinct epitopes. Monoclonal antibody therefore refers to an antibody population with single amino acid composition in each heavy and each light chain, except for possible well known alterations such as removal of C-terminal lysine from the antibody heavy chain. Monoclonal antibodies may have heterogeneous glycosylation within the antibody population. Monoclonal antibody may be monospecific or multispecific, or monovalent, bivalent or multivalent. A bispecific antibody is included in the term monoclonal antibody.

[0050] "Epitope" refers to a portion of an antigen to which an antibody specifically binds. Epitopes usually consist of chemically active (such as polar, non-polar, or hydrophobic) surface groupings of moieties such as amino acids or polysaccharide side chains and can have specific three-dimensional structural characteristics, as well as specific charge characteristics. An epitope can be composed of contiguous and/or discontiguous amino acids that form a conformational spatial unit. For a discontiguous epitope, amino acids from differing portions of the linear sequence of the antigen come in close proximity in 3-dimensional space through the folding of the protein molecule.

[0051] "Variant" refers to a polypeptide or a polynucleotide that differs from a reference polypeptide or a reference polynucleotide by one or more modifications for example, substitutions, insertions, or deletions. The term "mutation" as used herein is intended to mean one or more intentional substitutions which are made to a polypeptide or polynucleotide.

[0052] As used herein "90% identical to" encompasses at least 90% identical, 91% identical, 92% identical, 93% identical, 94% identical, 95% identical, 96% identical, 97% identical, 98% identical, 99% identical, or 100% identical to the reference item (e.g., a

biological sequence). The current specification uses the term "% identical" to describe a number of sequences. As would be understood, the term "% identical" means that in a comparison of two sequences over the specified region the two sequences have the specified number of identical residues in the same position. The level of identity may be determined using CLUSTAL W with default parameters.

[0053] "Treat," "treatment," and like terms refer to both therapeutic treatment and prophylactic or preventative measures, and includes reducing the severity and/or frequency of symptoms, eliminating symptoms and/or the underlying cause of the symptoms, reducing the frequency or likelihood of symptoms and/or their underlying cause, improving or remediating damage caused, directly or indirectly, by the eosinophilic asthma, hypereosinophilic syndrome, nasal polyposis with eosinophilic involvement, eosinophilic granulomatosis with polyangiitis, atopic dermatitis or eosinophilic esophagitis. Treatment also includes prolonging survival as compared to the expected survival of a subject not receiving treatment. Subjects to be treated include those that have the condition or disorder as well as those prone to have the condition or disorder or those in which the condition or disorder is to be prevented.

[0054] As used herein, "administering to the subject" and similar terms indicate a procedure by which the disclosed antibody molecules or compositions comprising the same are injected into a patient such that target cells, tissues, or segments of the body of the subject are contacted with the disclosed antibody molecules.

[0055] The phrase "therapeutically effective amount" refers to an amount of the antibody molecules, as described herein, effective to achieve a particular biological or therapeutic result such as, but not limited to, biological or therapeutic results disclosed, described, or exemplified herein. The therapeutically effective amount may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the composition to cause a desired response in a subject. Exemplary indicators of a therapeutically effect amount include, for example, improved well-being of the patient, reduction of a disease symptom, arrested or slowed progression of disease symptoms, and/or absence of disease symptoms.

[0056] The following abbreviations are used herein: *Alternaria alternata* (Alternaria), *Ascaris suum* (*A. suum*); complementarity-determining region (CDR); heavy chain (HC); light chain (LC); heavy chain variable region (VH); light chain variable region (VL); surface plasmon resonance (SPR).

Antibody molecules

[0057] Disclosed herein are human antibody molecules that immunospecifically bind to human IL-5. The human antibody molecules can immunospecifically bind to human IL-5 with an equilibrium affinity constant (K_D) of at least about 40 pM as determined by surface plasmon resonance (SPR). As used herein, "of at least about 40 pM" means that the disclosed antibodies immunospecifically bind human IL-5 with a K_D of less than or equal to about 40 pM. For example, the disclosed antibodies can immunospecifically bind human IL-5 with a K_D of about 40 pM, about 30 pM, about 20 pM, about 10 pM, or less than about 10 pM.

[0058] The disclosed human antibody molecules can comprise a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 4, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 6, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 8, a light chain consensus CDR1 comprising the amino acid sequence of SEQ ID NO: 1, a light chain consensus CDR2 comprising the amino acid sequence of SEQ ID NO: 2, and a light chain consensus CDR3 comprising the amino acid sequence of SEQ ID NO: 3.

[0059] The light chain consensus CDR1 comprises the amino acid sequence of $GX_1X_2X_3X_4X_5X_6KX_7X_8Y$ (SEQ ID NO: 1), wherein:

X_1 is G or K;

X_2 is N or D;

X_3 is N or H;

X_4 is I or A;

X_5 is G or D;

X_6 is S or K;

X_7 is N or H; and

X_8 is V or A.

[0060] In some embodiments, the light chain CDR1 amino acid sequence can comprise GGNNIGSKNVY (SEQ ID NO: 5). In some embodiments, the light chain CDR1 amino acid sequence can comprise GKNNIGSKNVY (SEQ ID NO: 21). In some embodiments, the light chain CDR1 amino acid sequence can comprise GGDNIGSKNVY (SEQ ID NO: 24). In some embodiments, the light chain CDR1 amino acid sequence can comprise GGNHIGSKNVY (SEQ ID NO: 27). In some embodiments, the light chain CDR1 amino acid sequence can comprise GGNNAGSKNVY (SEQ ID NO: 30). In some embodiments, the light chain CDR1 amino acid sequence can comprise GGNNIDSKNVY

(SEQ ID NO: 66). In some embodiments, the light chain CDR1 amino acid sequence can comprise GGNNIGKKNVY (SEQ ID NO: 33). In some embodiments, the light chain CDR1 amino acid sequence can comprise GGNNIGSKHVY (SEQ ID NO: 36). In some embodiments, the light chain CDR1 amino acid sequence can comprise GGNNIGSKNAY (SEQ ID NO: 39).

[0061] The light chain CDR2 amino acid sequence comprises DDX_8X_9RPS (SEQ ID NO: 2), wherein:

X_8 is S or L; and

X_9 is D or S.

[0062] In some embodiments, the light chain CDR2 amino acid sequence can comprise DDSDRPS (SEQ ID NO: 7). In some embodiments, the light chain CDR2 amino acid sequence can comprise DDLDRPS (SEQ ID NO: 42). In some embodiments, the light chain CDR2 amino acid sequence can comprise DDSSRPS (SEQ ID NO: 45).

[0063] The light chain CDR3 amino acid sequence comprises $QVWX_{10}SSSDX_{11}VX_{12}$ (SEQ ID NO: 3), wherein:

X_{10} is D or L;

X_{11} is H, S, Y, or D; and

X_{12} is V, A, or W.

[0064] In some embodiments, the light chain CDR3 amino acid sequence can comprise QVWDSSSDHVV (SEQ ID NO: 15). In some embodiments, the light chain CDR3 amino acid sequence can comprise QVWLSSSDHVV (SEQ ID NO: 48). In some embodiments, the light chain CDR3 amino acid sequence can comprise QVWDSSSDSVV (SEQ ID NO: 51). In some embodiments, the light chain CDR3 amino acid sequence can comprise QVWDSSSDYVV (SEQ ID NO: 54). In some embodiments, the light chain CDR3 amino acid sequence can comprise QVWDSSSDDVV (SEQ ID NO: 57). In some embodiments, the light chain CDR3 amino acid sequence can comprise QVWDSSSDHVA (SEQ ID NO: 60). In some embodiments, the light chain CDR3 amino acid sequence can comprise QVWDSSSDHVW (SEQ ID NO: 63).

[0065] The disclosed human antibody molecules can comprise a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 4, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 6, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 8, a light chain CDR1 comprising the amino acid sequence of SEQ ID NOs: 5, 21, 24, 27, 30, 33, 36, 39, or 66, a light chain CDR2 comprising the amino acid sequence of SEQ ID NOs: 7, 42, or 45, and a light chain CDR3 comprising the amino acid

sequence of SEQ ID NOs: 15, 48, 51, 54, 57, 60, or 63. Exemplary antibody molecules comprise a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 4, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 6, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 8, and

a. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 5, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 15;
b. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 21, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 15;
c. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 24, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 15;
d. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 27, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 15;
e. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 30, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 15;
f. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 33, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 15;
g. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 36, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 15;
h. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 39, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 15;
i. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 66, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 15;
j. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 5, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 42, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 15;

k. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 5, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 45, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 15;

l. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 5, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 48;

m. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 5, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 51;

n. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 5, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 54;

o. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 5, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 57;

p. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 5, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 60; or

q. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 5, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 63;

wherein the position of the amino acid residues of the CDR is determined according to AbM.

[0066] The disclosed antibody molecules can comprise a heavy chain variable region comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 16 and a light chain variable region comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 17, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, 52, 55, 58, 61, 64, or 67, wherein the variability (i.e. the at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity) occurs outside of the CDR sequence. Exemplary antibody molecules are provided in Table 1 and Table 15.

Table 1. Antibody chain/domain composition summary

Antibody ID	VH protein / (SEQ ID)	VL protein / (SEQ ID)	HC protein / (SEQ ID)	LC protein / (SEQ ID)
3A5	3A5 VH (SEQ ID NO: 10)	3A5 VL (SEQ ID NO: 11)	3A5 HC (SEQ ID NO: 12)	3A5 LC (SEQ ID NO: 13)
3A5.001	3A5 VH (SEQ ID NO: 10)	3A5 VL (SEQ ID NO: 11)	3A5.001 HC (SEQ ID NO: 14)	3A5 LC (SEQ ID NO: 13)
3A5.040	3A5.040 VH (SEQ ID NO: 16)	3A5.040 VL (SEQ ID NO: 17)	3A5.040 HC (SEQ ID NO: 18)	3A5.040 LC (SEQ ID NO: 19)
3A5.046	3A5.040 VH (SEQ ID NO: 16)	3A5.040 VL (SEQ ID NO: 17)	3A5.046 HC (SEQ ID NO: 20)	3A5.040 LC (SEQ ID NO: 19)
3A5.063	3A5.040 VH (SEQ ID NO: 16)	3A5.040 VL + G25K (SEQ ID NO: 22)	3A5.040 HC (SEQ ID NO: 18)	3A5.040 LC + G25K (SEQ ID NO: 23)
3A5.070	3A5.040 VH (SEQ ID NO: 16)	3A5.040 VL + N26D (SEQ ID NO: 25)	3A5.040 HC (SEQ ID NO: 18)	3A5.040 LC + N26D (SEQ ID NO: 26)
3A5.082	3A5.040 VH (SEQ ID NO: 16)	3A5.040 VL + N27H (SEQ ID NO: 28)	3A5.040 HC (SEQ ID NO: 18)	3A5.040 LC + N27H (SEQ ID NO: 29)
3A5.084	3A5.040 VH (SEQ ID NO: 16)	3A5.040 VL + I28A (SEQ ID NO: 31)	3A5.040 HC (SEQ ID NO: 18)	3A5.040 LC + I28A (SEQ ID NO: 32)
3A5.097	3A5.040 VH (SEQ ID NO: 16)	3A5.040 VL + G29D (SEQ ID NO: 67)	3A5.040 HC (SEQ ID NO: 18)	3A5.040 LC + G29D (SEQ ID NO: 68)
3A5.107	3A5.040 VH (SEQ ID NO: 16)	3A5.040 VL + S30K (SEQ ID NO: 34)	3A5.040 HC (SEQ ID NO: 18)	3A5.040 LC + S30K (SEQ ID NO: 35)
3A5.125	3A5.040 VH (SEQ ID NO: 16)	3A5.040 VL + N32H (SEQ ID NO: 37)	3A5.040 HC (SEQ ID NO: 18)	3A5.040 LC + N32H (SEQ ID NO: 38)
3A5.127	3A5.040 VH (SEQ ID NO: 16)	3A5.040 VL + V33A (SEQ ID NO: 40)	3A5.040 HC (SEQ ID NO: 18)	3A5.040 LC + V33A (SEQ ID NO: 41)
3A5.161	3A5.040 VH (SEQ ID NO: 16)	3A5.040 VL + S52L (SEQ ID NO: 43)	3A5.040 HC (SEQ ID NO: 18)	3A5.040 LC + S52L (SEQ ID NO: 44)

Antibody ID	VH protein / (SEQ ID)	VL protein / (SEQ ID)	HC protein / (SEQ ID)	LC protein / (SEQ ID)
3A5.169	3A5.040 VH (SEQ ID NO: 16)	3A5.040 VL + D53S (SEQ ID NO: 46)	3A5.040 HC (SEQ ID NO: 18)	3A5.040 LC + D53S (SEQ ID NO: 47)
3A5.232	3A5.040 VH (SEQ ID NO: 16)	3A5.040 VL + D92L (SEQ ID NO: 49)	3A5.040 HC (SEQ ID NO: 18)	3A5.040 LC + D92L (SEQ ID NO: 50)
3A5.276*	3A5.040 VH (SEQ ID NO: 16)	3A5.040 VL + H95bS (SEQ ID NO: 52)	3A5.040 HC (SEQ ID NO: 18)	3A5.040 LC + H95bS (SEQ ID NO: 53)
3A5.278*	3A5.040 VH (SEQ ID NO: 16)	3A5.040 VL + H95bY (SEQ ID NO: 55)	3A5.040 HC (SEQ ID NO: 18)	3A5.040 LC + H95bY (SEQ ID NO: 56)
3A5.279*	3A5.040 VH (SEQ ID NO: 16)	3A5.040 VL + H95bD (SEQ ID NO: 58)	3A5.040 HC (SEQ ID NO: 18)	3A5.040 LC + H95bD (SEQ ID NO: 59)
3A5.294	3A5.040 VH (SEQ ID NO: 16)	3A5.040 VL + V97A (SEQ ID NO: 61)	3A5.040 HC (SEQ ID NO: 18)	3A5.040 LC + V97A (SEQ ID NO: 62)
3A5.302	3A5.040 VH (SEQ ID NO: 16)	3A5.040 VL + V97W (SEQ ID NO: 64)	3A5.040 HC (SEQ ID NO: 18)	3A5.040 LC + V97W (SEQ ID NO: 65)

* The lower case "b" in each of these sequences refers to the Kabat numbering for the CDR position. Kabat numbering allows for CDRs of variable sizes, by using alphanumeric numbering to denote amino acid insertions at certain positions. In these CDR sequences, additional amino acids were present, which were numbered as positions 95a and 95b (corresponding to Kabat positions 95A and 95B respectively). Thus, for antibody 3A5.276, for example, H95bS indicates a histidine ("H") to serine ("S") mutation at position 95B according to Kabat number relative to the 3A5.040 VL chain. The lower case notation is therefore used here to distinguish the Kabat number, separate from the mutation at the indicated Kabat position.

[0067] In some embodiments, the disclosed antibody molecules can comprise a heavy chain variable region comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 16 and

a. a light chain variable region comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 17;

b. a light chain variable region comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 22;
c. a light chain variable region comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 25;
d. a light chain variable region comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 28;
e. a light chain variable region comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 31;
f. a light chain variable region comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 34;
g. a light chain variable region comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 37;
h. a light chain variable region comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 40;
i. a light chain variable region comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 43;
j. a light chain variable region comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 46;
k. a light chain variable region comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 49;
l. a light chain variable region comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 52;

m. a light chain variable region comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 55;

n. a light chain variable region comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 58;

o. a light chain variable region comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 61;

p. a light chain variable region comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 64; or

q. a light chain variable region comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 67,

wherein the variability (i.e. the at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity) occurs outside of the CDR sequence.

[0068] The disclosed antibody molecules can comprise one or more mutations, deletions, or insertions, in the framework and/or constant regions. In some embodiments, an IgG4 antibody molecule can comprise a S228P mutation. S228 is located in the hinge region of the IgG4 antibody molecule. Mutation of the serine ("S") to a proline ("P") serves to stabilize the hinge of the IgG4 and prevent Fab arm exchange in vitro and in vivo. In some embodiments, the antibody molecules can comprise one or more modifications which increase the in vivo half life of the antibody molecules. For instance in certain embodiments the antibody can comprise a M252Y mutation, a S254T mutation, and a T256E mutation (collectively referred to as the "YTE" mutation). M252, S254, and T256 are located in in the CH2 domain of the heavy chain. Mutation of these residues to tyrosine ("Y"), threonine ("T"), and glutamate ("E"), respectively, protects the antibody molecules from lysosomal degradation, thereby enhancing the serum half-life of the antibody molecules. Based on the example of other antibodies, it is contemplated that the introduction of the YTE mutation in an anti-IL-5 antibody may provide sufficient extension of serum half life to allow for administration regimes with 3 months or longer inter-dosing intervals. In some embodiments, the antibody molecules can comprise a deletion of the heavy chain C-terminal lysine residue. Deletion of the heavy chain C-terminal lysine residue reduces heterogeneity of the antibody

molecules when produced by mammalian cells. In some embodiments, the antibody molecules can comprise a combination of mutations, deletions, or insertions. For example, in some aspects, the disclosed antibody molecules can comprise a S228P mutation and a deletion of a heavy chain C-terminal lysine residue. The disclosed antibodies comprising a heavy chain sequence of SEQ ID NO: 18, for example, comprise a S228P mutation and a deletion of a heavy chain C-terminal lysine residue. In some aspects, the disclosed antibody molecule can comprise a S228P mutation, a M252Y mutation, a S254T mutation, a T256E mutation, and a deletion of a heavy chain C-terminal lysine residue. The 3A5.046 antibody, for example, which comprises a heavy chain of SEQ ID NO: 20, comprises a S228P mutation, a M252Y mutation, a S254T mutation, a T256E mutation, and a deletion of a heavy chain C-terminal lysine residue.

[0069] The antibody molecule can comprise an IgG1 or IgG4 heavy chain constant region and a lambda light chain constant region. In some embodiments, the antibody molecule comprises an IgG1 heavy chain constant region and a lambda light chain constant region (antibody 3A5, for example). In some embodiments, the antibody molecule comprises an IgG4 heavy chain constant region and a lambda light chain constant region.

[0070] The disclosed antibody molecules can comprise a heavy chain comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NOs: 18 or 20 and a light chain comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 19, 23, 26, 29, 32, 35, 38, 41, 44, 47, 50, 53, 56, 59, 62, 65, or 68, wherein the variability (i.e. the at least 90% identity) occurs outside of the CDR sequence. Exemplary antibody molecules are provided in Table 1 and Table 15. In some embodiments, the antibody molecules can comprise a heavy chain comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 18 and

a. a light chain comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 19;
b. a light chain comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 23;

c. a light chain comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 26;

d. a light chain comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 29;

e. a light chain comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 32;

f. a light chain comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 35;

g. a light chain comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 38;

h. a light chain comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 41;

i. a light chain comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 44;

j. a light chain comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 47;

k. a light chain comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 50;

l. a light chain comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 53;

m. a light chain comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 56;

n. a light chain comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 59;

o. a light chain comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 62;

p. a light chain comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 65; or

q. a light chain comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 68,

wherein the variability (i.e. the at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity) occurs outside of the CDR sequence.

[0071] The disclosed antibody molecules can comprise a heavy chain comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 20 and a light chain comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 19, wherein the variability (i.e. the at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identity) occurs outside of the CDR sequence.

[0072] In some embodiments, the antibody molecules are full length antibody molecules (with or without a deletion of the heavy chain C-terminal lysine residue). In other embodiments, the antibody molecules are antigen binding fragments. Suitable antibody binding fragments include, but are not limited to, a Fab fragment, a Fab2 fragment, or a single chain antibody.

[0073] The antibody molecules can have one or more of the following properties:

a. binds to human IL-5 with an equilibrium affinity constant (K_D) of at least about 40 pM as determined by surface plasmon resonance;

b. reduces binding of IL-5 to the IL-5 receptor;

c. has a serum half-life of at least about 20 days; or

d. binds human and cynomolgus monkey IL-5 but not mouse, rat, or guinea pig IL-5.

[0074] Pharmaceutical compositions comprising any of the disclosed antibody molecules are also provided.

[0075] Also provided are nucleic acid molecules encoding any of the disclosed antibody molecules and vectors comprising the disclosed nucleic acid molecules.

[0076] Cells transformed to express any of the disclosed antibody molecules are further provided.

Methods and uses

[0077] The disclosed antibody molecules, or pharmaceutical compositions comprising the same, can be used to treat eosinophilic asthma, hypereosinophilic syndrome, nasal polyposis with eosinophilic involvement, eosinophilic granulomatosis with polyangiitis, atopic dermatitis and eosinophilic esophagitis. Any of the antibody molecule characteristics disclosed herein apply equally to the antibodies used in the disclosed methods and uses.

[0078] Disclosed herein are methods of treating a subject having eosinophilic asthma, hypereosinophilic syndrome, nasal polyposis with eosinophilic involvement, eosinophilic granulomatosis with polyangiitis, atopic dermatitis or eosinophilic esophagitis comprising administering to the subject a therapeutically effective amount of any of the antibody molecules disclosed herein, or pharmaceutical compositions comprising the same, to treat the eosinophilic asthma, hypereosinophilic syndrome, nasal polyposis with eosinophilic involvement, eosinophilic granulomatosis with polyangiitis, atopic dermatitis or eosinophilic esophagitis.

[0079] The use of an effective amount of any of the disclosed antibody molecules, or pharmaceutical compositions comprising the same, in the treatment of eosinophilic asthma, hypereosinophilic syndrome, nasal polyposis with eosinophilic involvement, eosinophilic granulomatosis with polyangiitis, atopic dermatitis or eosinophilic esophagitis is also provided.

[0080] Also provided is the use of any of the disclosed antibody molecules, or pharmaceutical compositions comprising the same, in the manufacture of a medicament for the treatment of eosinophilic asthma, hypereosinophilic syndrome, nasal polyposis with eosinophilic involvement, eosinophilic granulomatosis with polyangiitis, atopic dermatitis or eosinophilic esophagitis.

EXAMPLES

[0081] The following examples are provided to further describe some of the embodiments disclosed herein. The examples are intended to illustrate, not to limit, the disclosed embodiments.

Generation of anti-human-IL-5 antibodies

[0082] Anti-human-IL-5 antibodies were obtained from transgenic rats (OMT) with human V-genes cloned into their genomes and which produce antibodies with human V-domains and rat Fc domains. Briefly, the transgenic rats were genetically immunized with DNA encoding IL-5 four times over 21 days (on days 0, 7, 14, 21) and boosted with recombinant human IL-5 at day 28 of the immunization protocol. Serum antibody titres were determined at days 0 and 38 of the immunization protocol by an ELISA assay using recombinant human IL-5. Briefly, sera from each animal were diluted in PBS 1% BSA and were tested using ELISA plates coated with 1 μg/ml human IL-5, or BSA as a control. A goat anti-rat IgG R-phycoerythrin conjugate (SouthernBiotech, #3030-09) was used at 10 μg/ml as a secondary antibody. Specific animals were chosen for hybridoma fusion based on these serum titres.

[0083] To generate hybridomas which produce monoclonal antibodies to human IL-5, splenocytes and/or lymph node cells from immunized animals were isolated and fused to P3X63Ag8.653 non-secreting mouse myeloma cells (ATCC, CRL-1580). Cells were plated at approximately 1 x 10^5 cells/mL in flat bottom microtiter plates, followed by a two week incubation in selective medium which included 10% fetal clone serum and 1 x HAT (Sigma). Hybridomas were expanded by serial passage through four media changes in 96-well plates (96-well stages 1 to 4), then into T25 and finally T75 flasks.

[0084] The supernatants from hybridoma clones were assayed during the hybridoma expansion process, initially in a whole-cell ELISA using cells transfected with GPI-anchored human IL-5 and then ELISA using a recombinant human IL-5 ELISA assay (the latter as described above). Hybridomas which survived the scale-up process to T75 stage and which gave signals above a given threshold for binding in both of these assays were frozen as cell pellets, for cloning and sequencing of Ig v-domains. Approximately 20 hybridomas producing chimeric IgGs were selected for cloning following these screening steps.

[0085] The human v-domains from the candidate chimeric IgGs were isolated by generation of cDNA from hybridoma cell pellets, PCR amplification of v-domains, subcloning, and DNA sequencing. A total of approximately 35 heavy and light chain combinations were obtained from the sequencing of these hybridomas. All antibodies were cloned into a mammalian expression vector and transiently transfected into HEK-293 cells. Antibodies were purified using standard Protein A purification protocols.

Functional testing and characterization of antibodies

[0086] Selected antibodies in human IgG1 format were first assayed for specificity in a human IL-5 ELISA. Briefly, antibodies were diluted in PBS 0.1% BSA and were tested using ELISA plates coated with 1 μg/ml human IL-5, or an irrelevant control protein. A horseradish peroxidase-conjugated Anti-IgG antibody was used as a secondary antibody.

[0087] Antibodies that showed immunospecific binding to human IL-5 were ranked for potency in a human IL-5-dependent cell proliferation assay using human TF-1.6G4 (a derivative of the human erythroleukemic cell line TF-1) cells. The TF-1.6G4 cell line was subcloned and selected for enhanced surface expression of IL-5Rα and consistent proliferative response to human IL-5. The TF-1.6G4 cell line was maintained in culture following standard conditions used for the TF-1 human erythroleukemic cell line (ATCC: CRL-2003). Briefly, dilutions of each antibody were incubated in the presence of 45 pM human IL-5 and 5 x 10^4 TF-1.6G4 cells per well, incubated for 48 h, and cell proliferation was determined using the CellTiter-Glo® Luminescent Cell Viability Assay (Promega, WI). All proliferation and inhibition curves were fitted using a three- or four-parameter dose-response model in GraphPad Prism 6 (Version 6.04) software. Table 2 summarizes these results.

Table 2. Summary of screening and characterization of an initial test panel in IgG1 format.

Test Antibody	IC50 (pM) in TF1.6G4	Equilibrium Affinity (K_D)	Inhibits IL-5Rα binding	Specificity confirmed by ELISA
3A5	35.07	36 pM	Yes	Yes
1A3	55.5	18 pM	Yes	Yes
2B4	56.75	42 pM	Yes	Yes
6G10	72.34	61 pM	Yes	Yes
1E8	72.45	28 pM	Yes	Yes
3G4	80.92	41 pM	Yes	Yes
6C9	81.89	41 pM	Yes	Yes
5H1	86.42	36 pM	Yes	Yes
1H10	93.26	18 pM	Yes	Yes

5H11	109.3	36 pM	No	Yes
5G9	184.4	52 pM	Yes	Yes
1B2	214.4	45 pM	Yes	Yes

[0088] In Table 2, the results of tests were ranked in order of TF1.6G4 assay potency. The initial test panel was selected based upon potency, affinity, IL-5Rα inhibition and sequence liabilities (immunogenicity and developability).

[0089] Biacore assays were used to determine the affinity of test antibodies to recombinant human IL-5 and their potency in inhibiting IL-5Rα binding to human IL-5. Table 2 summarizes these results. Binding affinity of test antibodies to human IL-5 (K_D; FIG. 6) was determined on a Biacore T200 system (GE Healthcare) by coating a Biacore Series S Sensor Chip Protein A (GE Healthcare) with selected purified IgG antibody to a capture level of 75 RU, then recombinant human IL-5 was injected at 60 μL/min across a 7-step two-fold serial dilution range, starting at 1 μg/mL. All experiments were run using HBS-EP+ buffer (GE Healthcare). The resulting sensorgrams were double-referenced (test flowcell values subtracted from control (Protein A surface with no coated antibody) flowcell values and also a buffer blank). Binding constants were determined by fitting a 1:1 Langmuir binding model to double-referenced sensorgrams.

[0090] To determine whether each test antibody inhibited the binding of IL-5 to IL-5Rα, either a Biacore T200 or a Biacore 3000 system (GE Healthcare) was used. A Biacore CM5 Sensor Chip was first derivatized with a Fab capture kit (GE Healthcare) in accordance with the manufacturer's instructions on two adjacent (test and control) flowcells. This surface was used to capture each purified IgG test antibody on a single test flowcell. Recombinant human IL-5 at 5 μg/mL or a buffer blank was then injected across both test and control flowcells, to saturate the test flowcell surface and control for non-specific association of IL-5, respectively. A second injection of purified IgG test antibody at 10 μg/mL or a buffer blank was performed on the test flowcell to block free IL-5 binding sites and control for dissociation of the IgG test antibody from the Fab capture antibody, respectively.

[0091] Subsequent injection of IL-5Rα-Fc (R&D Systems) at either 5 or 20 μg/mL or a buffer blank across both flowcells was used to determine whether the IgG test antibody blocked the interaction between IL-5 and IL-5Rα or to control for dissociation of IgG antibody from the Fab capture antibody during this step. Antibodies which inhibited the binding of IL-5 to IL-5Rα showed a markedly reduced signal upon injection of IL-5Rα

(Table 2). A triple reference subtraction method was used to analyze data in the manner detailed above. All data was exported from Biacore evaluation software and subtracted in Excel (Microsoft) software. All experiments were run using HBS-EP+ buffer (GE Healthcare).

[0092] A smaller panel of test antibodies (3A5, 5H11 and 2B4 in Table 2) was chosen on the basis of these results. The antibodies were reformatted as human IgG4 and tested in the same assays. The IgG4 version of antibody 3A5 (originally an IgG1) was designated as 3A5.001. This fully-human antibody was demonstrated to have equivalent potency to the original test 3A5 in IgG1 format (FIG. 1).

[0093] A variant of antibody 3A5.001 (designated 3A5.040) was prepared with specific amino acid substitutions (VH: S[68]T, N[82A]S; VL: S[2]Y, I[3]V, Y[92]D, wherein the residues in square brackets represent the Kabat positions) introduced in the V-domain regions to remove predicted T-cell epitopes. Antibody 3A5.040 was demonstrated to have equivalent potency to its parental antibody, 3A5.001 (FIG. 2) in the TF-1.6G4 assay.

CDR scanning of antibody 3A5.040

[0094] Generation of antibody 3A5.040 variants - Single-mutant variants of antibody 3A5.040 were made by substituting one of a group of nine representative amino acids – A, S, L, Y, D, Q, K, H, W – at each amino acid position in the light chain CDR1 (CDR-L1), the light chain CDR2 (CDR-L2), the heavy chain CDR1 (CDR-H1) and the heavy chain CDR2 (CDR-H2) (as defined by AbM nomenclature). Antibody variants were also made by substituting one of a group of ten representative amino acids – A, S, L, Y, D, Q, K, H, W, P – at each CDR amino acid position in the light chain CDR3 (CDR-L3), heavy chain CDR3 (CDR-H3), and at Kabat positions 93 and 94 in the variable heavy chain. A complete list of all single-mutant antibody variants generated is shown in FIG. 3 (variable heavy chain) and FIG. 4 (variable light chain), respectively.

[0095] Construction of Vectors Expressing Antibodies - Variable region variants were generated by back-translation of amino acid sequences into DNA sequences which were subsequently synthesized de novo by assembly of synthetic oligonucleotides. Variable heavy (VH) variants were subcloned into a mammalian expression vector containing a human constant region to produce full-length antibody heavy chains (human IgG4 heavy chain CH1, hinge, CH2, and CH3 domains). Similarly, variable light (VL) variants were subcloned into a mammalian expression vector containing a human lambda light chain constant region to produce full-length antibody lambda chains.

[0096] Expression of antibody variants - Antibodies were produced by co-transfecting separate expression vectors encoding antibody heavy chains and light chains into EXPI293® cells (Life Technologies, Carlsbad, CA). Each single-mutant chain was paired with a parental chain for protein expression in the EXPI293® system. For each 20 mL transfection, 3.6×10^7 cells were required in 20 mL of EXPI293® Expression Medium. On the day prior to transfection, cells were seeded at a density of 0.9×10^6 viable cells/mL and incubated overnight at 37° C in a humidified atmosphere of 8% CO_2 in air on an orbital shaker rotating at 200 rpm. On the day of transfection, the cell number and viability were determined using an automated cell counter. Only cultures with >98% viable cells were used. For each 20 mL transfection, lipid-DNA complexes were prepared by diluting 10 μg of heavy chain DNA and 10 μg of light chain DNA in OPTI-MEM® (Life Technologies, Carlsbad, CA) I Reduced Serum Medium (Cat. no. 31985-062) to a total volume of 1.0 mL. 54 μL of EXPIFECTAMINE® 293 Reagent (Life Technologies, Carlsbad, CA) was diluted in OPTI-MEM® I medium to a total volume of 1.0 mL. Both vials were mixed gently and incubated for 5 minutes at room temperature. Following incubation, the diluted DNA was mixed with the diluted EXPIFECTAMINE® 293 Reagent and the DNA-EXPIFECTAMINE® 293 Reagent mixture and incubated a further 20 minutes at room temperature to allow the formation of DNA-EXPIFECTAMINE® 293 Reagent complexes. Following incubation, 2 mL of DNA-EXPIFECTAMINE® 293 Reagent complex was added to each 50 mL bioreactor tube (TPP Techno Plastic Products AG). 2 mL of OPTI-MEM® (Life Technologies, Carlsbad, CA) I medium was added to the negative control tube instead of DNA-EXPIFECTAMINE® 293 Reagent complex. The cells were incubated in a 37° C incubator with a humidified atmosphere of 8% CO_2 in air on an orbital shaker rotating at 200 rpm. Approximately 16–18 hours post-transfection, 100 μL of EXPIFECTAMINE® 293 Transfection Enhancer 1 and 1.0 mL of EXPIFECTAMINE® 293 Transfection Enhancer 2 were added to each bioreactor. Supernatants were harvested at approximately 48 hours post-transfection.

[0097] Purification of antibody variants - Each antibody variant was expressed in EXPI293® cells in either 20 or 100 mL of cell culture. Cultures were spun down in 50 mL falcon tubes at 3000 x *g* for 20 minutes, and supernatants were filtered using a 0.22 μm filter. Supernatants were purified using a Gilson ASPEC GX274 robot. Briefly, SPE cartridges (Agilent, 12131014) packed with 1.2 mL MABSELECT SURE® protein A resin (GE Healthcare) were pre-equilibrated with 3 column volumes of 1X PBS. Supernatant was run over the columns followed by a 4 mL 1X PBS wash. Each column was washed with 9 mL of

1 M citric acid, pH 2.9. Antibodies were eluted with 2 mL 0.1 M citric acid, pH 2.9. Antibodies were desalted into Sørensens PBS (5 mM KH_2PO_4, 3 mM $Na_2HPO_4.2H_2O$, 145.4 mM NaCl (pH ~5.8)) using PD-10 columns (GE Healthcare).

[0098] Determination of 3A5.040 variant antibody titre in supernatant by Biacore - Supernatants containing antibody from expression in EXPI293® cells were analyzed using a Protein A series S chip on the Biacore T200 to determine their titre and rank them with respect to the parental antibody 3A5.040. Each supernatant sample was diluted with running buffer (1 x HBS-EP+, 350 mM NaCl) and captured by injection at 60 µL/min onto flow cell (FC) 2. The resulting capture level in response units (RUs) were measured on FC 2-1 by subtracting a report point 5 sec after cycle start from one 5 sec after injection. The surface was regenerated by injecting 50 mM NaOH for 12 sec at a flow rate of 60 µL/min onto FC 1 and 2 every 4 cycles. After each regeneration, the surface and sensorgram was stabilized for 120 sec by injection of running buffer. Multiple batches were run due to the large number of antibodies that were screened in this manner.

[0099] The capture levels (in Biacore response units "RU") obtained for each supernatant sample were adjusted by multiplying the values obtained for each 30 sec injection by the supernatant dilution factor, enabling comparison of capture levels between supernatants diluted to varying degrees across different experimental runs. The relative antibody expression level (titre) of each mutant was compared to a batch-specific 3A5.040 supernatant, (Table 3) using the following formula:

(adjusted 3A5.040 reference RU for 30 sec injection / adjusted variant antibody RU for 30 sec injection) x 100 = proportional titre of parental antibody (% 3A5.040 titre)

Formula 1

[0100] Variant antibodies with a higher titre than parent 3A5.040 antibody had a "% 3A5.040 titre" value >100% and those with a lower titre, a value <100%. This enabled the identification of variant antibodies that might have improved expression over the parental antibody, 3A5.040. The titres of some variants were not determined by Biacore analysis of supernatant samples, but were expressed and purified as above and their purified yields determined by spectrophotometric analysis (A_{280}), then compared to parental 3A5.040 antibody (Table 5).

[0101] Determination of 3A5.040 variant antibody IL-5-binding kinetics by Biacore - Supernatants containing antibody from expression in EXPI293® cells or purified antibodies were analyzed using a Protein A series S chip on a Biacore T200 system (GE Healthcare) to determine their binding affinity for recombinant human IL-5 and rank them with respect to the parental antibody 3A5.040.

[0102] Each antibody was diluted in running buffer (1 x HBS-EP+, 350 mM NaCl) and captured at 60 µL/min to approximately 50 RU on FC 2. The surface and sensorgram was then stabilized for 120 sec by injection of running buffer. Recombinant human IL-5 at 5 µg/mL or running buffer was injected onto FC 1 and 2 at a flow rate of 60 µL/min for 70 sec. The IL-5 was allowed to dissociate in running buffer for 300 sec. The surface was regenerated by injecting 50 mM NaOH for 12 sec at a flow rate of 60 µL/min onto FC 1 and 2. Buffer was injected to further clean up drift for 60 sec at a flow rate of 60 µL/min onto FC 1 and 2. The surface was stabilized for 300 sec with running buffer over FC 1 and 2. Supernatant containing the parental 3A5.040 antibody and that had been transfected with each batch was run approximately every 25 cycles throughout each run. A purified sample of 3A5.040 and an IgG4 lambda isotype control was run with every batch as a measure of inter-assay variability. Multiple batches were run due to the large number of antibodies that were screened in this manner.

[0103] Data was double-referenced (flow cell 2 was subtracted from flow cell 1 and a buffer blank) and sensorgrams fitted to a 1:1 Langmuir binding model with Biacore Evaluation software. A kd (off-rate) value was calculated for each 3A5.040 supernatant sample throughout the run and these were averaged to give a reference kd, with the exception of run 2.1, which only had one 3A5.040 supernatant sample (Table 3 and Tables 6-11). The calculated kd value for each supernatant antibody was compared against the 3A5.040 average reference kd using the following formula:

(3A5.040 reference kd / variant antibody kd) x 100 = proportional kd of parental antibody (% 3A5.040 kd)

Formula 2

[0104] Variant antibodies with a lower kd (slower off-rate) than parent 3A5.040 antibody had a "% 3A5.040 kd" value >100% and those with a higher kd (faster off-rate) a value <100%. This enabled the identification of variant antibodies that might have improved binding kinetics for IL-5 and therefore improved function over the parental antibody,

3A5.040. For variants where only purified protein was made (Table 6), the Biacore kinetic analysis was performed in triplicate as above using these purified antibodies and the average values from each triplicate analysis used to perform the proportional kd calculation, as above (Table 4 and Tables 8-11).

Table 3. Determination of supernatant 3A5.040 variant antibody titre and IL-5 binding kinetics by Biacore

Run #	Antibody ID	Replicate Number	Amino acid Substitution	Capture level	ka (1/Ms)	kd (1/s)	K_D (M)	Rmax (RU)	% 3A5.040 kd	% 3A5.040 titre
1.1	3A5.040	1	Wild type	51.6	7.20E+05	1.15E-04	1.60E-10	16.3		
1.1	3A5.040	2	Wild type	51.6	7.27E+05	8.96E-05	1.23E-10	16.6		
1.1	3A5.040	3	Wild type	51.8	7.18E+05	9.21E-05	1.28E-10	16.7		
1.1	3A5.040	4	Wild type	52	6.96E+05	9.95E-05	1.43E-10	16.8		
1.1	**3A5.040**	**Average**	**Wild type**	**51.75**	**7.15E+05**	**9.91E-05**	**1.39E-10**	**16.6**	**100**	**100**
1.1	IgG4 Isotype			54.4	N/A	N/A	N/A	0.7	N/A	N/A
1.1	3A5.040 (Purified)		Wild type	56.4	7.17E+05	1.06E-04	1.48E-10	17.8	93.0	
1.1	3A5.304		VH_G26A	54.6	7.41E+05	7.73E-05	1.04E-10	17.1	128	49
1.1	3A5.305		VH_G26S	53.1	7.36E+05	1.09E-04	1.48E-10	16.7	91	59
1.1	3A5.306		VH_G26L	49.1	7.49E+05	8.74E-05	1.17E-10	15.6	113	15
1.1	3A5.308		VH_G26D	52.5	6.75E+05	8.57E-05	1.27E-10	16.4	116	61
1.1	3A5.309		VH_G26Q	55.1	7.47E+05	9.23E-05	1.24E-10	17.4	107	86
1.1	3A5.310		VH_G26K	51.8	7.36E+05	1.01E-04	1.37E-10	16.4	98	100
1.1	3A5.311		VH_G26H	50.9	7.60E+05	1.11E-04	1.46E-10	16.3	89	85
1.1	3A5.312		VH_G26W	56.1	8.54E+05	1.21E-04	1.41E-10	18	82	107
1.1	3A5.313		VH_G27A	54.5	6.97E+05	1.17E-04	1.68E-10	17.3	85	99
1.1	3A5.314		VH_G27S	50.9	7.16E+05	9.81E-05	1.37E-10	16.2	101	95
1.1	3A5.315		VH_G27L	54.3	7.01E+05	1.31E-04	1.87E-10	17.1	76	118
1.1	3A5.316		VH_G27Y	56	6.66E+05	8.56E-04	1.29E-09	16.9	12	80
1.1	3A5.317		VH_G27D	57.4	6.56E+05	1.16E-04	1.76E-10	17.8	85	73
1.1	3A5.318		VH_G27Q	55.2	7.31E+05	1.49E-04	2.04E-10	17.4	67	82

Run #	Antibody ID	Replicate Number	Amino acid Substitution	Capture level	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	% 3A5.040 kd	% 3A5.04 0 titre
1.1	3A5.319		VH_G27K	54.8	7.70E+05	2.04E-04	2.65E-10	17.5	49	95
1.1	3A5.320		VH_G27H	54.4	7.12E+05	2.43E-04	3.42E-10	16.9	41	71
1.1	3A5.322		VH_S28A	58	7.49E+05	1.05E-04	1.41E-10	18	94	62
1.1	3A5.323		VH_S28L	53.8	7.18E+05	9.30E-05	1.30E-10	17	107	70
1.1	3A5.324		VH_S28Y	54.8	8.13E+05	8.60E-05	1.06E-10	17	115	51
1.1	3A5.325		VH_S28D	54.9	6.03E+05	9.16E-05	1.52E-10	17	108	68
1.1	3A5.326		VH_S28Q	56.9	6.78E+05	9.97E-05	1.47E-10	17.7	99	77
1.1	3A5.327		VH_S28K	53.7	7.22E+05	1.15E-04	1.59E-10	16.9	86	84
1.1	3A5.328		VH_S28H	54	7.82E+05	1.23E-04	1.57E-10	16.9	81	71
1.1	3A5.329		VH_S28W	55	8.33E+05	1.36E-04	1.63E-10	17	73	41
1.1	3A5.330		VH_I29A	56.3	6.54E+05	1.69E-04	2.58E-10	16.8	59	30
1.1	3A5.331		VH_I29S	53.3	5.87E+05	2.04E-04	3.48E-10	15.7	49	28
1.1	3A5.332		VH_I29L	55.3	8.26E+05	1.16E-04	1.41E-10	17.5	85	75
1.1	3A5.333		VH_I29Y	55.4	5.44E+05	9.31E-04	1.71E-09	15.7	11	24
1.1	3A5.334		VH_I29D	52.8	3.53E+06	5.37E-03	1.52E-09	11.9	2	21
1.1	3A5.336		VH_I29K	53.7	6.17E+05	6.75E-04	1.10E-09	14.8	15	29
1.1	3A5.338		VH_I29W	56.6	1.31E+06	2.34E-03	1.78E-09	14.9	4	38
1.1	3A5.340		VH_S30L	48.7	6.51E+05	1.47E-04	2.25E-10	15.6	67	153
1.1	3A5.341		VH_S30Y	54.3	7.54E+05	1.37E-04	1.82E-10	17.3	72	103
1.1	3A5.342		VH_S30D	54.9	6.17E+05	1.23E-04	2.00E-10	17.4	81	103
1.1	3A5.347		VH_N31A	53.8	7.53E+05	6.75E-04	8.97E-10	17.3	15	118
1.1	3A5.348		VH_N31S	54.6	7.82E+05	5.03E-04	6.44E-10	17.7	20	107
1.1	3A5.350		VH_N31Y	56.2	9.01E+05	8.80E-04	9.76E-10	17.6	11	NE
1.1	3A5.351		VH_N31D	59.8	6.40E+05	2.03E-04	3.17E-10	19.2	49	75
1.1	3A5.352		VH_N31Q	54.8	6.93E+05	4.21E-04	6.07E-10	17.7	24	156
1.1	3A5.353		VH_N31K	55.5	6.85E+05	7.54E-04	1.10E-09	17.7	13	170

Run #	Antibody ID	Replicate Number	Amino acid Substitution	Capture level	ka (1/Ms)	kd (1/s)	K_D (M)	Rmax (RU)	% 3A5.040 kd	% 3A5.04 0 titre
1.1	3A5.354		VH_N31H	53.7	7.63E+05	1.32E-04	1.73E-10	17.5	75	143
1.1	3A5.356		VH_G32A	52.3	5.25E+05	3.02E-04	5.76E-10	16.4	33	179
1.1	3A5.357		VH_G32S	49.2	6.02E+05	1.23E-03	2.04E-09	15.3	8	153
1.1	3A5.495		VH_S94K	55	6.76E+05	2.91E-04	4.31E-10	17.6	34	127
1.1	3A5.497		VH_S94W	56.8	1.67E+06	2.92E-03	1.75E-09	12.5	3	38
1.1	3A5.498		VH_S94P	55.5	4.45E+05	1.17E-04	2.63E-10	16	85	17
1.1	3A5.500		VH_L95S	2.7					NE	NE
1.1	3A5.504		VH_L95K	51.7	1.53E+06	3.12E-03	2.03E-09	11.3	3	67
1.1	3A5.505		VH_L95H	52.9	5.59E+05	6.66E-04	1.19E-09	16.3	15	88
1.1	3A5.507		VH_L95P	54.7					NB	40
1.1	3A5.509		VH_G96S	54.4	5.94E+05	1.92E-04	3.23E-10	17	52	88
1.1	3A5.510		VH_G96L	54	4.11E+06	7.90E-03	1.92E-09	8.5	1	63
1.1	3A5.513		VH_G96Q	54.8	4.45E+05	5.13E-04	1.15E-09	16.5	19	64
1.1	3A5.514		VH_G96K	54.9	5.14E+06	6.84E-03	1.33E-09	11.4	1	147
1.1	3A5.515		VH_G96H	53.2	4.37E+05	1.20E-03	2.74E-09	15.3	8	117
1.1	3A5.516		VH_G96W	53	1.31E+06	1.40E-02	1.07E-08	6.7	1	55
1.1	3A5.517		VH_G96P	47.8	1.35E+05	5.04E-04	3.73E-09	11.7	20	15
1.1	3A5.518		VH_N97A	52	5.35E+05	1.72E-04	3.21E-10	16.3	58	95
1.1	3A5.520		VH_N97L	54.5	4.73E+05	1.11E-04	2.35E-10	16	89	96
1.1	3A5.521		VH_N97Y	54.7	5.05E+05	3.34E-04	6.62E-10	16.1	30	75
1.1	3A5.523		VH_N97Q	53.7	5.06E+05	9.79E-05	1.94E-10	16.6	101	127
1.1	3A5.524		VH_N97K	52.5	2.89E+05	1.37E-04	4.75E-10	15.1	72	167
1.1	3A5.525		VH_N97H	53.1	4.11E+05	2.14E-04	5.20E-10	15	46	113
1.1	3A5.526		VH_N97W	53.7	5.28E+05	5.26E-04	9.95E-10	15.5	19	56
1.1	3A5.527		VH_N97P	55.1	4.21E+05	4.38E-04	1.04E-09	15.5	23	68
1.1	3A5.528		VH_W98A	57.6	7.26E+05	1.87E-04	2.57E-10	18.4	53	114

Run #	Antibody ID	Replicate Number	Amino acid Substitution	Capture level	ka (1/Ms)	kd (1/s)	K_D (M)	Rmax (RU)	% 3A5.040 kd	% 3A5.04 0 titre
1.1	3A5.529		VH_W98S	53.9	6.23E+05	2.36E-04	3.78E-10	16.8	42	83
1.1	3A5.530		VH_W98L	54.3	3.38E+05	1.72E-04	5.08E-10	14.9	58	38
1.1	3A5.531		VH_W98Y	56.3	7.15E+05	1.12E-04	1.56E-10	18.1	88	143
1.1	3A5.532		VH_W98D	56.4	2.17E+05	8.87E-05	4.09E-10	14.6	112	42
1.1	3A5.533		VH_W98Q	53.8	5.01E+05	1.54E-04	3.08E-10	15.8	64	51
1.1	3A5.534		VH_W98K	53.4	3.46E+05	8.25E-04	2.38E-09	11.5	12	73
1.1	3A5.535		VH_W98H	53.8	6.13E+05	1.45E-04	2.37E-10	17	68	81
1.1	3A5.536		VH_W98P	56.1	9.97E+04	8.17E-04	8.20E-09	14.2	12	31
1.1	3A5.537		VH_F99A	54.2	1.54E+05	4.90E-04	3.18E-09	13.7	20	37
1.1	3A5.538		VH_F99S	53.3	1.18E+05	1.02E-03	8.67E-09	9.9	10	40
1.1	3A5.539		VH_F99L	54.2	7.05E+05	1.15E-04	1.63E-10	16.7	86	55
1.1	3A5.540		VH_F99Y	55.6	5.27E+05	9.13E-05	1.73E-10	14.9	109	41
1.1	3A5.541		VH_F99D	53.9	1.46E+05	1.11E-02	7.56E-08	4.4	1	32
1.1	3A5.542		VH_F99Q	53.8	9.93E+04	1.00E-03	1.01E-08	13	10	35
1.1	3A5.543		VH_F99K	54.6					NB	38
1.1	3A5.544		VH_F99H	54.8	2.05E+05	9.50E-05	4.64E-10	14.5	104	41
1.1	3A5.545		VH_F99W	54.5	5.35E+04	4.09E-04	7.66E-09	6	24	29
1.1	3A5.546		VH_F99P	53.1					NB	43
1.1	3A5.547		VH_D101A	55.6	1.68E+05	1.40E-04	8.37E-10	14.7	71	69
1.1	3A5.548		VH_D101S	55.2	2.38E+05	1.11E-04	4.67E-10	15.3	89	78
1.1	3A5.549		VH_D101L	53.6	5.94E+05	4.76E-04	8.01E-10	16.3	21	43
1.1	3A5.551		VH_D101Q	54.5	5.93E+05	2.19E-04	3.69E-10	17.1	45	78
1.2	3A5.040	1	Wild type	50.3	7.40E+05	1.33E-04	1.80E-10	16.3		
1.2	3A5.040	2	Wild type	50.3	7.14E+05	8.22E-05	1.15E-10	16.1		
1.2	3A5.040	3	Wild type	50	7.28E+05	1.01E-04	1.39E-10	16.1		

Run #	Antibody ID	Replicate Number	Amino acid Substitution	Capture level	ka (1/Ms)	kd (1/s)	K_D (M)	Rmax (RU)	% 3A5.040 kd	% 3A5.04 0 titre
1.2	3A5.040	4	Wild type	50.2	7.32E+05	1.10E-04	1.50E-10	16.2		
1.2	3A5.040	5	Wild type	50.1	7.27E+05	9.36E-05	1.29E-10	16.1		
1.2	**3A5.040**	**Average**	**Wild type**	**50.2**	**7.28E+05**	**1.04E-04**	**1.43E-10**	**16.2**	**100**	**100**
1.2	IgG4 Isotype			50.8	N/A	N/A	N/A	0	N/A	
1.2	3A5.040 (Purified)		Wild type	52.6	7.35E+05	1.11E-04	1.51E-10	16.6	94	
1.2	3A5.553		VH_D101H	51.9	4.41E+05	1.63E-04	3.69E-10	15.5	64	66
1.2	3A5.555		VH_D101P	51.3	7.54E+03	8.00E-04	1.06E-07	23.6	13	39
1.2	3A5.556		VH_Y102A	50.6	6.60E+05	8.94E-05	1.35E-10	16.4	116	106
1.2	3A5.557		VH_Y102S	53.5	6.85E+05	1.11E-04	1.61E-10	17.2	94	135
1.2	3A5.558		VH_Y102L	53.2	7.40E+05	1.14E-04	1.54E-10	16.8	91	51
1.2	3A5.559		VH_Y102D	52.8	7.03E+05	1.41E-04	2.01E-10	16.7	74	51
1.2	3A5.560		VH_Y102Q	52.6	7.14E+05	1.08E-04	1.51E-10	16.9	96	87
1.2	3A5.561		VH_Y102K	55.9	7.23E+05	8.01E-05	1.11E-10	17.7	130	90
1.2	3A5.562		VH_Y102H	50.4	7.22E+05	1.00E-04	1.39E-10	16.4	104	132
1.2	3A5.563		VH_Y102W	50.9	7.51E+05	1.16E-04	1.54E-10	16.8	90	117
1.2	3A5.564		VH_Y102P	53	6.44E+05	1.29E-04	2.01E-10	15	81	32
2.1	3A5.040	1	Wild type	68.5	7.13E+05	1.16E-04	1.63E-10	22.6		
2.1	**3A5.040**	**Average**	**Wild type**	**68.5**	**7.13E+05**	**1.16E-04**	**1.63E-10**	**22.6**	**100**	**100**
2.1	IgG4 Isotype			60.7	N/A	N/A	N/A	1.6	N/A	
2.1	3A5.040 (Purified)		Wild type	75.6	7.37E+05	1.05E-04	1.42E-10	24.3	110	
2.1	3A5.048		VL_G24A	69	7.16E+05	9.18E-05	1.28E-10	22.7	126	104
2.1	3A5.049		VL_G24S	72.5	6.98E+05	1.03E-04	1.47E-10	23.7	113	104

Run #	Antibody ID	Replicate Number	Amino acid Substitution	Capture level	ka (1/Ms)	kd (1/s)	K_D (M)	Rmax (RU)	% 3A5.040 kd	% 3A5.04 0 titre
2.1	3A5.050		VL_G24L	73.8	6.79E+05	8.13E-05	1.20E-10	23.9	143	103
2.1	3A5.051		VL_G24Y	61.7	6.40E+05	1.12E-04	1.75E-10	20.3	104	91
2.1	3A5.052		VL_G24D	66.7	7.16E+05	9.71E-05	1.36E-10	21.9	119	104
2.1	3A5.053		VL_G24Q	72.6	6.99E+05	9.84E-05	1.41E-10	23.6	118	95
2.1	3A5.054		VL_G24K	74.2	7.12E+05	9.59E-05	1.35E-10	24.1	121	98
2.1	3A5.055		VL_G24H	60.9	6.90E+05	9.17E-05	1.33E-10	20.2	126	99
2.1	3A5.056		VL_G24W	64.4	6.41E+05	8.06E-05	1.26E-10	21.1	144	111
2.1	3A5.057		VL_G25A	69.9	7.04E+05	8.75E-05	1.24E-10	22.9	133	109
2.1	3A5.059		VL_G25L	63.1	7.16E+05	1.04E-04	1.45E-10	21	112	83
2.1	3A5.060		VL_G25Y	67.7	7.05E+05	8.55E-05	1.21E-10	22.2	136	96
2.1	3A5.061		VL_G25D	71.9	7.26E+05	1.11E-04	1.53E-10	23.4	105	94
2.1	3A5.062		VL_G25Q	73.2	6.52E+05	9.24E-05	1.42E-10	23.5	126	94
2.1	3A5.064		VL_G25H	60.4	6.90E+05	9.21E-05	1.33E-10	20.1	126	108
2.1	3A5.065		VL_G25W	70.8	7.37E+05	8.97E-05	1.22E-10	23.1	129	81
2.1	3A5.066		VL_N26A	76.8	7.27E+05	8.75E-05	1.20E-10	24.7	133	77
2.1	3A5.069		VL_N26Y	71.2	6.79E+05	8.73E-05	1.28E-10	22.9	133	100
2.1	3A5.070		VL_N26D	62.7	7.22E+05	7.87E-05	1.09E-10	20.7	147	95
2.1	3A5.071		VL_N26Q	67.4	7.05E+05	1.08E-04	1.53E-10	22	107	95
2.1	3A5.072		VL_N26K	69.7	7.04E+05	1.17E-04	1.66E-10	22.7	99	99
2.1	3A5.073		VL_N26H	74.8	7.15E+05	1.11E-04	1.55E-10	24	105	95
2.1	3A5.074		VL_N26W	62.6	6.41E+05	9.82E-05	1.53E-10	20.3	118	87
2.1	3A5.075		VL_N27A	62.7	6.55E+05	9.29E-05	1.42E-10	20.7	125	120
2.1	3A5.076		VL_N27S	71.7	7.04E+05	1.09E-04	1.55E-10	23.2	106	93
2.1	3A5.077		VL_N27L	71.7	6.73E+05	8.98E-05	1.33E-10	23.4	129	102
2.1	3A5.078		VL_N27Y	61.5	6.16E+05	1.02E-04	1.65E-10	20.3	114	103
2.1	3A5.080		VL_N27Q	68.3	6.52E+05	1.07E-04	1.64E-10	22.1	108	91

Run #	Antibody ID	Replicate Number	Amino acid Substitution	Capture level	ka (1/Ms)	kd (1/s)	K_D (M)	Rmax (RU)	% 3A5.040 kd	% 3A5.040 titre
2.1	3A5.081		VL_N27K	71.5	6.89E+05	8.84E-05	1.28E-10	23.2	131	96
2.1	3A5.082		VL_N27H	74.7	7.06E+05	7.85E-05	1.11E-10	24.1	148	90
2.1	3A5.084		VL_I28A	62.1	6.71E+05	6.20E-05	9.24E-11	20.3	187	91
2.1	3A5.085		VL_I28S	91.9	6.37E+05	1.16E-04	1.82E-10	31.3	100	47
2.1	3A5.086		VL_I28L	81.5	6.02E+05	1.04E-04	1.73E-10	27.2	112	62
2.1	3A5.087		VL_I28Y	73.1	7.07E+05	8.52E-05	1.20E-10	23.8	136	93
2.1	3A5.088		VL_I28D	80.3	5.56E+05	9.83E-05	1.77E-10	27.9	118	40
2.1	3A5.089		VL_I28Q	79.8	5.80E+05	1.03E-04	1.77E-10	27.8	113	54
2.1	3A5.093		VL_G29A	68.4	5.42E+05	1.10E-04	2.04E-10	22.6	105	59
2.1	3A5.094		VL_G29S	67.6	6.98E+05	9.31E-05	1.33E-10	21.9	119	93
2.2	3A5.040	1	Wild type	52.4	7.77E+05	1.05E-04	1.35E-10	17.9		
2.2	3A5.040	2	Wild type	52.7	7.89E+05	1.09E-04	1.38E-10	17.9		
2.2	3A5.040	3	Wild type	52.7	7.72E+05	1.37E-04	1.77E-10	18.1		
2.2	**3A5.040**	**Average**	**Wild type**	**52.6**	**7.79E+05**	**1.17E-04**	**1.50E-10**	**17.9**	**100**	**100**
2.2	IgG4 Isotype			56.6	N/A	N/A	N/A	0.5	N/A	
2.2	3A5.040 (Purified)		Wild type	54.9	7.93E+05	1.06E-04	1.33E-10	18.7	110	
2.2	3A5.095		VL_G29L	55.4	7.17E+05	9.08E-05	1.27E-10	18.7	122	75
2.2	3A5.096		VL_G29Y	56.7	6.92E+05	1.33E-04	1.92E-10	19.2	83	58
2.2	3A5.097		VL_G29D	56.2	7.31E+05	7.19E-05	9.84E-11	18.7	154	85
2.2	3A5.099		VL_G29K	49.9	7.18E+05	9.08E-05	1.26E-10	17.2	122	71
2.2	3A5.100		VL_G29H	52	7.38E+05	8.65E-05	1.17E-10	17.7	128	100
2.2	3A5.101		VL_G29W	55.8	7.59E+05	9.40E-05	1.24E-10	18.7	118	114
2.2	3A5.102		VL_S30A	56.3	6.85E+05	1.09E-04	1.58E-10	18.7	102	84

Run #	Antibody ID	Replicate Number	Amino acid Substitution	Capture level	ka (1/Ms)	kd (1/s)	K_D (M)	Rmax (RU)	% 3A5.040 kd	% 3A5.04 0 titre
2.2	3A5.103		VL_S30L	49.5	7.87E+05	9.94E-05	1.26E-10	16.9	112	126
2.2	3A5.104		VL_S30Y	54.7	8.17E+05	1.08E-04	1.33E-10	18.5	103	93
2.2	3A5.105		VL_S30D	56.4	8.20E+05	8.91E-05	1.09E-10	18.8	125	119
2.2	3A5.106		VL_S30Q	58.3	7.22E+05	9.10E-05	1.26E-10	19.7	122	78
2.2	3A5.107		VL_S30K	50.6	7.85E+05	7.34E-05	9.34E-11	17.3	151	102
2.2	3A5.113		VL_K31Y	53.8	8.35E+05	8.73E-05	1.05E-10	18.4	127	99
2.2	3A5.114		VL_K31D	54.5	4.89E+05	4.73E-04	9.65E-10	17.9	23	105
2.2	3A5.115		VL_K31Q	57.9	4.65E+05	4.60E-04	9.91E-10	19	24	85
2.2	3A5.116		VL_K31H	49.5	5.52E+05	2.46E-04	4.46E-10	16.7	45	104
2.2	3A5.117		VL_K31W	52.7	5.34E+05	1.33E-04	2.49E-10	17.7	83	125
2.2	3A5.118		VL_N32A	55.8	5.07E+05	6.39E-04	1.26E-09	18.3	17	67
2.2	3A5.121		VL_N32Y	56.1	9.57E+05	9.68E-05	1.01E-10	19.1	115	91
2.2	3A5.122		VL_N32D	49.8	5.68E+05	1.25E-04	2.20E-10	15.8	89	115
2.2	3A5.123		VL_N32Q	53.9	8.85E+05	1.25E-04	1.41E-10	18.6	89	102
2.2	3A5.125		VL_N32H	56.4	9.01E+05	7.73E-05	8.58E-11	19.2	144	90
2.2	3A5.126		VL_N32W	56.6	6.35E+05	9.26E-05	1.46E-10	18.8	120	79
2.2	3A5.127		VL_V33A	49.1	7.15E+05	8.05E-05	1.13E-10	16.6	138	74
2.2	3A5.128		VL_V33S	51.5	2.85E+05	9.65E-05	3.38E-10	13.7	115	126
2.2	3A5.130		VL_V33Y	56.1	7.41E+05	9.16E-05	1.24E-10	19	121	68
2.2	3A5.131		VL_V33D	52.4	7.40E+05	9.67E-05	1.31E-10	19.3	115	40
2.2	3A5.132		VL_V33Q	48.7	6.61E+05	1.38E-04	2.09E-10	16.7	80	50
2.2	3A5.135		VL_V33W	48.4	5.26E+05	1.04E-04	1.99E-10	18.8	107	24
2.2	3A5.137		VL_Y34S	48.3	6.96E+05	9.88E-05	1.42E-10	19	112	32
2.2	3A5.138		VL_Y34L	49.4	5.94E+05	2.16E-04	3.64E-10	16.6	51	56
2.2	3A5.139		VL_Y34D	52.8	4.63E+05	4.90E-04	1.06E-09	13.1	23	68
2.2	3A5.140		VL_Y34Q	54.4	7.01E+05	5.40E-04	7.71E-10	18.2	21	55

Run #	Antibody ID	Replicate Number	Amino acid Substitution	Capture level	ka (1/Ms)	kd (1/s)	K_D (M)	Rmax (RU)	% 3A5.040 kd	% 3A5.040 titre
2.2	3A5.141		VL_Y34K	56	8.16E+05	3.72E-04	4.56E-10	18.8	30	64
2.2	3A5.142		VL_Y34H	48.8	6.71E+05	5.00E-04	7.46E-10	16.3	22	82
2.2	3A5.143		VL_Y34W	53.5	6.98E+05	2.19E-03	3.13E-09	9.7	5	58
2.2	3A5.165		VL_S52K	52.6	5.32E+05	9.30E-04	1.75E-09	16.6	12	167
2.2	3A5.168		VL_D53A	57.2	1.20E+06	2.04E-03	1.71E-09	17.1	5	51
2.2	3A5.172		VL_D53Q	50.3	7.13E+05	1.08E-04	1.51E-10	17.1	103	97
2.2	3A5.174		VL_D53H	53	7.45E+05	1.23E-04	1.65E-10	17.7	90	120
2.2	3A5.186		VL_P55S	55.8	7.97E+05	1.08E-04	1.35E-10	18.6	103	108
2.2	3A5.199		VL_S56K	57.3	7.71E+05	1.18E-04	1.54E-10	18.8	94	104
2.2	3A5.201		VL_S56W	49.6	7.41E+05	1.24E-04	1.67E-10	17.1	90	92
2.2	3A5.210		VL_Q89P	53.5	3.80E+05	4.78E-04	1.26E-09	18	25	72
2.2	3A5.211		VL_V90A	55.7	7.65E+05	1.06E-04	1.39E-10	18.8	105	78
3.1	3A5.040	1	Wild type	53.3	7.72E+05	1.32E-04	1.71E-10	18.2		
3.1	3A5.040	2	Wild type	53.4	7.76E+05	1.15E-04	1.48E-10	18.1		
3.1	3A5.040	3	Wild type	53.3	7.73E+05	1.03E-04	1.34E-10	18.1		
3.1	3A5.040	4	Wild type	54	7.69E+05	1.14E-04	1.49E-10	18.5		
3.1	3A5.040	5	Wild type	53.8	7.84E+05	1.20E-04	1.53E-10	18.4		
3.1	**3A5.040**	**Average**	**Wild type**	**53.6**	**7.75E+05**	**1.17E-04**	**1.51E-10**	**18.2**	**100**	**100**
3.1	IgG4 Isotype			56	N/A	N/A	N/A	0.7	N/A	
3.1	3A5.040 (Purified)		Wild type	52.5	8.07E+05	1.40E-04	1.74E-10	17.9	83	
3.1	3A5.213		VL_V90L	53.7	7.49E+05	1.55E-04	2.06E-10	18.2	75	58
3.1	3A5.214		VL_V90Y	54	6.50E+05	2.92E-04	4.49E-10	18	40	85
3.1	3A5.215		VL_V90D	52.9	5.54E+05	4.19E-04	7.56E-10	19.9	28	27

Run #	Antibody ID	Replicate Number	Amino acid Substitution	Capture level	ka (1/Ms)	kd (1/s)	K_D (M)	Rmax (RU)	% 3A5.040 kd	% 3A5.04 0 titre
3.1	3A5.216		VL_V90Q	48.6	5.93E+05	1.88E-04	3.18E-10	16.3	62	74
3.1	3A5.217		VL_V90K	44.3	6.34E+05	8.30E-05	1.31E-10	17	141	48
3.1	3A5.218		VL_V90H	47.5	5.90E+05	2.99E-04	5.07E-10	17.6	39	60
3.1	3A5.219		VL_V90W	53.4	5.69E+05	6.64E-04	1.17E-09	17.9	18	77
3.1	3A5.220		VL_V90P	47.7	2.72E+05	7.61E-03	2.79E-08	1.7	2	76
3.1	3A5.221		VL_W91A	51.8	3.05E+05	7.08E-03	2.32E-08	2.4	2	79
3.1	3A5.223		VL_W91L	53.6	2.59E+06	2.55E-02	9.83E-09	7.7	0	98
3.1	3A5.224		VL_W91Y	45.1	8.82E+05	9.03E-04	1.02E-09	15.8	13	64
3.1	3A5.226		VL_W91Q	51.1	5.38E+06	3.79E-02	7.05E-09	6.8	0	75
3.1	3A5.227		VL_W91K	51.8					NB	71
3.1	3A5.228		VL_W91H	50.9	1.53E+06	7.24E-03	4.74E-09	9	2	62
3.1	3A5.229		VL_W91P	39.4	4.02E+05	7.40E-03	1.84E-08	1.4	2	36
3.1	3A5.230		VL_D92A	51.2	5.63E+05	9.94E-05	1.77E-10	16.5	118	113
3.1	3A5.231		VL_D92S	53.2	7.67E+05	9.46E-05	1.23E-10	17.5	124	113
3.1	3A5.232		VL_D92L	54.3	9.17E+05	7.59E-05	8.27E-11	18	154	130
3.1	3A5.233		VL_D92Y	47.7	1.11E+06	1.10E-04	9.92E-11	16.4	106	72
3.1	3A5.234		VL_D92Q	50.9	5.25E+05	1.39E-04	2.64E-10	15.7	84	194
3.1	3A5.235		VL_D92K	54.7	7.63E+05	8.84E-05	1.16E-10	18	132	92
3.1	3A5.236		VL_D92H	54.3	7.93E+05	1.09E-04	1.37E-10	17.6	107	122
3.1	3A5.237		VL_D92W	0.5					NE	NE
3.1	3A5.238		VL_D92P	46.8	5.21E+05	1.43E-04	2.75E-10	16.1	82	63
3.1	3A5.239		VL_S93A	52.2	3.12E+06	3.65E-03	1.17E-09	15.9	3	112
3.1	3A5.240		VL_S93L	54.8	2.39E+07	2.45E-01	1.03E-08	6.5	0	124
3.1	3A5.241		VL_S93Y	50.1	6.20E+05	7.48E-03	1.21E-08	2	2	118
3.1	3A5.242		VL_S93D	51.6	5.18E+05	1.68E-02	3.25E-08	2.9	1	73
3.1	3A5.243		VL_S93Q	54.4	1.90E+06	1.51E-02	7.95E-09	8.2	1	111

Run #	Antibody ID	Replicate Number	Amino acid Substitution	Capture level	ka (1/Ms)	kd (1/s)	K_D (M)	Rmax (RU)	% 3A5.040 kd	% 3A5.04 0 titre
3.1	3A5.244		VL_S93K	55.5					NB	162
3.1	3A5.245		VL_S93H	49.7	2.92E+06	2.23E-02	7.64E-09	7.3	1	133
3.1	3A5.246		VL_S93W	52.8	3.27E+05	4.33E-03	1.33E-08	0.8	3	115
3.1	3A5.247		VL_S93P	53.8	6.94E+05	5.33E-02	7.68E-08	1.7	0	112
3.1	3A5.248		VL_S94A	56.1	8.15E+05	1.22E-04	1.50E-10	19.1	96	101
3.1	3A5.249		VL_S94L	49.7	7.81E+05	5.00E-04	6.41E-10	17.1	23	90
3.1	3A5.253		VL_S94K	53	6.74E+05	1.48E-04	2.20E-10	17.9	79	109
3.1	3A5.254		VL_S94H	53.7	6.24E+05	1.51E-04	2.42E-10	18.1	77	104
3.1	3A5.256		VL_S94P	49.7	6.97E+05	1.27E-04	1.82E-10	16.7	92	139
3.1	3A5.257		VL_S95A	52.1	7.34E+05	1.19E-04	1.62E-10	17.7	98	99
3.1	3A5.258		VL_S95L	54	7.73E+05	1.13E-04	1.47E-10	18.3	104	99
3.1	3A5.259		VL_S95Y	55.7	8.35E+05	1.07E-04	1.28E-10	18.7	109	83
3.1	3A5.260		VL_S95D	49.2	6.07E+05	1.25E-04	2.07E-10	16.5	94	109
3.1	3A5.261		VL_S95Q	48.6	7.87E+05	9.19E-05	1.17E-10	17.8	127	62
3.1	3A5.262		VL_S95K	53.1	7.99E+05	1.01E-04	1.26E-10	18.2	116	118
3.1	3A5.263		VL_S95H	55.4	7.83E+05	1.00E-04	1.28E-10	18.7	117	101
3.1	3A5.264		VL_S95W	49	7.95E+05	1.27E-04	1.60E-10	16.5	92	87
3.1	3A5.265		VL_S95P	52.7	6.45E+05	5.55E-03	8.61E-09	7.1	2	147
3.1	3A5.266		VL_D95aA	53.7	5.78E+06	8.07E-03	1.40E-09	10.4	1	109
3.1	3A5.267		VL_D95aS	55.3	4.53E+05	1.21E-03	2.68E-09	16.7	10	101
3.1	3A5.268		VL_D95aL	48.5	9.19E+06	1.35E-02	1.47E-09	8.7	1	71
3.1	3A5.269		VL_D95aY	51.8	1.77E+06	6.74E-03	3.80E-09	8	2	95
3.1	3A5.270		VL_D95aQ	53.6	5.26E+06	7.11E-03	1.35E-09	11.4	2	110
3.1	3A5.271		VL_D95aK	53.8	3.92E+05	3.83E-02	9.77E-08	2	0	70
3.1	3A5.272		VL_D95aH	49.7	2.56E+06	4.90E-03	1.92E-09	10.1	2	188
3.1	3A5.273		VL_D95aW	53.1	1.27E+06	1.47E-02	1.15E-08	7.1	1	94

Run #	Antibody ID	Replicate Number	Amino acid Substitution	Capture level	ka (1/Ms)	kd (1/s)	K_D (M)	Rmax (RU)	% 3A5.040 kd	% 3A5.04 0 titre
3.1	3A5.274		VL_D95aP	54.6	1.17E+06	3.05E-03	2.61E-09	9.8	4	150
3.1	3A5.276		VL_H95bS	52.1	8.47E+05	7.33E-05	8.66E-11	19.6	160	61
3.1	3A5.281		VL_H95bK	45.5	7.08E+05	9.58E-05	1.35E-10	16.3	122	64
3.1	3A5.307		VH_G26Y	48.1	8.73E+05	1.02E-04	1.17E-10	18.3	115	60
3.1	3A5.321		VH_G27W	55	7.64E+05	5.59E-04	7.31E-10	18.4	21	97
3.1	3A5.335		VH_I29Q	37.9	5.64E+05	3.90E-04	6.92E-10	14.9	30	37
3.1	3A5.343		VH_S30Q	51.9	7.55E+05	1.06E-04	1.40E-10	17.7	110	121
3.1	3A5.344		VH_S30K	53.9	7.41E+05	1.39E-04	1.88E-10	18	84	156
3.1	3A5.345		VH_S30H	54.8	7.34E+05	1.46E-04	1.99E-10	18.7	80	77
3.1	3A5.349		VH_N31L	47.1	7.69E+05	7.13E-04	9.27E-10	16.3	16	69
3.1	3A5.355		VH_N31W	45.3	8.52E+05	4.80E-04	5.63E-10	17.3	24	59
3.1	3A5.359		VH_G32Y	53.7	3.28E+06	4.30E-03	1.31E-09	15.5	3	90
3.1	3A5.360		VH_G32D	54.2	1.05E+06	6.78E-03	6.44E-09	8.1	2	105
3.1	3A5.361		VH_G32Q	49.5	3.98E+06	6.22E-03	1.56E-09	11.8	2	133
3.1	3A5.362		VH_G32K	52.6	6.07E+05	2.20E-03	3.62E-09	7.6	5	171
3.1	3A5.363		VH_G32H	55.4	1.81E+06	3.01E-03	1.66E-09	15.3	4	114
3.1	3A5.364		VH_G32W	52.3	1.46E+07	1.27E-02	8.65E-10	13.5	1	66
3.1	3A5.365		VH_G33A	48.7	6.97E+05	9.24E-05	1.33E-10	16.6	127	116
3.1	3A5.366		VH_G33S	53	8.56E+05	2.68E-03	3.14E-09	8.3	4	117
3.1	3A5.367		VH_G33L	54.2	8.03E+05	3.05E-04	3.79E-10	17.9	38	82
3.1	3A5.368		VH_G33Y	55.4	3.97E+06	4.08E-03	1.03E-09	13.4	3	107
3.2	3A5.040	1	Wild type	54.7	6.75E+05	9.46E-05	1.40E-10	19		
3.2	3A5.040	2	Wild type	55.2	6.82E+05	7.26E-05	1.07E-10	19		
3.2	3A5.040	3	Wild type	55.7	7.17E+05	9.30E-05	1.30E-10	19.3		
3.2	3A5.040	4	Wild type	55.3	7.08E+05	8.82E-05	1.25E-10	19.1		

Run #	Antibody ID	Replicate Number	Amino acid Substitution	Capture level	ka (1/Ms)	kd (1/s)	K_D (M)	Rmax (RU)	% 3A5.040 kd	% 3A5.040 titre
3.2	3A5.040	5	Wild type	55.2	6.95E+05	1.05E-04	1.51E-10	19.2		
3.2	**3A5.040**	**Average**	**Wild type**	**55.2**	**6.95E+05**	**9.07E-05**	**1.31E-10**	**19.1**	**100**	**100**
3.2	IgG4 Isotype			55.8	N/A	N/A	N/A	0	N/A	
3.2	3A5.040 (Purified)		Wild type	54.5	7.12E+05	8.25E-05	1.16E-10	1.85E+01	110	
3.2	3A5.369		VH_G33D	52.4	9.85E+05	2.46E-03	2.50E-09	9.4	4	277
3.2	3A5.370		VH_G33Q	54.5	5.33E+05	1.07E-03	2.00E-09	17.2	8	279
3.2	3A5.371		VH_G33K	58.5	2.08E+06	2.02E-03	9.72E-10	14.1	4	350
3.2	3A5.372		VH_G33H	51.5	1.45E+06	2.67E-03	1.83E-09	14.4	3	273
3.2	3A5.373		VH_G33W	52.4	6.71E+05	1.32E-03	1.96E-09	15.9	7	172
3.2	3A5.374		VH_Y34A	56.4	5.91E+05	1.27E-04	2.16E-10	19.2	71	162
3.2	3A5.375		VH_Y34S	56.4	6.23E+05	1.24E-04	2.00E-10	19.1	73	159
3.2	3A5.376		VH_Y34L	50	5.79E+05	1.60E-04	2.77E-10	17.2	57	160
3.2	3A5.377		VH_Y34D	54.7	5.40E+05	6.04E-04	1.12E-09	18.1	15	103
3.2	3A5.378		VH_Y34Q	54.4	5.98E+05	1.51E-04	2.53E-10	18.5	60	165
3.2	3A5.379		VH_Y34K	56.6	6.17E+05	4.91E-04	7.96E-10	19.1	18	407
3.2	3A5.380		VH_Y34H	49.8	6.40E+05	7.06E-04	1.10E-09	16.7	13	223
3.2	3A5.382		VH_Y35A	52.8	2.48E+05	2.46E-03	9.91E-09	0.9	4	289
3.2	3A5.383		VH_Y35S	55.8	3.34E+05	8.50E-03	2.54E-08	1.9	1	129
3.2	3A5.384		VH_Y35L	57	5.98E+05	1.42E-03	2.37E-09	17.5	6	190
3.2	3A5.385		VH_Y35D	48.5	2.75E+06	6.13E-03	2.23E-09	8.1	1	87
3.2	3A5.386		VH_Y35Q	51.8	1.18E+07	2.72E-01	2.31E-08	5.4	0	127
3.2	3A5.387		VH_Y35K	56.2					NB	382
3.2	3A5.388		VH_Y35H	58	3.40E+05	9.25E-03	2.72E-08	3.3	1	195
3.2	3A5.389		VH_Y35W	50	3.65E+06	5.41E-03	1.48E-09	8.8	2	225

Run #	Antibody ID	Replicate Number	Amino acid Substitution	Capture level	ka (1/Ms)	kd (1/s)	K_D (M)	Rmax (RU)	% 3A5.040 kd	% 3A5.04 0 titre
3.2	3A5.390		VH_W35aA	47	6.84E+05	1.74E-03	2.55E-09	15.4	5	37
3.2	3A5.392		VH_W35aL	55	4.59E+05	1.14E-03	2.49E-09	17.1	8	100
3.2	3A5.393		VH_W35aY	49.1	6.34E+05	1.87E-04	2.94E-10	16.7	49	104
3.2	3A5.394		VH_W35aD	0.7					NE	NE
3.2	3A5.395		VH_W35aQ	50.4	5.46E+05	8.47E-04	1.55E-09	18.8	11	34
3.2	3A5.397		VH_W35aH	39.6	5.07E+05	2.44E-04	4.82E-10	15.8	37	53
3.2	3A5.399		VH_S35bL	46	1.08E+05	2.86E-04	2.64E-09	14.1	32	39
3.2	3A5.400		VH_S35bY	51.7	4.43E+05	7.06E-03	1.59E-08	1.8	1	88
3.2	3A5.402		VH_S35bQ	38.8	1.84E+05	5.15E-04	2.80E-09	13.6	18	45
3.2	3A5.404		VH_S35bH	48.8	6.18E+05	1.88E-03	3.05E-09	13.3	5	75
3.2	3A5.405		VH_S35bW	49.6	2.93E+05	7.19E-03	2.45E-08	0.7	1	50
3.2	3A5.406		VH_Y50A	50.6	4.79E+05	5.88E-04	1.23E-09	16.1	15	268
3.2	3A5.407		VH_Y50S	56.1	4.95E+05	3.64E-04	7.34E-10	17.5	25	327
3.2	3A5.408		VH_Y50L	57	4.31E+05	3.22E-04	7.46E-10	17.3	28	122
3.2	3A5.409		VH_Y50D	56.9	7.63E+05	1.45E-03	1.90E-09	16	6	169
3.2	3A5.410		VH_Y50Q	50.9	5.95E+05	3.69E-04	6.20E-10	17.1	25	241
3.2	3A5.411		VH_Y50K	53.5	5.51E+05	4.47E-04	8.11E-10	17.5	20	135
3.2	3A5.412		VH_Y50H	55.5	6.72E+05	7.88E-04	1.17E-09	18.2	12	300
3.2	3A5.413		VH_Y50W	57.2	6.67E+05	1.61E-03	2.41E-09	16.9	6	131
3.2	3A5.414		VH_I51A	51.9	7.29E+05	1.13E-04	1.56E-10	17.7	80	244
3.2	3A5.415		VH_I51S	54.2	7.38E+05	1.15E-04	1.56E-10	18.6	79	130
3.2	3A5.416		VH_I51L	54.6	6.62E+05	1.39E-04	2.10E-10	19	65	87
3.2	3A5.417		VH_I51Y	57.2	5.42E+05	7.77E-03	1.43E-08	7.9	1	106
3.2	3A5.418		VH_I51D	40.4	5.15E+05	6.36E-04	1.23E-09	15.8	14	48
3.2	3A5.419		VH_I51Q	51.6	6.26E+05	5.02E-04	8.01E-10	17.7	18	95
3.2	3A5.420		VH_I51K	53.3	7.42E+05	1.16E-03	1.57E-09	17.3	8	124

Run #	Antibody ID	Replicate Number	Amino acid Substitution	Capture level	ka (1/Ms)	kd (1/s)	K_D (M)	Rmax (RU)	% 3A5.040 kd	% 3A5.04 0 titre
3.2	3A5.421		VH_I51H	54.1	7.46E+06	8.34E-03	1.12E-09	13.4	1	93
3.2	3A5.422		VH_I51W	49.7	3.18E+05	3.31E-03	1.04E-08	0.9	3	139
3.2	3A5.423		VH_Y52A	54.9	1.49E+07	1.08E-02	7.23E-10	11.8	1	304
3.2	3A5.424		VH_Y52S	57.3	6.79E+05	1.29E-03	1.89E-09	11.7	7	325
3.2	3A5.425		VH_Y52L	59.4	1.90E+06	8.83E-03	4.66E-09	10.1	1	209
3.2	3A5.426		VH_Y52D	51.7					NB	333
3.2	3A5.427		VH_Y52Q	55.5	1.86E+06	8.86E-03	4.76E-09	9.2	1	264
3.2	3A5.428		VH_Y52K	58.4					NB	348
3.2	3A5.429		VH_Y52H	61.5	5.62E+05	2.91E-04	5.17E-10	20.6	31	286
3.2	3A5.430		VH_Y52W	48.6	6.79E+05	1.26E-03	1.86E-09	15.9	7	102
3.2	3A5.431		VH_Y53A	53	6.79E+05	5.21E-04	7.67E-10	17.9	17	249
3.2	3A5.432		VH_Y53S	55	6.94E+05	1.57E-04	2.26E-10	18.8	58	226
3.2	3A5.433		VH_Y53L	57.3	6.02E+05	4.43E-04	7.36E-10	19.1	20	102
3.2	3A5.434		VH_Y53D	50.8	4.80E+05	5.94E-04	1.24E-09	16.6	15	182
3.2	3A5.435		VH_Y53Q	53.4	6.27E+05	4.41E-04	7.03E-10	17.9	21	206
3.2	3A5.436		VH_Y53K	56.7	6.17E+05	9.61E-04	1.56E-09	18.1	9	232
3.2	3A5.437		VH_Y53H	57	6.71E+05	1.91E-04	2.85E-10	19.1	47	206
3.2	3A5.438		VH_Y53W	49.2	6.91E+05	2.35E-04	3.40E-10	16.8	39	152
3.2	3A5.439		VH_S54A	53.1	6.98E+05	1.54E-04	2.20E-10	18.1	59	112
3.2	3A5.440		VH_S54L	53.4	9.17E+06	8.95E-03	9.76E-10	13.6	1	158
3.2	3A5.441		VH_S54Y	55	1.57E+06	2.17E-03	1.38E-09	16.5	4	92
3.2	3A5.442		VH_S54D	51.4	8.06E+05	2.02E-03	2.50E-09	14.4	4	200
3.2	3A5.443		VH_S54Q	54	6.04E+05	1.07E-03	1.77E-09	17.6	8	150
3.2	3A5.444		VH_S54K	55.6	2.65E+06	3.55E-03	1.34E-09	15.5	3	201
3.2	3A5.445		VH_S54H	57.5	7.10E+05	4.59E-04	6.46E-10	19.3	20	97
3.2	3A5.446		VH_S54W	46.7	7.24E+05	8.68E-04	1.20E-09	14.8	10	112

Run #	Antibody ID	Replicate Number	Amino acid Substitution	Capture level	ka (1/Ms)	kd (1/s)	K_D (M)	Rmax (RU)	% 3A5.040 kd	% 3A5.04 0 titre
3.2	3A5.447		VH_G55A	45.7	6.76E+05	1.05E-04	1.55E-10	17.1	86	68
3.2	3A5.448		VH_G55S	48.4	7.30E+05	1.24E-04	1.70E-10	18	73	72
3.2	3A5.449		VH_G55L	47.7	6.14E+05	6.30E-04	1.03E-09	17.7	14	66
3.2	3A5.450		VH_G55Y	38.6	6.88E+05	7.06E-04	1.03E-09	14.2	13	49
4.1	3A5.040	1	Wild type	82.7	1.00E+06	1.16E-04	1.16E-10	24.9		
4.1	3A5.040	2	Wild type	82.7	1.02E+06	1.07E-04	1.04E-10	25.1		
4.1	3A5.040	3	Wild type	85.2	1.03E+06	1.12E-04	1.09E-10	25.1		
4.1	3A5.040	4	Wild type	85.1	1.01E+06	1.06E-04	1.05E-10	25.3		
4.1	3A5.040	5	Wild type	83.5	9.91E+05	9.29E-05	9.37E-11	25.3		
4.1	**3A5.040**	**Average**	**Wild type**	**83.84**	**1.01E+06**	**1.07E-04**	**1.06E-10**	**25.14**	**100**	**100**
4.1	IgG4 Isotype			61.4	N/A	N/A	N/A	0	N/A	
4.1	3A5.040 (Purified)		Wild type	84.2	1.06E+06	1.09E-04	1.03E-10	23.8	98	
4.1	3A5.133		VL_V33K	52.7	7.83E+05	1.34E-04	1.71E-10	15.9	80	15
4.1	3A5.222		VL_W91S	62.8	1.38E+06	2.85E-03	2.06E-09	12.5	4	14
4.1	3A5.391		VH_W35aS	68.4	6.35E+05	1.19E-03	1.87E-09	15.6	9	22
4.1	3A5.396		VH_W35aK	65.9	7.21E+05	2.08E-03	2.88E-09	9.4	5	26
4.1	3A5.401		VH_S35bD	53.1	5.96E+05	1.19E-04	2.01E-10	14.5	90	16
4.1	3A5.403		VH_S35bK	53.1	1.83E+05	1.23E-02	6.68E-08	2.8	1	12
4.1	3A5.275		VL_H95bA	69.7	5.47E+05	1.62E-04	2.95E-10	18	66	24
4.1	3A5.282		VL_H95bW	77.5	7.18E+05	1.07E-04	1.49E-10	21.1	100	152
4.1	3A5.283		VL_H95bP	63.4	5.90E+05	4.22E-02	7.15E-08	3.6	0	154
4.1	3A5.285		VL_V96S	74.4	9.02E+05	2.01E-04	2.23E-10	19.9	53	21
4.1	3A5.287		VL_V96Y	92.4	7.33E+06	1.50E-03	2.05E-10	17.6	7	62

Run #	Antibody ID	Replicate Number	Amino acid Substitution	Capture level	ka (1/Ms)	kd (1/s)	K_D (M)	Rmax (RU)	% 3A5.040 kd	% 3A5.04 0 titre
4.1	3A5.288		VL_V96D	68.8	7.32E+05	1.30E-03	1.78E-09	16.8	8	9.5
4.1	3A5.289		VL_V96Q	77.1	1.62E+06	6.54E-04	4.03E-10	20.4	16	25
4.1	3A5.290		VL_V96K	64.6	8.08E+05	2.32E-03	2.87E-09	13.1	5	15
4.1	3A5.291		VL_V96H	5.2					NB	45
4.1	3A5.292		VL_V96W	66.4	3.83E+07	2.01E-02	5.26E-10	10.6	1	19
4.1	3A5.293		VL_V96P	81.5	8.54E+05	5.22E-04	6.11E-10	23.4	20	106
4.1	3A5.110		VL_K31A	74	7.01E+05	1.86E-04	2.65E-10	21.1	58	122
4.1	3A5.111		VL_K31S	79.2	7.10E+05	1.36E-04	1.92E-10	23.6	79	109
4.1	3A5.112		VL_K31L	79.9	6.30E+05	3.91E-04	6.21E-10	22.3	27	125
4.1	3A5.134		VL_V33H	5.8					NB	52
4.1	3A5.136		VL_Y34A	59.9	1.05E+06	3.45E-04	3.28E-10	17.2	31	170
4.1	3A5.206		VL_Q89D	71.6	5.68E+05	8.76E-05	1.54E-10	18.6	122	12
4.1	3A5.225		VL_W91D	114.2	6.31E+05	1.05E-02	1.66E-08	3.7	1	74
4.1	3A5.250		VL_S94Y	74.6	8.14E+05	3.48E-04	4.27E-10	20.3	31	147
4.1	3A5.252		VL_S94Q	63.4	8.25E+05	1.65E-04	2.00E-10	18	65	136
4.2	3A5.040	1	Wild type	50.4	6.96E+05	1.03E-04	1.48E-10	16.2		
4.2	3A5.040	2	Wild type	50.5	7.10E+05	1.06E-04	1.49E-10	16		
4.2	**3A5.040**	**Average**	**Wild type**	**50.4**	**7.03E+05**	**1.05E-04**	**1.49E-10**	**16.1**	**100**	**100**
4.2	IgG4 Isotype			52.5	N/A	N/A	N/A		N/A	
4.2	3A5.040 (Purified)		Wild type	48.7	7.21E+05	6.63E-05	9.20E-11	16.5	150	
4.2	3A5.451		VH_G55D	33.1	4.54E+05	2.50E-04	5.50E-10	9.9	42	39
4.2	3A5.452		VH_G55Q	37.2	6.09E+05	1.94E-04	3.18E-10	11.7	54	42
4.2	3A5.453		VH_G55K	43.8	5.49E+05	2.07E-04	3.76E-10	12.4	50	51

Run #	Antibody ID	Replicate Number	Amino acid Substitution	Capture level	ka (1/Ms)	kd (1/s)	K_D (M)	Rmax (RU)	% 3A5.040 kd	% 3A5.04 0 titre
4.2	3A5.454		VH_G55H	38.2	5.92E+05	1.81E-04	3.05E-10	11.7	58	41
4.2	3A5.455		VH_G55W	31.2	6.17E+05	6.65E-04	1.08E-09	10	16	33
4.2	3A5.456		VH_S56A	49.7	6.44E+05	1.18E-04	1.84E-10	15.5	89	104
4.2	3A5.457		VH_S56L	51.1	5.49E+05	8.63E-05	1.57E-10	15.6	121	101
4.2	3A5.458		VH_S56Y	47.6	5.44E+05	1.92E-04	3.53E-10	14.2	54	85
4.2	3A5.459		VH_S56D	49	5.05E+05	4.57E-04	9.06E-10	15	23	84
4.2	3A5.460		VH_S56Q	50.2	5.90E+05	9.69E-05	1.64E-10	15.8	108	106
4.2	3A5.461		VH_S56K	52.9	6.11E+05	7.84E-05	1.28E-10	16.6	133	119
4.2	3A5.463		VH_S56W	47.7	4.72E+05	2.85E-04	6.03E-10	13.9	37	98
4.2	3A5.464		VH_T57A	50	7.50E+05	1.26E-04	1.67E-10	16.1	83	104
4.2	3A5.465		VH_T57S	48.5	7.29E+05	1.26E-04	1.73E-10	15.6	83	69
4.2	3A5.467		VH_T57Y	44	7.66E+05	9.50E-05	1.24E-10	13.8	110	49
4.2	3A5.468		VH_T57D	42.5	7.02E+05	9.89E-05	1.41E-10	14	106	46
4.2	3A5.469		VH_T57Q	45.1	7.24E+05	1.07E-04	1.48E-10	14.2	98	58
4.2	3A5.470		VH_T57K	46.5	7.28E+05	1.21E-04	1.66E-10	14.6	86	61
4.2	3A5.471		VH_T57H	43.8	7.34E+05	1.09E-04	1.49E-10	13.9	96	50
4.2	3A5.472		VH_T57W	39.2	7.57E+05	1.34E-04	1.77E-10	13.3	78	40
4.2	3A5.473		VH_Y58A	48.1	1.56E+06	2.86E-03	1.83E-09	13	4	95
4.2	3A5.474		VH_Y58S	50.7	2.76E+06	3.84E-03	1.39E-09	13.7	3	101
4.2	3A5.475		VH_Y58L	48.6	5.58E+06	5.88E-03	1.05E-09	8.3	2	70
4.2	3A5.476		VH_Y58D	42.4	1.89E+07	1.68E-02	8.88E-10	7.3	1	47
4.2	3A5.477		VH_Y58Q	46.6	6.62E+05	1.33E-03	2.02E-09	13.9	8	75
4.2	3A5.478		VH_Y58K	49.2	5.75E+05	1.31E-03	2.28E-09	14.6	8	102
4.2	3A5.479		VH_Y58H	50.6	6.68E+05	5.75E-04	8.62E-10	15.8	18	91
4.2	3A5.480		VH_Y58W	48.1	6.58E+05	5.53E-04	8.41E-10	14.7	19	79
4.2	3A5.481		VH_A93S	45.3	7.18E+05	9.31E-05	1.30E-10	13.9	112	58

Run #	Antibody ID	Replicate Number	Amino acid Substitution	Capture level	ka (1/Ms)	kd (1/s)	K_D (M)	Rmax (RU)	% 3A5.040 kd	% 3A5.04 0 titre
4.2	3A5.482		VH_A93L	13	2.55E+05	2.02E-04	7.90E-10	5.2	52	17
4.2	3A5.484		VH_A93D	0.5					NE	NE
4.2	3A5.485		VH_A93Q	40.4	6.48E+05	1.00E-04	1.54E-10	12.7	105	44
4.2	3A5.486		VH_A93K	17					NE	NE
4.2	3A5.487		VH_A93H	28.8					NE	NE
4.2	3A5.489		VH_A93P	6.5					NE	NE
4.2	3A5.491		VH_S94L	37.4	5.33E+05	8.11E-04	1.52E-09	12.5	13	40
4.2	3A5.492		VH_S94Y	30.3	3.27E+05	1.10E-03	3.37E-09	9.7	10	30
4.2	3A5.493		VH_S94D	4.6					NE	NE
4.2	3A5.494		VH_S94Q	42	6.74E+05	6.37E-04	9.45E-10	13.6	16	49
4.2	3A5.496		VH_S94H	47.1	2.19E+06	4.62E-03	2.11E-09	6.5	2	72
4.2	3A5.501		VH_L95Y	49	4.17E+06	5.88E-03	1.41E-09	12.4	2	96
4.2	3A5.502		VH_L95D	21.2					NB	22
4.2	3A5.506		VH_L95W	46.4	6.20E+06	7.36E-03	1.19E-09	8.4	1	68
4.2	3A5.511		VH_G96Y	45.5					NB	59
4.2	3A5.519		VH_N97S	48	5.61E+05	2.27E-04	4.04E-10	14.9	46	80
4.2	3A5.552		VH_D101K	47.1	6.10E+05	3.63E-04	5.95E-10	14.6	29	67
4.2	3A5.358		VH_G32L	48.4	2.01E+06	3.83E-03	1.91E-09	12.3	3	75
4.2	3A5.381		VH_Y34W	42.4	7.09E+05	2.18E-04	3.07E-10	14	48	47
4.2	3A5.398		VH_S35bA	47	6.82E+05	1.02E-04	1.50E-10	14.7	102	88
4.2	3A5.488		VH_A93W	14.2					NB	17
4.2	3A5.490		VH_S94A	49.6	6.78E+05	8.70E-05	1.28E-10	15.1	120	104
4.2	3A5.499		VH_L95A	43.4	3.09E+06	7.48E-03	2.42E-09	10.4	1	51
4.2	3A5.508		VH_G96A	47.1	5.77E+05	1.25E-04	2.17E-10	14.8	84	75
4.2	3A5.522		VH_N97D	49	1.00E+06	1.92E-04	1.91E-10	15.5	54	91
4.2	3A5.554		VH_D101W	32.7	1.38E+05	6.18E-04	4.47E-09	8.3	17	33

Run #	Antibody ID	Replicate Number	Amino acid Substitution	Capture level	ka (1/Ms)	kd (1/s)	K_D (M)	Rmax (RU)	% 3A5.040 kd	% 3A5.040 titre
4.2	3A5.144		VL_D50A	47.1	5.29E+05	1.67E-04	3.15E-10	14.5	63	77
4.2	3A5.145		VL_D50S	48.2	5.74E+05	1.05E-04	1.83E-10	15.1	100	90
4.2	3A5.146		VL_D50L	48	5.92E+05	2.59E-04	4.38E-10	15	40	86
4.2	3A5.147		VL_D50Y	48	5.36E+05	1.95E-04	3.63E-10	15	54	78
4.2	3A5.148		VL_D50Q	47	5.99E+05	1.93E-04	3.22E-10	15	54	70
4.2	3A5.149		VL_D50K	45.8	6.00E+05	1.61E-04	2.68E-10	13.2	65	74
4.2	3A5.150		VL_D50H	48.2	4.07E+05	1.68E-04	4.14E-10	14.3	62	95
4.2	3A5.151		VL_D50W	48	5.36E+05	2.35E-04	4.38E-10	15	44	74
4.2	3A5.152		VL_D51A	47	6.34E+05	1.34E-04	2.11E-10	14.6	78	88
4.2	3A5.153		VL_D51S	46.1	8.53E+05	1.60E-04	1.87E-10	14.1	65	72
4.2	3A5.154		VL_D51L	47.8	6.22E+05	1.63E-04	2.63E-10	14.3	64	83
4.2	3A5.155		VL_D51Y	48.1	6.14E+05	1.78E-04	2.90E-10	13.7	59	75
4.2	3A5.156		VL_D51Q	47.8	6.48E+05	1.15E-04	1.77E-10	15	91	85
4.2	3A5.157		VL_D51K	45.2	5.85E+05	1.20E-04	2.05E-10	13.2	87	68
4.2	3A5.158		VL_D51H	48.3	6.15E+05	1.82E-04	2.95E-10	14.7	57	86
4.2	3A5.159		VL_D51W	45.7	4.93E+05	1.96E-04	3.98E-10	14.1	53	57
4.2	3A5.160		VL_S52A	47.7	6.61E+05	1.11E-04	1.68E-10	15.2	94	80
4.2	3A5.161		VL_S52L	47.8	6.87E+05	5.74E-05	8.36E-11	15	182	106
4.2	3A5.162		VL_S52Y	49	7.26E+05	9.91E-05	1.36E-10	15.8	105	114
5.1	3A5.040	1	Wild type	49.9	6.56E+05	1.22E-04	1.86E-10	14.5		
5.1	3A5.040	2	Wild type	48.5	6.43E+05	1.12E-04	1.75E-10	14.4		
5.1	3A5.040	3	Wild type	48.1	6.67E+05	1.25E-04	1.87E-10	13.7		
5.1	3A5.040	4	Wild type	50.4	6.63E+05	1.17E-04	1.77E-10	14.4		
5.1	**3A5.040**	**Average**	**Wild type**	**49.2**	**6.57E+05**	**1.19E-04**	**1.81E-10**	**14.3**	**100**	**100**

Run #	Antibody ID	Replicate Number	Amino acid Substitution	Capture level	ka (1/Ms)	kd (1/s)	K_D (M)	Rmax (RU)	% 3A5.040 kd	% 3A5.04 0 titre
5.1	IgG4 Isotype			51.2	N/A	N/A	N/A	0.1	N/A	
5.1	3A5.040 (Purified)		Wild type	48.9	7.07E+05	1.08E-04	1.53E-10	15.6	110	
5.1	3A5.337		VH_I29H	48.1	4.79E+05	1.12E-03	2.34E-09	13.7	11	24
5.1	3A5.339		VH_S30A	50.7	6.79E+05	1.12E-04	1.65E-10	16.3	106	6
5.1	3A5.346		VH_S30W	53.4	6.42E+05	1.32E-04	2.06E-10	16.7	90	69
5.1	3A5.058		VL_G25S	47.6	6.93E+05	1.08E-04	1.56E-10	15.7	110	43
5.1	3A5.090		VL_I28K	49.1	5.73E+05	1.04E-04	1.81E-10	16.2	114	51
5.1	3A5.092		VL_I28W	47	6.13E+05	1.30E-04	2.12E-10	15.5	92	35
5.1	3A5.212		VL_V90S	46.1	5.71E+05	3.11E-04	5.45E-10	14.6	38	4.8
5.1	3A5.251		VL_S94D	52.9	2.77E+05	4.98E-04	1.79E-09	15.5	24	7
5.1	3A5.255		VL_S94W	48.5	5.54E+05	2.86E-04	5.16E-10	14.7	42	19
5.1	3A5.299		VL_V97Q	48.5	5.86E+05	9.90E-05	1.69E-10	15.5	120	71
5.1	3A5.462		VH_S56H	50	6.35E+05	1.16E-04	1.83E-10	15.9	103	41
5.1	3A5.466		VH_T57L	44.9	6.39E+05	1.02E-04	1.59E-10	14.2	117	14
5.1	3A5.483		VH_A93Y	38.2					NB	8
5.1	3A5.503		VH_L95Q	48.5	4.04E+05	6.18E-04	1.53E-09	14.4	19	18
5.1	3A5.163		VL_S52D	49.3	6.65E+05	1.01E-04	1.52E-10	16.4	118	177
5.1	3A5.164		VL_S52Q	49.6	6.57E+05	1.17E-04	1.78E-10	15.8	102	9.8
5.1	3A5.166		VL_S52H	51.6	6.71E+05	1.11E-04	1.66E-10	16.9	107	167
5.1	3A5.167		VL_S52W	52.3	7.19E+05	1.11E-04	1.55E-10	17.2	107	166
5.1	3A5.169		VL_D53S	50.6	6.38E+05	6.35E-05	9.97E-11	16.5	187	151
5.1	3A5.170		VL_D53L	48.8	6.87E+05	9.50E-05	1.38E-10	15.8	125	143
5.1	3A5.171		VL_D53Y	51	6.79E+05	1.09E-04	1.60E-10	16.1	109	208
5.1	3A5.173		VL_D53K	52.6	6.35E+05	1.09E-04	1.71E-10	16.7	109	175
5.1	3A5.175		VL_D53W	50	5.88E+05	9.74E-05	1.66E-10	15.7	122	178

Run #	Antibody ID	Replicate Number	Amino acid Substitution	Capture level	ka (1/Ms)	kd (1/s)	K_D (M)	Rmax (RU)	% 3A5.040 kd	% 3A5.04 0 titre
5.1	3A5.176		VL_R54A	50.4	6.51E+05	9.75E-05	1.50E-10	16.8	122	138
5.1	3A5.177		VL_R54S	50.1	6.45E+05	1.11E-04	1.72E-10	16.8	107	131
5.1	3A5.178		VL_R54L	51.5	6.60E+05	1.01E-04	1.53E-10	17	118	135
5.1	3A5.179		VL_R54Y	49.2	6.66E+05	1.24E-04	1.86E-10	16.4	96	138
5.1	3A5.180		VL_R54D	49.5	6.79E+05	9.89E-05	1.46E-10	16.6	120	128
5.1	3A5.181		VL_R54Q	51.3	6.58E+05	9.55E-05	1.45E-10	17	125	148
5.1	3A5.182		VL_R54K	51.5	6.50E+05	1.17E-04	1.79E-10	17	102	165
5.1	3A5.183		VL_R54H	49.1	6.47E+05	8.44E-05	1.30E-10	16.3	141	137
5.1	3A5.184		VL_R54W	50	6.14E+05	1.22E-04	1.99E-10	15.8	98	7.5
5.1	3A5.185		VL_P55A	51.9	6.87E+05	1.34E-04	1.95E-10	16.5	89	8.9
5.1	3A5.187		VL_P55L	49.6	7.00E+05	9.58E-05	1.37E-10	16.3	124	153
5.1	3A5.188		VL_P55Y	49.2	6.61E+05	1.19E-04	1.80E-10	16.4	100	127
5.1	3A5.189		VL_P55D	51.1	6.48E+05	9.21E-05	1.42E-10	16.7	129	155
5.1	3A5.190		VL_P55Q	48.8	6.55E+05	1.08E-04	1.64E-10	16.4	110	151
5.1	3A5.191		VL_P55K	49.3	6.38E+05	1.05E-04	1.64E-10	16.3	113	137
5.1	3A5.192		VL_P55H	51.5	6.51E+05	1.16E-04	1.78E-10	16.7	103	176
5.1	3A5.193		VL_P55W	51.5	6.41E+05	8.80E-05	1.37E-10	16.8	135	160
5.1	3A5.194		VL_S56A	49.8	6.41E+05	1.06E-04	1.65E-10	16.1	112	143
5.1	3A5.195		VL_S56L	49.6	6.85E+05	1.06E-04	1.54E-10	16.3	112	131
5.1	3A5.196		VL_S56Y	50.2	6.89E+05	1.14E-04	1.66E-10	16.5	104	123
5.1	3A5.197		VL_S56D	50.1	6.87E+05	1.19E-04	1.73E-10	16.5	100	153
5.1	3A5.198		VL_S56Q	49.6	6.86E+05	8.85E-05	1.29E-10	16.4	134	131
5.1	3A5.200		VL_S56H	49.3	6.83E+05	1.15E-04	1.68E-10	16.3	103	138
5.1	3A5.207		VL_Q89K	49.9	6.84E+05	1.27E-04	1.86E-10	16.4	94	136
5.1	3A5.209		VL_Q89W	48.6	5.57E+05	1.27E-04	2.28E-10	15.7	94	72
5.1	3A5.278		VL_H95bY	49.9	7.65E+05	7.90E-05	1.03E-10	16.3	151	139

Run #	Antibody ID	Replicate Number	Amino acid Substitution	Capture level	ka (1/Ms)	kd (1/s)	K_D (M)	Rmax (RU)	% 3A5.040 kd	% 3A5.040 titre
5.1	3A5.279		VL_H95bD	49.6	7.01E+05	7.84E-05	1.12E-10	16.5	152	210
5.1	3A5.280		VL_H95bQ	50.3	7.47E+05	1.51E-04	2.02E-10	16.6	79	133
5.1	3A5.284		VL_V96A	48.2	7.24E+05	1.88E-04	2.60E-10	15.9	63	65
5.1	3A5.286		VL_V96L	48.4	6.50E+05	1.94E-04	2.98E-10	15.9	61	79
5.1	3A5.294		VL_V97A	48.6	6.27E+05	7.68E-05	1.23E-10	16	155	133
5.1	3A5.295		VL_V97S	48.6	6.12E+05	1.07E-04	1.74E-10	15.9	111	110
5.1	3A5.296		VL_V97L	48	6.71E+05	9.60E-05	1.43E-10	15.9	124	95
5.1	3A5.297		VL_V97Y	48.4	6.72E+05	1.07E-04	1.60E-10	16.2	111	90
5.1	3A5.298		VL_V97D	47.7	5.94E+05	1.30E-04	2.18E-10	15.8	92	96
5.1	3A5.300		VL_V97K	50.1	5.88E+05	1.18E-04	2.01E-10	15.8	101	4.7
5.1	3A5.301		VL_V97H	49.4	6.34E+05	8.79E-05	1.39E-10	16.1	135	168
5.1	3A5.063		VL_G25K	49	6.90E+05	7.21E-05	1.05E-10	16.2	165	90
5.1	3A5.067		VL_N26S	49	6.52E+05	1.10E-04	1.69E-10	16	108	162
5.1	3A5.083		VL_N27W	49.6	6.03E+05	1.29E-04	2.14E-10	16.4	92	148
5.1	3A5.091		VL_I28H	47.7	5.71E+05	1.30E-04	2.27E-10	15.7	92	75
5.1	3A5.098		VL_G29Q	49.7	6.53E+05	1.05E-04	1.61E-10	16.2	113	139
5.1	3A5.108		VL_S30H	49.4	6.95E+05	1.02E-04	1.46E-10	16.2	117	145
5.1	3A5.109		VL_S30W	48	6.77E+05	1.35E-04	2.00E-10	15.5	88	112
5.1	3A5.119		VL_N32S	48.6	8.35E+05	1.08E-04	1.29E-10	16.3	110	98
5.1	3A5.120		VL_N32L	49.2	8.72E+05	1.03E-04	1.18E-10	16.4	116	119
5.1	3A5.129		VL_V33L	48.8	5.80E+05	1.42E-04	2.45E-10	15.8	84	99
5.1	3A5.277		VL_H95bL	50.4	6.79E+05	1.40E-04	2.06E-10	16.6	85	180
5.1	3A5.302		VL_V97W	47.7	7.18E+05	7.59E-05	1.06E-10	15.9	157	73
5.1	3A5.303		VL_V97P	48.7	6.99E+05	1.21E-04	1.73E-10	16.2	98	21

This table contains a summary of the calculated kinetic and titre data for each antibody supernatant tested. Variant antibodies with a lower kd (slower off-rate) than parent 3A5.040 antibody have a "% 3A5.040 kd" value >100% and those with a higher kd (faster off-rate) a value <100%.

Variant antibodies with a higher titre than parent 3A5.040 antibody have a "% 3A5.040 titre" value >100% and those with a lower titre, a value <100%. N/A, non-applicable. NB, No binding. NE, No expression.

Table 4. Determination of purified 3A5.040 variant antibody IL-5 binding kinetics by Biacore

Run #	Antibody ID	Replicates	Amino acid Substitution	Capture level	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	% 3A5.040 kd
6	3A5.040 (batch 6)	1	Wild type	48.6	1.44E+06	2.32E-04	1.61E-10	16	
6	3A5.040 (batch 6)	2	Wild type	49.4	1.44E+06	2.14E-04	1.48E-10	15.7	
6	3A5.040 (batch 6)	3	Wild type	49.2	1.36E+06	2.61E-04	1.93E-10	16	
6	3A5.040 (batch 6)	4	Wild type	49.2	1.36E+06	2.46E-04	1.80E-10	16	
6	3A5.040 (batch 6)	5	Wild type	49.3	1.47E+06	2.52E-04	1.71E-10	16.1	
6	3A5.040 (batch 6)	6	Wild type	49.2	1.45E+06	2.13E-04	1.47E-10	16	
6	3A5.040 (batch 6)	7	Wild type	49.2	1.41E+06	2.29E-04	1.63E-10	16.1	
6	3A5.040 (batch 6)	8	Wild type	50.9	1.40E+06	2.45E-04	1.75E-10	16.8	
6	**3A5.040 (batch 6)**	**Average**	**Wild type**	**49.3**	**1.42E+06**	**2.37E-04**	**1.67E-10**	**16.1**	**100**
6	IgG4 iso	1		48.8	N/A	N/A	N/A	0	
6	IgG4 iso	2		48.9	N/A	N/A	N/A	0	
6	IgG4 iso	3		48.8	N/A	N/A	N/A	0	
6	**IgG4 Isotype**	**Average**		49.8	N/A	N/A	N/A	**0**	N/A
6	3A5.040 (Purified)	1	Wild type	49.6	1.43E+06	2.39E-04	1.68E-10	16.1	
6	3A5.040 (Purified)	2	Wild type	49.8	1.48E+06	2.85E-04	1.93E-10	16.2	
6	3A5.040 (Purified)	3	Wild type	49.7	1.45E+06	2.32E-04	1.60E-10	16.1	
6	**3A5.040 (Purified)**	**Average**	Wild type	**49.7**	**1.45E+06**	**2.52E-04**	**1.74E-10**	**16.1**	**94**
6	3A5.237	1	VL_D92W	47.9	1.57E+06	2.67E-04	1.70E-10	15.5	
6	3A5.237	2	VL_D92W	48.7	1.55E+06	2.58E-04	1.66E-10	15.6	

Run #	Antibody ID	Replicates	Amino acid Substitution	Capture level	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	% 3A5.040 kd
6	3A5.237	3	VL_D92W	48.5	1.52E+06	2.12E-04	1.40E-10	15.7	
6	**3A5.237**	**Average**	**VL_D92W**	**48.3**	**1.55E+06**	**2.46E-04**	**1.59E-10**	**15.6**	**96**
6	3A5.161	1	VL_S52L	49.4	1.47E+06	2.62E-04	1.78E-10	16.2	
6	3A5.161	2	VL_S52L	49.9	1.43E+06	2.41E-04	1.69E-10	16.2	
6	3A5.161	3	VL_S52L	49.9	1.40E+06	2.19E-04	1.57E-10	16.4	
6	**3A5.161**	**Average**	**VL_S52L**	**49.7**	**1.43E+06**	**2.41E-04**	**1.68E-10**	**16.2**	**99**
6	3A5.169	1	VL_D53S	48.9	1.23E+06	2.43E-04	1.98E-10	15.6	
6	3A5.169	2	VL_D53S	49.5	1.26E+06	2.44E-04	1.93E-10	15.9	
6	3A5.169	3	VL_D53S	49.7	1.23E+06	2.46E-04	1.99E-10	16.1	
6	**3A5.169**	**Average**	**VL_D53S**	**49.3**	**1.24E+06**	**2.44E-04**	**1.97E-10**	**15.8**	**97**
6	3A5.183	1	VL_R54H	47.9	1.44E+06	2.32E-04	1.61E-10	15.6	
6	3A5.183	2	VL_R54H	48.2	1.44E+06	2.50E-04	1.74E-10	15.8	
6	3A5.183	3	VL_R54H	48.4	1.39E+06	2.04E-04	1.47E-10	15.8	
6	**3A5.183**	**Average**	**VL_R54H**	**48.1**	**1.42E+06**	**2.29E-04**	**1.61E-10**	**15.7**	**104**
6	3A5.193	1	VL_P55W	48.5	1.32E+06	2.32E-04	1.76E-10	15.7	
6	3A5.193	2	VL_P55W	48.3	1.34E+06	2.51E-04	1.88E-10	15.3	
6	3A5.193	3	VL_P55W	48.7	1.29E+06	2.57E-04	1.99E-10	15.6	
6	**3A5.193**	**Average**	**VL_P55W**	**48.5**	**1.32E+06**	**2.47E-04**	**1.88E-10**	**15.5**	**96**
6	3A5.198	1	VL_S56Q	49.1	1.42E+06	2.43E-04	1.71E-10	16	
6	3A5.198	2	VL_S56Q	49	1.49E+06	2.90E-04	1.95E-10	15.7	
6	3A5.198	3	VL_S56Q	49.3	1.42E+06	2.38E-04	1.68E-10	15.9	
6	**3A5.198**	**Average**	**VL_S56Q**	**49.1**	**1.44E+06**	**2.57E-04**	**1.78E-10**	**15.8**	**92**
6	3A5.278	1	VL_H95bY	48.3	1.55E+06	2.53E-04	1.63E-10	15.9	
6	3A5.278	2	VL_H95bY	48.2	1.62E+06	2.43E-04	1.49E-10	15.7	
6	3A5.278	3	VL_H95bY	48.5	1.57E+06	2.14E-04	1.36E-10	15.8	
6	**3A5.278**	**Average**	**VL_H95bY**	**48.3**	**1.58E+06**	**2.37E-04**	**1.49E-10**	**15.8**	**100**

Run #	Antibody ID	Replicates	Amino acid Substitution	Capture level	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	% 3A5.040 kd
6	3A5.279	1	VL_H95bD	50	1.58E+06	2.50E-04	1.58E-10	16.3	
6	3A5.279	2	VL_H95bD	49.7	1.61E+06	2.42E-04	1.50E-10	16.1	
6	3A5.279	3	VL_H95bD	50	1.61E+06	2.43E-04	1.51E-10	16.4	
6	**3A5.279**	**Average**	**VL_H95bD**	**49.9**	**1.60E+06**	**2.45E-04**	**1.53E-10**	**16.2**	**97**
6	3A5.294	1	VL_V97A	49.1	1.31E+06	2.54E-04	1.94E-10	15.9	
6	3A5.294	2	VL_V97A	48.6	1.31E+06	2.13E-04	1.62E-10	15.7	
6	3A5.294	3	VL_V97A	48.6	1.37E+06	2.15E-04	1.57E-10	15.6	
6	**3A5.294**	**Average**	**VL_V97A**	**48.7**	**1.33E+06**	**2.27E-04**	**1.71E-10**	**15.7**	**104**
6	3A5.301	1	VL_V97H	48.4	1.51E+06	2.76E-04	1.83E-10	15.8	
6	3A5.301	2	VL_V97H	48.1	1.58E+06	1.06E-04	6.71E-11	15.6	
6	3A5.301	3	VL_V97H	47.8	1.60E+06	2.45E-04	1.53E-10	15.4	
6	**3A5.301**	**Average**	**VL_V97H**	**48.1**	**1.56E+06**	**2.09E-04**	**1.34E-10**	**15.6**	**114**
6	3A5.063	1	VL_G25K	48	1.37E+06	2.61E-04	1.90E-10	15.7	
6	3A5.063	2	VL_G25K	48.1	1.36E+06	2.70E-04	1.99E-10	15.5	
6	3A5.063	3	VL_G25K	47.8	1.42E+06	2.50E-04	1.76E-10	15.3	
6	**3A5.063**	**Average**	**VL_G25K**	**47.9**	**1.38E+06**	**2.60E-04**	**1.88E-10**	**15.5**	**91**
6	3A5.302	1	VL_V97W	48.9	1.65E+06	2.35E-04	1.42E-10	16	
6	3A5.302	2	VL_V97W	48.9	1.69E+06	2.35E-04	1.39E-10	15.8	
6	3A5.302	3	VL_V97W	48.5	1.66E+06	2.40E-04	1.45E-10	15.7	
6	**3A5.302**	**Average**	**VL_V97W**	**48.7**	**1.67E+06**	**2.37E-04**	**1.42E-10**	**15.8**	**100**
6	3A5.202	1	VL_Q89A	48.9	1.09E+06	2.49E-04	2.29E-10	15.8	
6	3A5.202	2	VL_Q89A	48.7	1.07E+06	1.89E-04	1.77E-10	15.6	
6	3A5.202	3	VL_Q89A	48.8	1.09E+06	2.44E-04	2.25E-10	15.7	
6	**3A5.202**	**Average**	**VL_Q89A**	**48.8**	**1.08E+06**	**2.27E-04**	**2.10E-10**	**15.7**	**104**
6	3A5.203	1	VL_Q89S	49	1.28E+06	2.82E-04	2.20E-10	15.9	
6	3A5.203	2	VL_Q89S	48.6	1.28E+06	2.26E-04	1.76E-10	15.6	

Run #	Antibody ID	Replicates	Amino acid Substitution	Capture level	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	% 3A5.040 kd
6	3A5.203	3	VL_Q89S	48.9	1.27E+06	2.36E-04	1.86E-10	15.7	
6	**3A5.203**	**Average**	**VL_Q89S**	**48.8**	**1.28E+06**	**2.48E-04**	**1.94E-10**	**15.7**	**96**
6	3A5.204	1	VL_Q89L	49.9	5.01E+05	2.20E-04	4.38E-10	14.4	
6	3A5.204	2	VL_Q89L	49.9	5.02E+05	1.88E-04	3.74E-10	14.2	
6	3A5.204	3	VL_Q89L	49.9	4.95E+05	2.11E-04	4.26E-10	14.3	
6	**3A5.204**	**Average**	**VL_Q89L**	**49.9**	**4.99E+05**	**2.06E-04**	**4.13E-10**	**14.3**	**115**
6	3A5.205	1	VL_Q89Y	48.4	9.87E+05	2.42E-04	2.45E-10	15.5	
6	3A5.205	2	VL_Q89Y	48.6	1.04E+06	2.37E-04	2.28E-10	15.6	
6	3A5.205	3	VL_Q89Y	48.5	1.05E+06	2.60E-04	2.47E-10	15.6	
6	**3A5.205**	**Average**	**VL_Q89Y**	**48.5**	**1.03E+06**	**2.46E-04**	**2.40E-10**	**15.5**	**96**
6	3A5.208	1	VL_Q89H	51	9.41E+05	2.53E-04	2.68E-10	16	
6	3A5.208	2	VL_Q89H	51.1	9.45E+05	2.52E-04	2.66E-10	16.1	
6	3A5.208	3	VL_Q89H	51	9.54E+05	2.88E-04	3.02E-10	16	
6	**3A5.208**	**Average**	**VL_Q89H**	**51**	**9.47E+05**	**2.64E-04**	**2.79E-10**	**16**	**90**
6	3A5.550	1	VH_D101Y	48.3	1.16E+06	4.40E-04	3.81E-10	15.5	
6	3A5.550	2	VH_D101Y	48.5	1.17E+06	4.54E-04	3.87E-10	15.7	
6	3A5.550	3	VH_D101Y	48.3	1.19E+06	4.86E-04	4.10E-10	15.5	
6	**3A5.550**	**Average**	**VH_D101Y**	**48.3**	**1.17E+06**	**4.60E-04**	**3.93E-10**	**15.5**	**51**
6	3A5.512	1	VH_G96D	50.4	1.70E+07	8.63E-03	5.07E-10	13.7	
6	3A5.512	2	VH_G96D	50.7	1.88E+07	9.87E-03	5.26E-10	13.8	
6	3A5.512	3	VH_G96D	50.5	1.28E+06	1.52E-03	1.19E-09	12.5	
6	**3A5.512**	**Average**	**VH_G96D**	**50.5**	**1.24E+07**	**6.67E-03**	**7.41E-10**	**13.3**	**3.5**
6	3A5.124	1	VL_N32K	50.9	9.94E+05	2.46E-04	2.47E-10	16.3	
6	3A5.124	2	VL_N32K	51.2	1.05E+06	2.62E-04	2.49E-10	16.5	
6	3A5.124	3	VL_N32K	50.7	1.02E+06	2.28E-04	2.24E-10	16.3	
6	**3A5.124**	**Average**	**VL_N32K**	**50.9**	**1.02E+06**	**2.45E-04**	**2.40E-10**	**16.3**	**97**

Run #	Antibody ID	Replicates	Amino acid Substitution	Capture level	ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	% 3A5.040 kd
7	3A5.040 (batch 7)	1	Wild type	51.2	1.37E+06	2.30E-04	1.68E-10	16.4	
7	3A5.040 (batch 7)	2	Wild type	51.6	1.43E+06	2.15E-04	1.50E-10	16.6	
7	3A5.040 (batch 7)	3	Wild type	51.6	1.42E+06	2.84E-04	2.00E-10	16.6	
7	**3A5.040 (batch 7)**	**Average**	**Wild type**	**51.4**	**1.41E+06**	**2.43E-04**	**1.73E-10**	**16.5**	**100**
7	IgG4 Isotype	1		48.8	N/A	N/A	N/A	0	
7	IgG4 Isotype	2		48.9	N/A	N/A	N/A	0	
7	IgG4 Isotype	3		48.8	N/A	N/A	N/A	0	
7	**IgG4 Isotype**	**Average**		49.8	N/A	N/A	N/A	**0**	N/A
7	3A5.040 (Purified)	1	Wild type	49.6	1.43E+06	2.39E-04	1.68E-10	16.1	
7	3A5.040 (Purified)	2	Wild type	49.8	1.48E+06	2.85E-04	1.93E-10	16.2	
7	3A5.040 (Purified)	3	Wild type	49.7	1.45E+06	2.32E-04	1.60E-10	16.1	
7	**3A5.040 (Purified)**	**Average**	Wild type	**49.7**	**1.45E+06**	**2.52E-04**	**1.74E-10**	**16.1**	**94**
7	3A5.068	1	VL_N26L	52.3	1.29E+06	2.68E-04	2.07E-10	16.8	
7	3A5.068	2	VL_N26L	53	1.39E+06	2.08E-04	1.50E-10	17.1	
7	3A5.068	3	VL_N26L	53.1	1.43E+06	2.69E-04	1.88E-10	17.2	
7	**3A5.068**	**Average**	**VL_N26L**	**52.8**	**1.37E+06**	**2.48E-04**	**1.82E-10**	**17**	**98**
7	3A5.079	1	VL_N27D	49.3	1.22E+06	2.29E-04	1.88E-10	16.1	
7	3A5.079	2	VL_N27D	50	1.29E+06	2.39E-04	1.85E-10	16.4	
7	3A5.079	3	VL_N27D	49.9	1.25E+06	2.63E-04	2.09E-10	16.2	
7	**3A5.079**	**Average**	**VL_N27D**	**49.7**	**1.25E+06**	**2.44E-04**	**1.94E-10**	**16.2**	**100**

This table contains a summary of the calculated kinetic data for each purified antibody tested. Variant antibodies with a lower kd (slower off-rate) than parent 3A5.040 antibody have a "% 3A5.040 kd" value >100% and those with a higher kd (faster off-rate) a value <100%. Runs 6 and 7 were transfected separately but run in the same biacore batch, and therefore use the same isotype and 3A5.040 (purified) controls. N/A: non-applicable.

Table 5. Purified protein expression yield for selected 3A5.040 antibody variants

Run #	Antibody ID	Amino acid Substitution	% parent 3A5.040 purified yield
6	3A5.040	Parental sequence	100
6	3A5.237	VL_D92W	89
6	3A5.161	VL_S52L	160
6	3A5.169	VL_D53S	173
6	3A5.183	VL_R54H	172
6	3A5.193	VL_P55W	187
6	3A5.198	VL_S56Q	205
6	3A5.278	VL_H95bY	210
6	3A5.279	VL_H95bD	143
6	3A5.294	VL_V97A	140
6	3A5.301	VL_V97H	151
6	3A5.063	VL_G25K	110
6	3A5.302	VL_V97W	156
6	3A5.202	VL_Q89A	64
6	3A5.203	VL_Q89S	129
6	3A5.204	VL_Q89L	61
6	3A5.205	VL_Q89Y	41
6	3A5.208	VL_Q89H	54
6	3A5.550	VH_D101Y	88
6	3A5.512	VH_G96D	72
6	3A5.124	VL_N32K	128
7	3A5.040	Parental Sequence	100
7	3A5.068	VL_N26L	96
7	3A5.079	VL_N27D	99

Table 6. VH CDR1 Scanning Matrix

	VH CDR1																							
	26		27		28		29		30		31		32		33		34		35		35A		35B	
sc	**G**		**G**		**S**		**I**		**S**		**N**		**G**		**G**		**Y**		**Y**		**W**		**S**	
A	0.5	1.3	1	0.8	0.6	0.9	0.3	0.6	0.1	1.1	1.2	0.1	1.8	0.3	1.2	1.3	1.6	0.7	2.9	0	0.4	0.1	0.9	1
S	0.6	0.9	1	1			0.3	0.5			1.1	0.2	1.5	0.1	1.2	0	1.6	0.7	1.3	0	0.2	0.1		
L	0.2	1.1	1.2	0.8	0.7	1.1	0.8	0.9	1.5	0.7	0.7	0.2	0.8	0	0.8	0.4	1.6	0.6	1.9	0.1	1	0.1	0.4	0.3
Y	0.6	1.1	0.8	0.1	0.5	1.2	0.2	0.1	1	0.7	0.6	0.1	0.9	0	1.1	0					1	0.5	0.9	0
D	0.6	1.2	0.7	0.9	0.7	1.1	0.2	0	1	0.8	0.8	0.5	1.1	0	2.8	0	1	0.2	0.9	0	NE	NE	0.2	0.9
Q	0.9	1.1	0.8	0.7	0.8	1	0.4	0.3	1.2	1.1	1.6	0.2	1.3	0.1	2.8	0.1	1.7	0.6	1.3	0	0.3	0.1	0.5	0.2
K	1	1	1	0.5	0.8	0.9	0.3	0.1	1.6	0.8	1.7	0.1	1.7	0	3.5	0	4.1	0.2	3.8	NB	0.3	0.1	0.1	0
H	0.9	0.9	0.7	0.4	0.7	0.8	0.2	0.1	0.8	0.8	1.4	0.8	1.1	0	2.7	0	2.2	0.1	2	0	0.5	0.4	0.8	0
W	1.1	0.8	1	0.2	0.4	0.7	0.4	0	0.7	0.9	0.6	0.2	0.7	0	1.7	0.1	0.5	0.5	2.3	0			0.5	0
P																								

Summary of difference in 3A5.040 variant antibody titre and kd for variants of VH CDR1 (AbM definition). Kabat amino acid numbering and parent 3A5.040 amino acids are given in the top row. Mutated residue identities are listed in the left column. The leftmost value in each cell is the proportional titre of each variant vs parent 3A5.040 (>1 = higher titre, <1 = lower titre), while the right value is the proportional kd (>1 = lower kd, <1 = higher kd) of each variant vs parent 3A5.040. Variants not made are marked in grey. NB, no binding. NE, no expression. (VH CDR1 sequence disclosed as residues 26-37 of SEQ ID NO: 73).

Table 7. VH CDR2 Scanning Matrix

	VH CDR2															
	50		51		52		53		54		55		56		57		58	
sc	Y		I		Y		Y		S		G		S		T		Y	
A	2.7	0.2	2.4	0.8	3	0	2.5	0.2	1.1	0.6	0.7	0.9	1	0.9	1	0.8	1	0
S	3.3	0.2	1.3	0.8	3.3	0.1	2.3	0.6			0.7	0.7			0.7	0.8	1	0
L	1.2	0.3	0.9	0.7	2.1	0	1	0.2	1.6	0	0.7	0.1	1	1.2	0.1	1.2	0.7	0
Y			1.1	0					0.9	0	0.5	0.1	0.9	0.5	0.5	1.1		
D	1.7	0.1	0.5	0.1	3.3	NB	1.8	0.2	2	0	0.4	0.4	0.8	0.2	0.5	1.1	0.5	0
Q	2.4	0.2	1	0.2	2.6	0	2.1	0.2	1.5	0.1	0.4	0.5	1.1	1.1	0.6	1	0.8	0.1
K	1.4	0.2	1.2	0.1	3.5	NB	2.3	0.1	2	0	0.5	0.5	1.2	1.3	0.6	0.9	1	0.1
H	3	0.1	0.9	0	2.9	0.3	2.1	0.5	1	0.2	0.4	0.6	0.4	1	0.5	1	0.9	0.2
W	1.3	0.1	1.4	0	1	0.1	1.5	0.4	1.1	0.1	0.3	0.2	1	0.4	0.4	0.8	0.8	0.2
P																		

Summary of difference in 3A5.040 variant antibody titre and kd for variants of VH CDR2 (AbM definition). Kabat amino acid numbering and parent 3A5.040 amino acids are given in the top row. Mutated residue identities are listed in the left column. The leftmost value in each cell is the proportional titre of each variant vs parent 3A5.040 (>1 = higher titre, <1 = lower titre), while the right value is the proportional kd (>1 = lower kd, <1 = higher kd) of each variant vs parent 3A5.040. Variants not made are marked in grey. NB, no binding. NE, no expression. (VH CDR2 sequence disclosed as residues 52-60 of SEQ ID NO: 73).

Table 8. VH CDR3 Scanning Matrix

	VH CDR3																	
	93		94		95		96		97		98		99		101		102	
sc	**A**		**S**		**L**		**G**		**N**		**W**		**F**		**D**		**Y**	
A			1	1.2	0.5	0	0.8	0.8	1	0.6	1.1	0.5	0.4	0.2	0.7	0.7	1.1	1.2
S	0.6	1.1			NE	NE	0.9	0.5	0.8	0.5	0.8	0.4	0.4	0.1	0.8	0.9	1.4	0.9
L	0.2	0.5	0.4	0.1			0.6	0	1	0.9	0.4	0.6	0.6	0.9	0.4	0.2	0.5	0.9
Y	0.1	NB	0.3	0.1	1	0	0.6	NB	0.8	0.3	1.4	0.9	0.4	1.1	0.9	0.5		
D	NE	NE	NE	NE	0.2	NB	0.7	0	0.9	0.5	0.4	1.1	0.3	0			0.5	0.7
Q	0.4	1	0.5	0.2	0.2	0.2	0.6	0.2	1.3	1	0.5	0.6	0.4	0.1	0.8	0.5	0.9	1
K	0.2	NB	1.3	0.3	0.7	0	1.5	0	1.7	0.7	0.7	0.1	0.4	NB	0.7	0.3	0.9	1.3
H	0.3	NB	0.7	0	0.9	0.1	1.2	0.1	1.1	0.5	0.8	0.7	0.4	1	0.7	0.6	1.3	1
W	0.2	NB	0.4	0.0	0.7	0	0.6	0	0.6	0.2			0.3	0.2	0.3	0.2	1.2	0.9
P	0.1	NB	0.2	0.8	0.4	NB	0.2	0.2	0.7	0.2	0.3	0.1	0.4	NB	0.4	0.1	0.3	0.8

Summary of difference in 3A5.040 variant antibody titre and kd for variants of VH CDR3 (AbM definition) and Kabat amino acid positions 93 and 94. Kabat amino acid numbering and parent 3A5.040 amino acids are given in the top row. Mutated residue identities are listed in the left column. The leftmost value in each cell is the proportional titre of each variant vs parent 3A5.040 (>1 = higher titre, <1 = lower titre), while the right value is the proportional kd (>1 = lower kd, <1 = higher kd) of each variant vs parent 3A5.040. Variants not made are marked in grey. NB, no binding. NE, no expression. (VH CDR3 sequence disclosed as residues 98-106 of SEQ ID NO: 73).

Table 9. VL CDR1 Scanning Matrix

	VL CDR1																			
	24		25		26		27		28		29		30		31		32		33		34	
sc	G		G		N		N		I		G		S		K		N		V		Y	
A	1	1.3	1.1	1.3	0.8	1.3	1.2	1.2	0.9	1.9	0.6	1.1	0.8	1.1	1.2	0.6	0.7	0.2	0.7	1.5	1.7	0.3
S	1	1.1	0.4	1.1	1.6	1.1	0.9	1.1	0.5	1	0.9	1.2			1.1	0.8	1	1.1	1.3	1.2	0.3	1.2
L	1	1.4	0.8	1.1	1	1	1	1.3	0.6	1.1	0.8	1.3	1.3	1.2	1.3	0.3	1.2	1.2	1	0.8	0.6	0.5
Y	0.9	1	1	1.4	1	1.3	1	1.1	0.9	1.4	0.6	0.9	0.9	1.1	1	1.3	0.9	1.2	0.7	1.3		
D	1	1.2	0.9	1	1	1.5	1	1	0.4	1.2	0.9	1.6	1.2	1.3	1.1	0.2	1.2	0.9	0.4	1.2	0.7	0.2
Q	1	1.2	0.9	1.3	1	1.1	0.9	1.1	0.5	1.1	1.4	1.1	0.8	1.3	0.9	0.3	1	0.9	0.5	0.8	0.6	0.2
K	1	1.2	0.9	1.7	1	1	1	1.3	0.5	1.1	0.7	1.3	1	1.6			1.3	1	0.1	1	0.6	0.3
H	1	1.3	1.1	1.3	1	1	0.9	1.5	0.8	0.9	1	1.4	1.5	1.2	1	0.5	0.9	1.5	0.5	NB	0.8	0.2
W	1.1	1.4	0.8	1.3	0.9	1.2	1.5	0.9	0.4	0.9	1.1	1.2	1.1	0.9	1.3	0.9	0.8	1.3	0.2	1.1	0.6	0.1
P																						

Summary of difference in 3A5.040 variant antibody titre and kd for variants of VL CDR1 (AbM definition). Kabat amino acid numbering and parent 3A5.040 amino acids are given in the top row. Mutated residue identities are listed in the left column. The leftmost value in each cell is the proportional titre of each variant vs parent 3A5.040 (>1 = higher titre, <1 = lower titre), while the right value is the proportional kd (>1 = lower kd, <1 = higher kd) of each variant vs parent 3A5.040. Variants not made are marked in grey. NB, no binding. NE, no expression. (VL CDR1 sequence disclosed as residues 23-33 of SEQ ID NO: 74).

Table 10. VL CDR2 Scanning Matrix

	VL CDR2													
	50		51		52		53		54		55		56	
sc	**D**		**D**		**S**		**D**		**R**		**P**		**S**	
A	0.8	0.6	0.9	0.8	0.8	0.9	0.5	0.1	1.4	1.2	0.1	0.9	1.4	1.1
S	0.9	1	0.7	0.7			1.5	1.9	1.3	1.1	1.1	1		
L	0.9	0.4	0.8	0.6	1.1	1.8	1.4	1.3	1.4	1.2	1.5	1.2	1.3	1.1
Y	0.8	0.5	0.8	0.6	1.1	1.1	2.1	1.1	1.4	1.0	1.3	1	1.2	1
D					1.8	1.2			1.3	1.2	1.6	1.3	1.5	1
Q	0.7	0.5	0.9	0.9	0.1	1	1	1	1.5	1.2	1.5	1.1	1.3	1.3
K	0.7	0.6	0.7	0.9	1.7	0.1	1.8	1.1	1.7	1.0	1.4	1.1	1	0.9
H	1	0.6	0.9	0.6	1.7	1.1	1.2	0.9	1.4	1.4	1.8	1	1.4	1
W	0.7	0.4	0.6	0.5	1.7	1.1	1.8	1.2	0.1	1.0	1.6	1.4	0.9	0.9
P														

Summary of difference in 3A5.040 variant antibody titre and kd for variants of VL CDR2 (AbM definition). Kabat amino acid numbering and parent 3A5.040 amino acids are given in the top row. Mutated residue identities are listed in the left column. The leftmost value in each cell is the proportional titre of each variant vs parent 3A5.040 (>1 = higher titre, <1 = lower titre), while the right value is the proportional kd (>1 = lower kd, <1 = higher kd) of each variant vs parent 3A5.040. Variants not made are marked in grey. NB, no binding. NE, no expression. (VL CDR2 sequence disclosed as residues 49-55 of SEQ ID NO: 74).

Table 11. VL CDR3 Scanning Matrix

	VL CDR3																					
	89		90		91		92		93		94		95		95A		95B		96		97	
sc	**Q**		**V**		**W**		**D**		**S**		**S**		**S**		**D**		**H**		**V**		**V**	
A	0.6	1	0.8	1	0.8	0	1.1	1.2	1.1	0	1	1	1	1	1.1	0	0.2	0.7	0.7	0.6	1.3	1.5
S	1.3	1	0	0.4	1	0	1.1	1.2							1	0.1	0.6	1.6	0.2	0.5	1.1	1.1
L	0.6	1.2	0.6	0.8	1	0	1.3	1.5	1.2	0	0.9	0.2	1	1	0.7	0	1.8	0.9	0.8	0.6	1	1.2
Y	0.4	1	0.9	0.4	0.6	0.1	0.7	1.1	1.2	0	1.5	0.3	0.8	1.1	1	0	1.4	1.5	0.6	0.1	0.9	1.1
D	0.1	1.2	0.3	0.3	0.7	0			0.7	0	0.1	0.2	1.1	0.9			2.1	1.5	0.1	0.1	1	0.9
Q			0.8	0.6	0.8	0	1.9	0.8	1.1	0	1.4	0.6	0.6	1.3	1.1	0	1.3	0.8	0.3	0.2	0.7	1.2
K	1.4	0.9	0.5	1.4	0.7	NB	0.9	1.3	1.6	NB	1.1	0.8	1.2	1.2	0.7	0	0.6	1.2	0.2	0	0	1
H	0.5	0.9	0.6	0.4	0.6	0	1.2	1.1	1.3	0	1	0.8	1	1.2	1.9	0			0.5	NB	1.7	1.4
W	0.7	0.9	0.8	0.2			NE	NE	1.2	0	0.2	0.4	0.9	0.9	0.9	0	1.5	1	0.2	0	0.7	1.6
P	0.7	0.2	0.8	0	0.4	0	0.6	0.8	1.1	0	1.4	0.9	1.5	0	1.5	0	1.5	0	1.1	0.2	0.2	1

Summary of difference in 3A5.040 variant antibody titre and kd for variants of VL CDR3 (AbM definition). Kabat amino acid numbering and parent 3A5.040 amino acids are given in the top row. Mutated residue identities are listed in the left column. The leftmost value in each cell is the proportional titre of each variant vs parent 3A5.040 (>1 = higher titre, <1 = lower titre), while the right value is the proportional kd (>1 = lower kd, <1 = higher kd) of each variant vs parent 3A5.040. Variants not made are marked in grey. NB, no binding. NE, no expression. (VL CDR3 sequence disclosed as residues 88-98 of SEQ ID NO: 74).

Expression vector construction

[0105] Nucleotide sequence can influence gene expression and subsequent protein expression level. Several different nucleotide sequences were examined for optimal expression of 3A5.046. These sequences are summarized in the following table:

Table 12. Nucleotide sequence

Gene Name	SEQ ID Nos:
3A5.046 VH	SEQ ID NO: 69
3A5.046 VL	SEQ ID NO: 71
3A5.046 HC constant region	SEQ ID NO: 70
3A5.046 LC constant region	SEQ ID NO: 72

Measurement of the affinity of antibody 3A5.046 for human recombinant IL-5 by SPR

[0106] The affinity of antibody 3A5.046 for recombinant human IL-5 was determined using a Biacore T200 system (GE Healthcare). Briefly, a commercial mouse anti-human IgG antibody (Thermo Scientific) was coupled to two adjacent (control and test) flowcells on a Biacore CM5 chip (GE Healthcare) according to the manufacturer's recommendations. The 3A5.046 antibody was captured at a low density (approximately 125 RU) on the test flowcell surface and dilutions of recombinant human IL-5 or a buffer blank were injected over both test and control flowcells, at 30 μL/min (FIG. 6, Table 13).

[0107] The resulting sensorgrams were double-referenced (test flowcell values subtracted from control (anti-human IgG-coupled surface with no coated antibody) flowcell values and also a buffer blank). Subtracted sensorgrams from injections of human IL-5 at 2.5, 1.25, 0.625, 0.313, and 0.156 μg/mL were fitted to a 1:1 Langmuir binding model using Biacore Evaluation software to determine binding constants from duplicate assays (Table 13).

Table 13. Kinetic constants from a multi-concentration Biacore kinetic analysis of 3A5.046 antibody binding to recombinant human IL-5 at 2.5, 1.25, 0.625, 0.313 and 0.156 μg/mL

Antibody	Experiment	ka (1/Ms)	kd (1/s)	KD (pM)	Chi^2 (RU^2)
3A5.046	Repeat 1	8.16E+05	1.58E-05	19.4	0.0269
	Repeat 2	8.49E+05	1.84E-05	21.7	0.0296

[0108] These results demonstrate that antibody 3A5.046 has a high affinity for recombinant human IL-5.

Potency of 3A5.046 compared to mepolizumab in the TF-1.6G4 cell line proliferation assay

[0109] 3A5.046 and mepolizumab were run in the TF-1.6G4 cell line proliferation assay. 3A5.046 and mepolizumab inhibited human IL-5 proliferation with a mean IC_{50} of 13.8 pM and 534 pM respectively (See Table 14 and FIG. 7A). Both antibodies demonstrated inhibition of cynomolgus monkey IL-5 on the TF1.6G4 cell line (FIG 7B), with a mean IC_{50} for 3A5.046 of 43.8 pM and for mepolizumab of 584 pM.

Table 14.

Antibody	Agonist	Number of Observations	Mean (pM)	Std. Dev.
Mepolizumab	Cynomolgus IL-5	4	584.0982	129.9019
	Human IL-5	4	534.2803	150.2546
3A5.046	Cynomolgus IL-5	8	43.80916	12.62095
	Human IL-5	8	13.83667	4.219783

Detection of native IL5 from primary cells via ELISA using anti-IL-5 antibodies of the invention

[0110] Antibody 3A5 was used as a capture reagent in a sandwich ELISA. Paired with a commercially available detection antibody (TRFk5R; R&D systems, #MAB405) quantification of recombinant IL-5 levels in spiked buffer samples could be determined (FIG. 8). This method was then applied to the detection of native IL-5 secreted by primary cells. CD4+ T-cells from four donors were stimulated to secrete IL-5. The IL-5 levels were then determined using the sandwich ELISA with antibody 3A5 as the capture reagent. Three out of four donor T-cells responded to T-cell stimulation and had detectable IL-5 levels in the cell culture supernatant (FIG. 8). Similar studies were performed on human IL-5 secreted from primary human donor CD4+ T-cells using antibody 3A5.046 as a capture agent, and the results obtained were consistent with the results obtained with antibody 3A5 (data not shown).

Anti-IL-5 antibody inhibition of eosinophil differentiation

[0111] A survival assay using CD34+ cord blood cells was used to assess the capacity of anti-IL-5 antibodies to inhibit the IL-5 dependent differentiation of bone marrow progenitors to eosinophils and to assess the capacity of anti-IL-5 antibodies to inhibit phenotypically mature eosinophil survival. In IL-5 treated control cells, phenotypically mature eosinophils were the predominant population at day 28 (Figure 9, shaded region in graph). Antibody 3A5.046 was able to inhibit the differentiation of CD34+ cord blood cells, incubated with IL-5 for 28-days, into eosinophils. Antibody 3A5.046 was a more potent inhibitor of IL-5 mediated eosinophil differentiation than mepolizumab (FIG. 9).

X-ray crystallography analysis

[0112] The molecular structure of the complex between antibody 3A5.046 Fab and recombinant human IL-5 is investigated by X-ray crystallography. To prepare for X-ray crystallography experiments, 3A5.046 is digested by papain, which cleaves the intact antibody in the hinge region, separating the Fc and Fab domains. The 3A5.046 Fab is purified by standard Protein A affinity chromatography and complexed with recombinant non-glycosylated human IL-5. The 3A5.046 Fab:human IL-5 complex is purified for crystallization experiments using standard size-exclusion chromatography. The complex is set up in variable concentrations, into commercially available sparse-matrix crystallization screens for broad sampling of crystallization conditions. Optimisations of any 'hit' conditions that provide crystals of the complex from the sparse-matrix screens are performed to improve upon crystal morphology and crystal diffraction as required.

[0113] Crystals of the 3A5.046 Fab:human IL-5 complex are harvested, flash-frozen in liquid nitrogen and transported to a synchrotron facility for diffraction tests and data collection. Crystal diffraction testing is performed at a synchrotron, which houses high energy X-ray micro beam lines for producing high-resolution diffraction. In this way, X-ray diffraction data on crystals of 3A5.046 Fab:human IL-5 complex is collected. An initial structure model of the complex may be obtained using standard molecular replacement techniques with published molecular structures of IL-5 and Fab as templates. The final structure of the 3A5.046 Fab and human IL-5 complex may be obtained by iterative refinement of the structure model, until the errors of fitting are better than 30% (final R_{free} of 0.3) and chemical bonding parameters (e.g. the distribution of bond lengths and angles, stereochemistry and hydrogen bonds) are within acceptable limits.

Characterisation of antibody 3A5.046 binding to IL-5 from non-human model species

[0114] Antibody 3A5.046 was tested by Biacore assay using a T200 system (GE Healthcare) for binding to recombinant cytokines human IL-5, rat IL-5, mouse IL-5, and guinea pig IL-5. This panel of non-human IL-5s was chosen to represent major animal model species used in preclinical development. An isotype control antibody (IgG4) and antibody 3A5.046 were immobilized on flowcells 1 and 2 of a Series S CM5 chip (GE Healthcare), respectively, using standard amine coupling methods. Cytokines were diluted to 1 and 10 μg/ml in HBS-EP+ running buffer (GE Healthcare) and injected across flowcells 1 and 2. Buffer-only injections across flowcells 1 and 2 were included for double-referencing. Data analysis was performed using Biacore T200 evaluation software. The resulting sensorgrams were double-referenced (test flowcell values subtracted from control flowcell values and also a buffer blank).

[0115] Antibody 3A5.046 was found to bind to human IL-5 and cynomolgus monkey IL-5, but not to mouse IL-5, rat IL-5, or guinea pig IL-5 (FIG. 10A – FIG. 10E). This indicated that 3A5.046 could be used in cynomolgus macaque preclinical models.

Antibody 3A5.046 does not bind to other human cytokines closely related to IL-5

[0116] Antibody 3A5.046 was tested by Biacore assay using a T200 system (GE Healthcare) for binding to recombinant human cytokines IL-2, IL-3, IL-4, IL-5, granulocyte macrophage colony stimulating factor (GM-CSF), macrophage colony stimulating factor (M-CSF), and growth hormone (GH). This representative panel of closely-related human cytokines was chosen based on their structural and functional similarity to human IL-5. An isotype control antibody (IgG4) and antibody 3A5.046 were immobilized on flowcells 1 and 2 of a Series S CM5 chip (GE Healthcare), respectively, using standard amine coupling methods. Cytokines were diluted to 1 and 10 μg/ml in HBS-EP+ running buffer (GE Healthcare) and injected across flowcells 1 and 2. Buffer-only injections across flowcells 1 and 2 were included for double-referencing. Data analysis was performed using Biacore T200 evaluation software. The resulting sensorgrams were double-referenced (test flowcell values subtracted from control flowcell values and also a buffer blank).

[0117] Antibody 3A5.046 was found to bind only to human IL-5 and not human cytokines IL-2, IL-3, IL-4, GM-CSF, M-CSF, or GH (FIG. 11A – FIG. 11D), thus demonstrating high specificity of 3A5.046 for human IL-5.

Evaluation of antibody 3A5.046 in an *Ascaris suum*-induced cynomolgus monkey airways eosinophilia model

[0118] Antibody 3A5.046 was tested using the *Ascaris suum* cynomolgus model of acute airways eosinophilia as described in Hart, T.K., et al., Preclinical efficacy and safety of mepolizumab (SB-240563), a humanized monoclonal antibody to IL-5, in cynomolgus monkeys. J Allergy Clin Immunol, 2001. 108(2): p. 250-7.

[0119] Sixteen female *cynomolgus* macaques that had been previously sensitized to *Ascaris suum* were assessed for level of retained sensitivity by intradermal challenge with *A. suum*. Fourteen of these animals were selected for participation in the study based on the skin wheal response to challenge and randomized into two groups of n=7 per group. Two weeks after intradermal skin wheal testing, baseline blood and bronchoalveolar lavage fluid (BALF) samples were collected (Day 8). About 24 hours after baseline sample collection, animals were treated with either placebo (comprising aqueous buffer pH 6.3 with 200 mM arginine and 25 mM histidine) or antibody 3A5.046 (10 mg/kg intravenously, in aqueous buffer pH 6.3 with 200 mM arginine and 25 mM histidine) in a blinded manner (Day 7). One week after treatment with placebo or antibody a second intradermal *A. suum* challenge was performed and an *A. suum* inhalation challenge was given to all animals by delivery of an equal amount of *A. suum* extract (Greer Laboratories Inc.; 5 mg/ml in sterile water) administered via PARI LC nebulizer (Day 0). Skin wheal diameter was measured 15 minutes after challenge. Two days after *A. suum* inhalation challenge, blood and BALF samples were collected. Additional blood samples for haematology endpoints and PK analysis were collected weekly starting on Day 10 until Day 45.

[0120] There was no significant difference in the skin wheal responses between the first and second intradermal *A. suum* challenges. All animals showed an increase in eosinophils in the BALF as a result of *A. suum* challenge but in animals treated with antibody 3A5.046, this increase was negligible. There were significantly fewer eosinophils in the BALF of animals treated with antibody 3A5.046, compared to placebo-treated animals 48 hours after *A. suum* challenge ($p<0.01$; Mann-Whitney test; FIG. 12).

[0121] *A. suum* challenge also led to significantly increased blood eosinophils over baseline in placebo-treated animals to day 10 post-challenge (FIG. 13A). Treatment with antibody 3A5.046 led to a significant decrease in blood eosinophils to levels below baseline (FIG. 13A), and this depression in blood eosinophil numbers was maintained over a period of at least 52 days after initial dose (FIG. 13B).

[0122] In summary, treatment with 3A5.046 significantly reduced *A. suum*-induced airways eosinophilia 48 hours after challenge, and significantly decreased blood eosinophils, to below baseline levels, for at least 52 days following a single intravenous (IV) 10 mg/kg dose.

Investigation of antibody function in a humanized IL-5 rat model of airways eosinophilia

[0123] *Alternaria alternata* (Alternaria) is a fungal allergen that is known to trigger asthma in humans and can cause eosinophilia and asthma-like symptoms in rodents. When challenged with Alternaria, humanized IL-5 knock-in rats (animals in which the rat IL-5 has been replaced by human IL-5) show elevated eosinophil levels in bronchoalveolar lavage fluid (BALF) from lungs (FIG. 14).

[0124] A single intratracheal instillation of Alternaria suspension is administered to humanized IL-5 rats, and blood and BALF samples are collected 2, 3 or 4 days after Alternaria administration. Typically in this model eosinophils are significantly increased in BALF samples and may be either increased or unchanged in blood samples. Test antibodies are administered prior to induction of eosinophilia with Alternaria and assessed for their ability to reduce eosinophil numbers in BALF and blood.

[0125] Those skilled in the art will appreciate that numerous changes and modifications can be made to the preferred embodiments of the invention and that such changes and modifications can be made without departing from the spirit of the invention. It is, therefore, intended that the appended claims cover all such equivalent variations as fall within the true spirit and scope of the invention.

[0126] The disclosures of each patent, patent application, and publication cited or described in this document are hereby incorporated herein by reference, in its entirety.

Table 15. Sequences

Protein chain	Sequence	Protein Chain	Sequence
Consensus LCDR1	$GX_1X_2X_3X_4X_5X_6KX_7X_8Y$ SEQ ID NO: 1		
Consensus LCDR2	DDX_8X_9RPS SEQ ID NO: 2		
Consensus LCDR3	$QVWX_{10}SSSDX_{11}VX_{12}$ SEQ ID NO: 3		
Antibody 3A5			
3A5 HCDR1	GGSISNGGYYWS SEQ ID NO: 4	3A5 LCDR1	GGNNIGSKNVY SEQ ID NO: 5
3A5 HCDR2	YIYYSGSTY SEQ ID NO: 6	3A5 LCDR2	DDSDRPS SEQ ID NO: 7
3A5 HCDR3	LGNWFDY SEQ ID NO: 8	3A5 LCDR3	QVWYSSSDHVV SEQ ID NO: 9
3A5 VH	QVQLQESGPGLVKPSQTLSLTCTVSGGSISNGGYYWSWIRQHPGKGLEWI GYIYYSGSTYYNPSLKSRVSISVDTSKNQFSLKLNSVTAADTAVYYCASL GNWFDYWGQGTLVTVSS SEQ ID NO: 10		
3A5 VL	SSILTQPPSVSVAPGQTARITCGGNNIGSKNVYWYQQKPGQAPVLVVHDD SDRPSGIPERFSGSNSGNTATLTISRVEVGDEADYSCQVWYSSSDHVVFGG GTKLTVLG SEQ ID NO: 11		
3A5 HC	QVQLQESGPGLVKPSQTLSLTCTVSGGSISNGGYYWSWIRQHPGKGLEWI GYIYYSGSTYYNPSLKSRVSISVDTSKNQFSLKLNSVTAADTAVYYCASL GNWFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDT LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV YTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG SEQ ID NO: 12		
3A5 LC	SSILTQPPSVSVAPGQTARITCGGNNIGSKNVYWYQQKPGQAPVLVVHDD SDRPSGIPERFSGSNSGNTATLTISRVEVGDEADYSCQVWYSSSDHVVFGG GTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWK ADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEG STVEKTVAPTECS		

Protein chain	Sequence	Protein Chain	Sequence
	SEQ ID NO: 13		
Antibody 3A5.001			
3A5.001 HCDR1	GGSISNGGYYWS SEQ ID NO: 4	3A5.001 LCDR1	GGNNIGSKNVY SEQ ID NO: 5
3A5.001 HCDR2	YIYYSGSTY SEQ ID NO: 6	3A5.001 LCDR2	DDSDRPS SEQ ID NO: 7
3A5.001 HCDR3	LGNWFDY SEQ ID NO: 8	3A5.001 LCDR3	QVWYSSSDHVV SEQ ID NO: 9
3A5.001 VH	QVQLQESGPGLVKPSQTLSLTCTVSGGSISNGGYYWSWIRQHPGKGLEWI GYIYYSGSTYYNPSLKSRVSISVDTSKNQFSLKLNSVTAADTAVYYCASL GNWFDYWGQGTLVTVSS SEQ ID NO: 10		
3A5.001 VL	SSILTQPPSVSVAPGQTARITCGGNNIGSKNVYWYQQKPGQAPVLVVHDD SDRPSGIPERFSGSNSGNTATLTISRVEVGDEADYSCQVWYSSSDHVVFGG GTKLTVLG SEQ ID NO: 11		
3A5.001 HC	QVQLQESGPGLVKPSQTLSLTCTVSGGSISNGGYYWSWIRQHPGKGLEWI GYIYYSGSTYYNPSLKSRVSISVDTSKNQFSLKLNSVTAADTAVYYCASL GNWFDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYF PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCN VDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPP SQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG SEQ ID NO: 14		
3A5.001 LC	SSILTQPPSVSVAPGQTARITCGGNNIGSKNVYWYQQKPGQAPVLVVHDD SDRPSGIPERFSGSNSGNTATLTISRVEVGDEADYSCQVWYSSSDHVVFGG GTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWK ADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEG STVEKTVAPTECS SEQ ID NO: 13		
Antibody 3A5.040			
3A5.040 HCDR1	GGSISNGGYYWS SEQ ID NO: 4	3A5.040 LCDR1	GGNNIGSKNVY SEQ ID NO: 5
3A5.040 HCDR2	YIYYSGSTY SEQ ID NO: 6	3A5.040 LCDR2	DDSDRPS SEQ ID NO: 7
3A5.040 HCDR3	LGNWFDY SEQ ID NO: 8	3A5.040 LCDR3	QVWDSSSDHVV SEQ ID NO: 15
3A5.040 VH	QVQLQESGPGLVKPSQTLSLTCTVSGGSISNGGYYWSWIRQHPGKGLEWI GYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCASLG NWFDYWGQGTLVTVSS		

Protein chain	Sequence	Protein Chain	Sequence
	SEQ ID NO: 16		
3A5.040 VL	SYVLTQPPSVSVAPGQTARITCGGNNIGSKNVYWYQQKPGQAPVLVVHD DSDRPSGIPERFSGSNSGNTATLTISRVEVGDEADYSCQVWDSSSDHVVFG GGTKLTVLG SEQ ID NO: 17		
3A5.040 HC	QVQLQESGPGLVKPSQTLSLTCTVSGGSISNGGYYWSWIRQHPGKGLEWI GYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCASLG NWFDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCN VDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPP SQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG SEQ ID NO: 18		
3A5.040 LC	SYVLTQPPSVSVAPGQTARITCGGNNIGSKNVYWYQQKPGQAPVLVVHD DSDRPSGIPERFSGSNSGNTATLTISRVEVGDEADYSCQVWDSSSDHVVFG GGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAW KADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHE GSTVEKTVAPTECS SEQ ID NO: 19		
Antibody 3A5.046			
3A5.046 HCDR1	GGSISNGGYYWS SEQ ID NO: 4	3A5.046 LCDR1	GGNNIGSKNVY SEQ ID NO: 5
3A5.046 HCDR2	YIYYSGSTY SEQ ID NO: 6	3A5.046 LCDR2	DDSDRPS SEQ ID NO: 7
3A5.046 HCDR3	LGNWFDY SEQ ID NO: 8	3A5.046 LCDR3	QVWDSSSDHVV SEQ ID NO: 15
3A5.046 VH	QVQLQESGPGLVKPSQTLSLTCTVSGGSISNGGYYWSWIRQHPGKGLEWI GYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCASLG NWFDYWGQGTLVTVSS SEQ ID NO: 16		
3A5.046 VL	SYVLTQPPSVSVAPGQTARITCGGNNIGSKNVYWYQQKPGQAPVLVVHD DSDRPSGIPERFSGSNSGNTATLTISRVEVGDEADYSCQVWDSSSDHVVFG GGTKLTVLG SEQ ID NO: 17		
3A5.046 HC	QVQLQESGPGLVKPSQTLSLTCTVSGGSISNGGYYWSWIRQHPGKGLEWI GYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCASLG NWFDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCN VDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLYITR EPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPP SQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS		

Protein chain	Sequence	Protein Chain	Sequence
	FFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG SEQ ID NO: 20		
3A5.046 LC	SYVLTQPPSVSVAPGQTARITCGGNNIGSKNVYWYQQKPGQAPVLVVHD DSDRPSGIPERFSGSNSGNTATLTISRVEVGDEADYSCQVWDSSSDHVVFG GGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAW KADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHE GSTVEKTVAPTECS SEQ ID NO: 19		
Antibody 3A5.063			
3A5.063 HCDR1	GGSISNGGYYWS SEQ ID NO: 4	3A5.063 LCDR1	GKNNIGSKNVY SEQ ID NO: 21
3A5.063 HCDR2	YIYYSGSTY SEQ ID NO: 6	3A5.063 LCDR2	DDSDRPS SEQ ID NO: 7
3A5.063 HCDR3	LGNWFDY SEQ ID NO: 8	3A5.063 LCDR3	QVWDSSSDHVV SEQ ID NO: 15
3A5.063 VH	QVQLQESGPGLVKPSQTLSLTCTVSGGSISNGGYYWSWIRQHPGKGLEWI GYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCASLG NWFDYWGQGTLVTVSS SEQ ID NO: 16		
3A5.063 VL G25K	SYVLTQPPSVSVAPGQTARITCGKNNIGSKNVYWYQQKPGQAPVLVVHD DSDRPSGIPERFSGSNSGNTATLTISRVEVGDEADYSCQVWDSSSDHVVFG GGTKLTVLG SEQ ID NO: 22		
3A5.063 HC	QVQLQESGPGLVKPSQTLSLTCTVSGGSISNGGYYWSWIRQHPGKGLEWI GYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCASLG NWFDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCN VDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPP SQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG SEQ ID NO: 18		
3A5.063 LC G25K	SYVLTQPPSVSVAPGQTARITCGKNNIGSKNVYWYQQKPGQAPVLVVHD DSDRPSGIPERFSGSNSGNTATLTISRVEVGDEADYSCQVWDSSSDHVVFG GGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAW KADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHE GSTVEKTVAPTECS SEQ ID NO: 23		
Antibody 3A5.070			
3A5.070 HCDR1	GGSISNGGYYWS SEQ ID NO: 4	3A5.070 LCDR1	GGDNIGSKNVY SEQ ID NO: 24
3A5.070 HCDR2	YIYYSGSTY	3A5.070 LCDR2	DDSDRPS

Protein chain	Sequence	Protein Chain	Sequence
	SEQ ID NO: 6		SEQ ID NO: 7
3A5.070 HCDR3	LGNWFDY SEQ ID NO: 8	3A5.070 LCDR3	QVWDSSSDHVV SEQ ID NO: 15
3A5.070 VH	QVQLQESGPGLVKPSQTLSLTCTVSGGSISNGGYYWSWIRQHPGKGLEWI GYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCASLG NWFDYWGQGTLVTVSS SEQ ID NO: 16		
3A5.070 VL N26D	SYVLTQPPSVSVAPGQTARITCGGDNIGSKNVYWYQQKPGQAPVLVVHD DSDRPSGIPERFSGSNSGNTATLTISRVEVGDEADYSCQVWDSSSDHVVFG GGTKLTVLG SEQ ID NO: 25		
3A5.070 HC	QVQLQESGPGLVKPSQTLSLTCTVSGGSISNGGYYWSWIRQHPGKGLEWI GYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCASLG NWFDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCN VDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPP SQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG SEQ ID NO: 18		
3A5.070 LC N26D	SYVLTQPPSVSVAPGQTARITCGGDNIGSKNVYWYQQKPGQAPVLVVHD DSDRPSGIPERFSGSNSGNTATLTISRVEVGDEADYSCQVWDSSSDHVVFG GGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAW KADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHE GSTVEKTVAPTECS SEQ ID NO: 26		
Antibody 3A5.082			
3A5.082 HCDR1	GGSISNGGYYWS SEQ ID NO: 4	3A5.082 LCDR1	GGNHIGSKNVY SEQ ID NO: 27
3A5.082 HCDR2	YIYYSGSTY SEQ ID NO: 6	3A5.082 LCDR2	DDSDRPS SEQ ID NO: 7
3A5.082 HCDR3	LGNWFDY SEQ ID NO: 8	3A5.082 LCDR3	QVWDSSSDHVV SEQ ID NO: 15
3A5.082 VH	QVQLQESGPGLVKPSQTLSLTCTVSGGSISNGGYYWSWIRQHPGKGLEWI GYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCASLG NWFDYWGQGTLVTVSS SEQ ID NO: 16		
3A5.082 VL N27H	SYVLTQPPSVSVAPGQTARITCGGNHIGSKNVYWYQQKPGQAPVLVVHD DSDRPSGIPERFSGSNSGNTATLTISRVEVGDEADYSCQVWDSSSDHVVFG GGTKLTVLG SEQ ID NO: 28		

Protein chain	Sequence	Protein Chain	Sequence
3A5.082 HC	QVQLQESGPGLVKPSQTLSLTCTVSGGSISNGGYYWSWIRQHPGKGLEWI GYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCASLG NWFDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCN VDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPP SQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG SEQ ID NO: 18		
3A5.082 LC N27H	SYVLTQPPSVSVAPGQTARITCGGNHIGSKNVYWYQQKPGQAPVLVVHD DSDRPSGIPERFSGSNSGNTATLTISRVEVGDEADYSCQVWDSSSDHVVFG GGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAW KADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHE GSTVEKTVAPTECS SEQ ID NO: 29		
Antibody 3A5.084			
3A5.084 HCDR1	GGSISNGGYYWS SEQ ID NO: 4	3A5.084 LCDR1	GGNNAGSKNVY SEQ ID NO: 30
3A5.084 HCDR2	YIYYSGSTY SEQ ID NO: 6	3A5.084 LCDR2	DDSDRPS SEQ ID NO: 7
3A5.084 HCDR3	LGNWFDY SEQ ID NO: 8	3A5.084 LCDR3	QVWDSSSDHVV SEQ ID NO: 15
3A5.084 VH	QVQLQESGPGLVKPSQTLSLTCTVSGGSISNGGYYWSWIRQHPGKGLEWI GYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCASLG NWFDYWGQGTLVTVSS SEQ ID NO: 16		
3A5.084 VL I28A	SYVLTQPPSVSVAPGQTARITCGGNNAGSKNVYWYQQKPGQAPVLVVH DDSDRPSGIPERFSGSNSGNTATLTISRVEVGDEADYSCQVWDSSSDHVVF GGGTKLTVLG SEQ ID NO: 31		
3A5.084 HC	QVQLQESGPGLVKPSQTLSLTCTVSGGSISNGGYYWSWIRQHPGKGLEWI GYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCASLG NWFDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCN VDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPP SQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG SEQ ID NO: 18		
3A5.084 LC I28A	SYVLTQPPSVSVAPGQTARITCGGNNAGSKNVYWYQQKPGQAPVLVVH DDSDRPSGIPERFSGSNSGNTATLTISRVEVGDEADYSCQVWDSSSDHVVF GGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVA WKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVT		

Protein chain	Sequence	Protein Chain	Sequence
	HEGSTVEKTVAPTECS SEQ ID NO: 32		
Antibody 3A5.107			
3A5.107 HCDR1	GGSISNGGYYWS SEQ ID NO: 4	3A5.107 LCDR1	GGNNIGKKNVY SEQ ID NO: 33
3A5.107 HCDR2	YIYYSGSTY SEQ ID NO: 6	3A5.107 LCDR2	DDSDRPS SEQ ID NO: 7
3A5.107 HCDR3	LGNWFDY SEQ ID NO: 8	3A5.107 LCDR3	QVWDSSSDHVV SEQ ID NO: 15
3A5.107 VH	QVQLQESGPGLVKPSQTLSLTCTVSGGSISNGGYYWSWIRQHPGKGLEWI GYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCASLG NWFDYWGQGTLVTVSS SEQ ID NO: 16		
3A5.107 VL S30K	SYVLTQPPSVSVAPGQTARITCGGNNIGKKNVYWYQQKPGQAPVLVVHD DSDRPSGIPERFSGSNSGNTATLTISRVEVGDEADYSCQVWDSSSDHVVFG GGTKLTVLG SEQ ID NO: 34		
3A5.107 HC	QVQLQESGPGLVKPSQTLSLTCTVSGGSISNGGYYWSWIRQHPGKGLEWI GYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCASLG NWFDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCN VDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPP SQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG SEQ ID NO: 18		
3A5.107 LC S30K	SYVLTQPPSVSVAPGQTARITCGGNNIGKKNVYWYQQKPGQAPVLVVHD DSDRPSGIPERFSGSNSGNTATLTISRVEVGDEADYSCQVWDSSSDHVVFG GGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAW KADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHE GSTVEKTVAPTECS SEQ ID NO: 35		
Antibody 3A5.125			
3A5.125 HCDR1	GGSISNGGYYWS SEQ ID NO: 4	3A5.125 LCDR1	GGNNIGSKHVY SEQ ID NO: 36
3A5.125 HCDR2	YIYYSGSTY SEQ ID NO: 6	3A5.125 LCDR2	DDSDRPS SEQ ID NO: 7
3A5.125 HCDR3	LGNWFDY SEQ ID NO: 8	3A5.125 LCDR3	QVWDSSSDHVV SEQ ID NO: 15
3A5.125 VH	QVQLQESGPGLVKPSQTLSLTCTVSGGSISNGGYYWSWIRQHPGKGLEWI GYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCASLG		

Protein chain	Sequence	Protein Chain	Sequence
	NWFDYWGQGTLVTVSS SEQ ID NO: 16		
3A5.125 VL N32H	SYVLTQPPSVSVAPGQTARITCGGNNIGSKHVYWYQQKPGQAPVLVVHD DSDRPSGIPERFSGSNSGNTATLTISRVEVGDEADYSCQVWDSSSDHVVFG GGTKLTVLG SEQ ID NO: 37		
3A5.125 HC	QVQLQESGPGLVKPSQTLSLTCTVSGGSISNGGYYWSWIRQHPGKGLEWI GYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCASLG NWFDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCN VDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPP SQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG SEQ ID NO: 18		
3A5.125 LC N32H	SYVLTQPPSVSVAPGQTARITCGGNNIGSKHVYWYQQKPGQAPVLVVHD DSDRPSGIPERFSGSNSGNTATLTISRVEVGDEADYSCQVWDSSSDHVVFG GGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAW KADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHE GSTVEKTVAPTECS SEQ ID NO: 38		
Antibody 3A5.127			
3A5.127 HCDR1	GGSISNGGYYWS SEQ ID NO: 4	3A5.127 LCDR1	GGNNIGSKNAY SEQ ID NO: 39
3A5.127 HCDR2	YIYYSGSTY SEQ ID NO: 6	3A5.127 LCDR2	DDSDRPS SEQ ID NO: 7
3A5.127 HCDR3	LGNWFDY SEQ ID NO: 8	3A5.127 LCDR3	QVWDSSSDHVV SEQ ID NO: 15
3A5.127 VH	QVQLQESGPGLVKPSQTLSLTCTVSGGSISNGGYYWSWIRQHPGKGLEWI GYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCASLG NWFDYWGQGTLVTVSS SEQ ID NO: 16		
3A5.127 VL V33A	SYVLTQPPSVSVAPGQTARITCGGNNIGSKNAYWYQQKPGQAPVLVVHD DSDRPSGIPERFSGSNSGNTATLTISRVEVGDEADYSCQVWDSSSDHVVFG GGTKLTVLG SEQ ID NO: 40		
3A5.127 HC	QVQLQESGPGLVKPSQTLSLTCTVSGGSISNGGYYWSWIRQHPGKGLEWI GYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCASLG NWFDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCN VDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPP		

Protein chain	Sequence	Protein Chain	Sequence
	SQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG SEQ ID NO: 18		
3A5.127 LC V33A	SYVLTQPPSVSVAPGQTARITCGGNNIGSKNAYWYQQKPGQAPVLVVHD DSDRPSGIPERFSGSNSGNTATLTISRVEVGDEADYSCQVWDSSSDHVVFG GGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAW KADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHE GSTVEKTVAPTECS SEQ ID NO: 41		
Antibody 3A5.161			
3A5.161 HCDR1	GGSISNGGYYWS SEQ ID NO: 4	3A5.161 LCDR1	GGNNIGSKNVY SEQ ID NO: 5
3A5.161 HCDR2	YIYYSGSTY SEQ ID NO: 6	3A5.161 LCDR2	DDLDRPS SEQ ID NO: 42
3A5.161 HCDR3	LGNWFDY SEQ ID NO: 8	3A5.161 LCDR3	QVWDSSSDHVV SEQ ID NO: 15
3A5.161 VH	QVQLQESGPGLVKPSQTLSLTCTVSGGSISNGGYYWSWIRQHPGKGLEWI GYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCASLG NWFDYWGQGTLVTVSS SEQ ID NO: 16		
3A5.161 VL S52L	SYVLTQPPSVSVAPGQTARITCGGNNIGSKNVYWYQQKPGQAPVLVVHD DLDRPSGIPERFSGSNSGNTATLTISRVEVGDEADYSCQVWDSSSDHVVF GGGTKLTVLG SEQ ID NO: 43		
3A5.161 HC	QVQLQESGPGLVKPSQTLSLTCTVSGGSISNGGYYWSWIRQHPGKGLEWI GYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCASLG NWFDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCN VDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPP SQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG SEQ ID NO: 18		
3A5.161 LC S52L	SYVLTQPPSVSVAPGQTARITCGGNNIGSKNVYWYQQKPGQAPVLVVHD DLDRPSGIPERFSGSNSGNTATLTISRVEVGDEADYSCQVWDSSSDHVVF GGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVA WKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVT HEGSTVEKTVAPTECS SEQ ID NO: 44		
Antibody 3A5.169			
3A5.169 HCDR1	GGSISNGGYYWS SEQ ID NO: 4	3A5.169 LCDR1	GGNNIGSKNVY SEQ ID NO: 5

Protein chain	Sequence	Protein Chain	Sequence
3A5.169 HCDR2	YIYYSGSTY SEQ ID NO: 6	3A5.169 LCDR2	DDSSRPS SEQ ID NO: 45
3A5.169 HCDR3	LGNWFDY SEQ ID NO: 8	3A5.169 LCDR3	QVWDSSSDHVV SEQ ID NO: 15
3A5.169 VH	QVQLQESGPGLVKPSQTLSLTCTVSGGSISNGGYYWSWIRQHPGKGLEWI GYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCASLG NWFDYWGQGTLVTVSS SEQ ID NO: 16		
3A5.169 VL D53S	SYVLTQPPSVSVAPGQTARITCGGNNIGSKNVYWYQQKPGQAPVLVVHD DSSRPSGIPERFSGSNSGNTATLTISRVEVGDEADYSCQVWDSSSDHVVFG GGTKLTVLG SEQ ID NO: 46		
3A5.169 HC	QVQLQESGPGLVKPSQTLSLTCTVSGGSISNGGYYWSWIRQHPGKGLEWI GYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCASLG NWFDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCN VDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPP SQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG SEQ ID NO: 18		
3A5.169 LC D53S	SYVLTQPPSVSVAPGQTARITCGGNNIGSKNVYWYQQKPGQAPVLVVHD DSSRPSGIPERFSGSNSGNTATLTISRVEVGDEADYSCQVWDSSSDHVVFG GGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAW KADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHE GSTVEKTVAPTECS SEQ ID NO: 47		
Antibody 3A5.232			
3A5.232 HCDR1	GGSISNGGYYWS SEQ ID NO: 4	3A5.232 LCDR1	GGNNIGSKNVY SEQ ID NO: 5
3A5.232 HCDR2	YIYYSGSTY SEQ ID NO: 6	3A5.232 LCDR2	DDSDRPS SEQ ID NO: 7
3A5.232 HCDR3	LGNWFDY SEQ ID NO: 8	3A5.232 LCDR3	QVWLSSSDHVV SEQ ID NO: 48
3A5.232 VH	QVQLQESGPGLVKPSQTLSLTCTVSGGSISNGGYYWSWIRQHPGKGLEWI GYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCASLG NWFDYWGQGTLVTVSS SEQ ID NO: 16		
3A5.232 VL D92L	SYVLTQPPSVSVAPGQTARITCGGNNIGSKNVYWYQQKPGQAPVLVVHD DSDRPSGIPERFSGSNSGNTATLTISRVEVGDEADYSCQVWLSSSDHVVFG GGTKLTVLG		

Protein chain	Sequence	Protein Chain	Sequence
	SEQ ID NO: 49		
3A5.232 HC	QVQLQESGPGLVKPSQTLSLTCTVSGGSISNGGYYWSWIRQHPGKGLEWI GYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCASLG NWFDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCN VDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPP SQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG SEQ ID NO: 18		
3A5.232 LC D92L	SYVLTQPPSVSVAPGQTARITCGGNNIGSKNVYWYQQKPGQAPVLVVHD DSDRPSGIPERFSGSNSGNTATLTISRVEVGDEADYSCQVWLSSSDHVVFG GGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAW KADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHE GSTVEKTVAPTECS SEQ ID NO: 50		
Antibody 3A5.276			
3A5.276 HCDR1	GGSISNGGYYWS SEQ ID NO: 4	3A5.276 LCDR1	GGNNIGSKNVY SEQ ID NO: 5
3A5.276 HCDR2	YIYYSGSTY SEQ ID NO: 6	3A5.276 LCDR2	DDSDRPS SEQ ID NO: 7
3A5.276 HCDR3	LGNWFDY SEQ ID NO: 8	3A5.276 LCDR3	QVWDSSSDSVV SEQ ID NO: 51
3A5.276 VH	QVQLQESGPGLVKPSQTLSLTCTVSGGSISNGGYYWSWIRQHPGKGLEWI GYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCASLG NWFDYWGQGTLVTVSS SEQ ID NO: 16		
3A5.276 VL H95bS	SYVLTQPPSVSVAPGQTARITCGGNNIGSKNVYWYQQKPGQAPVLVVHD DSDRPSGIPERFSGSNSGNTATLTISRVEVGDEADYSCQVWDSSSDSVVFG GGTKLTVLG SEQ ID NO: 52		
3A5.276 HC	QVQLQESGPGLVKPSQTLSLTCTVSGGSISNGGYYWSWIRQHPGKGLEWI GYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCASLG NWFDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCN VDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPP SQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG SEQ ID NO: 18		
3A5.276 LC H95bS	SYVLTQPPSVSVAPGQTARITCGGNNIGSKNVYWYQQKPGQAPVLVVHD DSDRPSGIPERFSGSNSGNTATLTISRVEVGDEADYSCQVWDSSSDSVVFG GGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAW		

Protein chain	Sequence	Protein Chain	Sequence
	KADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHE GSTVEKTVAPTECS SEQ ID NO: 53		
Antibody 3A5.278			
3A5.278 HCDR1	GGSISNGGYYWS SEQ ID NO: 4	3A5.278 LCDR1	GGNNIGSKNVY SEQ ID NO: 5
3A5.278 HCDR2	YIYYSGSTY SEQ ID NO: 6	3A5.278 LCDR2	DDSDRPS SEQ ID NO: 7
3A5.278 HCDR3	LGNWFDY SEQ ID NO: 8	3A5.278 LCDR3	QVWDSSSDYVV SEQ ID NO: 54
3A5.278 VH	QVQLQESGPGLVKPSQTLSLTCTVSGGSISNGGYYWSWIRQHPGKGLEWI GYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCASLG NWFDYWGQGTLVTVSS SEQ ID NO: 16		
3A5.278 VL H95bY	SYVLTQPPSVSVAPGQTARITCGGNNIGSKNVYWYQQKPGQAPVLVVHD DSDRPSGIPERFSGSNSGNTATLTISRVEVGDEADYSCQVWDSSSDYVVFG GGTKLTVLG SEQ ID NO: 55		
3A5.278 HC	QVQLQESGPGLVKPSQTLSLTCTVSGGSISNGGYYWSWIRQHPGKGLEWI GYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCASLG NWFDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCN VDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPP SQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG SEQ ID NO: 18		
3A5.278 LC H95bY	SYVLTQPPSVSVAPGQTARITCGGNNIGSKNVYWYQQKPGQAPVLVVHD DSDRPSGIPERFSGSNSGNTATLTISRVEVGDEADYSCQVWDSSSDYVVFG GGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAW KADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHE GSTVEKTVAPTECS SEQ ID NO: 56		
Antibody 3A5.279			
3A5.279 HCDR1	GGSISNGGYYWS SEQ ID NO: 4	3A5.279 LCDR1	GGNNIGSKNVY SEQ ID NO: 5
3A5.279 HCDR2	YIYYSGSTY SEQ ID NO: 6	3A5.279 LCDR2	DDSDRPS SEQ ID NO: 7
3A5.279 HCDR3	LGNWFDY SEQ ID NO: 8	3A5.279 LCDR3	QVWDSSSDDVV SEQ ID NO: 57
3A5.279 VH	QVQLQESGPGLVKPSQTLSLTCTVSGGSISNGGYYWSWIRQHPGKGLEWI		

Protein chain	Sequence	Protein Chain	Sequence
	GYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCASLG NWFDYWGQGTLVTVSS SEQ ID NO: 16		
3A5.279 VL H95bD	SYVLTQPPSVSVAPGQTARITCGGNNIGSKNVYWYQQKPGQAPVLVVHD DSDRPSGIPERFSGSNSGNTATLTISRVEVGDEADYSCQVWDSSSDDVVFG GGTKLTVLG SEQ ID NO: 58		
3A5.279 HC	QVQLQESGPGLVKPSQTLSLTCTVSGGSISNGGYYWSWIRQHPGKGLEWI GYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCASLG NWFDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCN VDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPP SQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG SEQ ID NO: 18		
3A5.279 LC H95bD	SYVLTQPPSVSVAPGQTARITCGGNNIGSKNVYWYQQKPGQAPVLVVHD DSDRPSGIPERFSGSNSGNTATLTISRVEVGDEADYSCQVWDSSSDDVVFG GGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAW KADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHE GSTVEKTVAPTECS SEQ ID NO: 59		
Antibody 3A5.294			
3A5.294 HCDR1	GGSISNGGYYWS SEQ ID NO: 4	3A5.294 LCDR1	GGNNIGSKNVY SEQ ID NO: 5
3A5.294 HCDR2	YIYYSGSTY SEQ ID NO: 6	3A5.294 LCDR2	DDSDRPS SEQ ID NO: 7
3A5.294 HCDR3	LGNWFDY SEQ ID NO: 8	3A5.294 LCDR3	QVWDSSSDHVA SEQ ID NO: 60
3A5.294 VH	QVQLQESGPGLVKPSQTLSLTCTVSGGSISNGGYYWSWIRQHPGKGLEWI GYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCASLG NWFDYWGQGTLVTVSS SEQ ID NO: 16		
3A5.294 VL V97A	SYVLTQPPSVSVAPGQTARITCGGNNIGSKNVYWYQQKPGQAPVLVVHD DSDRPSGIPERFSGSNSGNTATLTISRVEVGDEADYSCQVWDSSSDHVAFG GGTKLTVLG SEQ ID NO: 61		
3A5.294 HC	QVQLQESGPGLVKPSQTLSLTCTVSGGSISNGGYYWSWIRQHPGKGLEWI GYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCASLG NWFDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCN VDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVV		

Protein chain	Sequence	Protein Chain	Sequence
	SVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPP SQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG SEQ ID NO: 18		
3A5.294 LC V97A	SYVLTQPPSVSVAPGQTARITCGGNNIGSKNVYWYQQKPGQAPVLVVHD DSDRPSGIPERFSGSNSGNTATLTISRVEVGDEADYSCQVWDSSSDHVAFG GGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAW KADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHE GSTVEKTVAPTECS SEQ ID NO: 62		
Antibody 3A5.302			
3A5.302 HCDR1	GGSISNGGYYWS SEQ ID NO: 4	3A5.302 LCDR1	GGNNIGSKNVY SEQ ID NO: 5
3A5.302 HCDR2	YIYYSGSTY SEQ ID NO: 6	3A5.302 LCDR2	DDSDRPS SEQ ID NO: 7
3A5.302 HCDR3	LGNWFDY SEQ ID NO: 8	3A5.302 LCDR3	QVWDSSSDHVW SEQ ID NO: 63
3A5.302 VH	QVQLQESGPGLVKPSQTLSLTCTVSGGSISNGGYYWSWIRQHPGKGLEWI GYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCASLG NWFDYWGQGTLVTVSS SEQ ID NO: 16		
3A5.302 VL V97W	SYVLTQPPSVSVAPGQTARITCGGNNIGSKNVYWYQQKPGQAPVLVVHD DSDRPSGIPERFSGSNSGNTATLTISRVEVGDEADYSCQVWDSSSDHVWF GGGTKLTVLG SEQ ID NO: 64		
3A5.302 HC	QVQLQESGPGLVKPSQTLSLTCTVSGGSISNGGYYWSWIRQHPGKGLEWI GYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCASLG NWFDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCN VDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPP SQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG SEQ ID NO: 18		
3A5.302 LC V97W	SYVLTQPPSVSVAPGQTARITCGGNNIGSKNVYWYQQKPGQAPVLVVHD DSDRPSGIPERFSGSNSGNTATLTISRVEVGDEADYSCQVWDSSSDHVWF GGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVA WKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVT HEGSTVEKTVAPTECS SEQ ID NO: 65		
3A5.097			
3A5.097 HCDR1	GGSISNGGYYWS	3A5.097 LCDR1	GGNNIDSKNVY

Protein chain	Sequence	Protein Chain	Sequence
	SEQ ID NO: 4		SEQ ID NO: 66
3A5.097 HCDR2	YIYYSGSTY SEQ ID NO: 6	3A5.097 LCDR2	DDSDRPS SEQ ID NO: 7
3A5.097 HCDR3	LGNWFDY SEQ ID NO: 8	3A5.097 LCDR3	QVWDSSSDHVV SEQ ID NO: 15
3A5.097 VH	QVQLQESGPGLVKPSQTLSLTCTVSGGSISNGGYYWSWIRQHPGKGLEWI GYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCASLG NWFDYWGQGTLVTVSS SEQ ID NO: 16		
3A5.097 VL G29D	SYVLTQPPSVSVAPGQTARITCGGNNIDSKNVYWYQQKPGQAPVLVVHD DSDRPSGIPERFSGSNSGNTATLTISRVEVGDEADYSCQVWDSSSDHVVFG GGTKLTVLG SEQ ID NO: 67		
3A5.097 HC	QVQLQESGPGLVKPSQTLSLTCTVSGGSISNGGYYWSWIRQHPGKGLEWI GYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCASLG NWFDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCN VDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPP SQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG SEQ ID NO: 18		
3A5.097 LC G29D	SYVLTQPPSVSVAPGQTARITCGGNNIDSKNVYWYQQKPGQAPVLVVHD DSDRPSGIPERFSGSNSGNTATLTISRVEVGDEADYSCQVWDSSSDHVVFG GGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAW KADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHE GSTVEKTVAPTECS SEQ ID NO: 68		
3A5.046 VH nucleotide sequence (synthetic)	CAGGTGCAGCTGCAGGAATCTGGCCCTGGCCTGGTCAAGCCCAGCCA GACCCTGAGCCTGACCTGTACCGTGTCCGGCGGCAGCATCAGCAACGG CGGCTACTACTGGTCCTGGATCAGACAGCACCCCGGCAAGGGCCTGG AATGGATCGGCTACATCTACTACAGCGGCAGCACCTACTACAACCCCA GCCTGAAGTCCAGAGTGACCATCAGCGTGGACACCAGCAAGAACCAG TTCAGCCTGAAGCTGAGCAGCGTGACAGCCGCCGACACCGCCGTGTAC TACTGCGCCAGCCTGGGCAATTGGTTCGACTACTGGGGCCAGGGCACC CTCGTGACAGTGTCCTCA SEQ ID NO: 69		
3A5.046 human HC constant region nucleotide sequence (synthetic)	GCTAGCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCCTTGTAGCAGA AGCACCAGCGAGAGCACAGCCGCCCTGGGCTGCCTGGTGAAAGACTA CTTCCCCGAGCCCGTCACCGTGTCCTGGAACAGCGGAGCCCTGACCAG CGGCGTGCACACCTTTCCAGCCGTGCTGCAGAGCAGCGGCCTGTACAG CCTGAGCAGCGTGGTGACAGTGCCCTCCAGCAGCCTGGGCACCAAGA CCTACACCTGTAACGTGGACCACAAGCCCAGCAACACCAAGGTGGAC AAGCGGGTGGAATCTAAGTACGGCCCACCCTGCCCCCCCTGCCCTGCC CCTGAATTTCTGGGCGGACCCTCCGTGTTCCTGTTCCCCCCAAAGCCCA		

Protein chain	Sequence	Protein Chain	Sequence
	AGGACACCCTGTATATCACTCGGGAGCCCGAAGTGACCTGCGTGGTGG TGGACGTGTCCCAGGAAGATCCCGAGGTCCAGTTCAATTGGTACGTGG ACGGCGTGGAAGTGCACAACGCCAAGACCAAGCCCAGAGAGGAACA GTTCAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCA GGACTGGCTGAACGGCAAAGAGTACAAGTGCAAAGTCTCCAACAAGG GCCTGCCCAGCTCCATCGAGAAAACCATCAGCAAGGCCAAGGGCCAG CCCCGCGAGCCTCAGGTGTACACACTGCCCCCCAGCCAGGAAGAGAT GACCAAGAACCAGGTGTCCCTGACCTGTCTGGTGAAAGGCTTCTACCC CAGCGATATCGCCGTGGAATGGGAGAGCAACGGCCAGCCCGAGAACA ACTACAAGACCACCCCCCCTGTGCTGGACAGCGACGGCAGCTTCTTCC TGTACTCCCGGCTGACCGTGGACAAGAGCCGGTGGCAGGAAGGCAAC GTCTTCAGCTGCAGCGTGATGCACGAGGCCCTGCACAACCACTACACC CAGAAGTCCCTGAGCCTGAGCCTGGGC SEQ ID NO: 70		
3A5.046 VL nucleotide sequence (synthetic)	AGCTACGTGCTGACCCAGCCTCCTAGCGTGTCCGTGGCCCCTGGCCAG ACCGCCAGAATCACCTGTGGCGGCAACAACATCGGCAGCAAGAACGT GTACTGGTATCAGCAGAAGCCCGGCCAGGCCCCCGTGCTGGTGGTGCA CGACGACAGCGACAGACCCAGCGGCATCCCCGAGCGGTTCAGCGGCA GCAACAGCGGCAATACCGCCACCCTGACCATCAGCCGGGTGGAAGTG GGCGACGAGGCCGACTACAGCTGCCAGGTCTGGGACAGCAGCAGCGA CCACGTGGTGTTCGGCGGAGGCACCAAGCTGACCGTCCTAGGT SEQ ID NO: 71		
3A5.046 human LC constant region nucleotide sequence (synthetic)	CAGCCCAAGGCCGCTCCCAGCGTGACCCTGTTCCCCCCAAGCAGCGAG GAACTGCAGGCCAACAAGGCCACCCTGGTGTGCCTGATCAGCGACTTC TACCCTGGGGCCGTGACCGTGGCCTGGAAGGCCGATAGCAGCCCTGTG AAGGCCGGCGTGGAAACCACCACCCCCTCCAAGCAGAGCAACAACAA ATACGCCGCCAGCAGCTACCTGTCCCTGACCCCCGAGCAGTGGAAGTC CCACCGGTCCTACAGCTGCCAGGTGACACACGAGGGCAGCACCGTGG AAAAGACCGTGGCCCCCACCGAGTGCAGC SEQ ID NO: 72		

EMBODIMENTS

[0127] The following list of embodiments is intended to complement, rather than displace or supersede, the previous descriptions.

Embodiment 1. A human antibody molecule that immunospecifically binds to human IL-5 with an equilibrium affinity constant (K_D) of at least about 40 pM as determined by surface plasmon resonance.

Embodiment 2. A human antibody molecule that immunospecifically binds to human IL-5, the antibody molecule comprising:

a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 4, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 6, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 8, a light chain CDR1 comprising the amino acid sequence of SEQ ID NOs: 5, 21, 24, 27, 30, 33, 36, 39, or 66, a light chain CDR2 comprising the amino acid sequence of SEQ ID NOs: 7, 42, or 45, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NOs: 15, 48, 51, 54, 57, 60, or 63.

Embodiment 3. The antibody molecule of embodiment 1 or 2, wherein the antibody molecule comprises a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 4, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 6, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 8, and

a. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 5, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 15;
b. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 21, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 15;
c. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 24, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 15;

d. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 27, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 15;
e. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 30, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 15;
f. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 33, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 15;
g. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 36, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 15;
h. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 39, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 15;
i. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 66, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 15;
j. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 5, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 42, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 15;
k. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 5, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 45, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 15;
l. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 5, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 48;
m. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 5, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 51;

n. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 5, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 54;

o. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 5, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 57;

p. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 5, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 60; or

q. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 5, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 63;

wherein the position of the amino acid residues of the CDR is determined according to AbM.

Embodiment 4. The antibody molecule of embodiment 3, wherein the antibody molecule comprises a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 4, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 6, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 8, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 5, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 15.

Embodiment 5. The antibody molecule of any one of the previous embodiments, wherein the antibody molecule comprises a heavy chain variable region comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 16 and

a. a light chain variable region comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 17;

b. a light chain variable region comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 22;

c. a light chain variable region comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 25;
d. a light chain variable region comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 28;
e. a light chain variable region comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 31;
f. a light chain variable region comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 34;
g. a light chain variable region comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 37;
h. a light chain variable region comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 40;
i. a light chain variable region comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 43;
j. a light chain variable region comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 46;
k. a light chain variable region comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 49;
l. a light chain variable region comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 52;
m. a light chain variable region comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 55;

n. a light chain variable region comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 58;
o. a light chain variable region comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 61;
p. a light chain variable region comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 64; or
q. a light chain variable region comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 67.

Embodiment 6. The antibody molecule of any one of the previous embodiments, wherein the antibody molecule comprises a heavy chain variable region comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 16 and a light chain variable region comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 17.

Embodiment 7. The antibody molecule of any one of the previous embodiments, wherein the antibody molecule comprises:
a. a S228P mutation;
b. a M252Y mutation, a S254T mutation, and a T256E mutation;
c. a deletion of a heavy chain C-terminal lysine residue; or
d. any combination of a to c.

Embodiment 8. The antibody molecule of embodiment 7, wherein the antibody molecule comprises a S228P mutation and a deletion of a heavy chain C-terminal lysine residue.

Embodiment 9. The antibody molecule of embodiment 7, wherein the antibody molecule comprises a S228P mutation, a M252Y mutation, a S254T mutation, a T256E mutation, and a deletion of a heavy chain C-terminal lysine residue.

Embodiment 10. The antibody molecule of any one of the previous embodiments, wherein the antibody molecule comprises an IgG4 heavy chain constant region and a lambda light chain constant region.

Embodiment 11. The antibody molecule of any one of the previous embodiments, wherein the antibody molecule comprises a heavy chain comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 18 and

a. a light chain comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 19;
b. a light chain comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 23;
c. a light chain comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 26;
d. a light chain comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 29;
e. a light chain comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 32;
f. a light chain comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 35;
g. a light chain comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 38;

h. a light chain comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 41;

i. a light chain comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 44;

j. a light chain comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 47;

k. a light chain comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 50;

l. a light chain comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 53;

m. a light chain comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 56;

n. a light chain comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 59;

o. a light chain comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 62;

p. a light chain comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 65; or

q. a light chain comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 68.

Embodiment 12. The antibody molecule of any one of embodiments 1-10, wherein the antibody molecule comprises a heavy chain comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to

the amino acid sequence of SEQ ID NO: 20 and a light chain comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 19.

Embodiment 13. The antibody molecule of embodiment 2 or embodiment 3, wherein the antibody molecule is a Fab fragment, a Fab2 fragment, or a single chain antibody.

Embodiment 14. The antibody molecule of any one of the previous embodiments, wherein the antibody molecule has one or more of the following properties:

a. reduces binding of IL-5 to the IL-5 receptor;
b. has a serum half-life of at least about 20 days; or
c. binds human and cynomolgus monkey IL-5 but not mouse, rat, or guinea pig IL-5.

Embodiment 15. The antibody molecule of embodiment 2, wherein the antibody molecule binds to human IL-5 with an equilibrium affinity constant (K_D) of at least about 40 pM as determined by surface plasmon resonance.

Embodiment 16. A pharmaceutical composition comprising the antibody molecule of any one of embodiments 1 to 15.

Embodiment 17. A nucleic acid molecule encoding the antibody molecule of any one of embodiments 1 to 15.

Embodiment 18. A vector comprising the nucleic acid molecule of embodiment 17.

Embodiment 19. A cell transformed to express the antibody molecule of any one of embodiments 1 to 15.

Embodiment 20. A method of treating a subject having eosinophilic asthma, hypereosinophilic syndrome, nasal polyposis with eosinophilic involvement, eosinophilic granulomatosis with polyangiitis, atopic dermatitis, or eosinophilic esophagitis comprising:

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administering to the subject a therapeutically effective amount of the antibody molecule of any one of embodiments 1 to 15 or the pharmaceutical composition of embodiment 16 to treat the eosinophilic asthma, hypereosinophilic syndrome, nasal polyposis with eosinophilic involvement, eosinophilic granulomatosis with polyangiitis, atopic dermatitis or eosinophilic esophagitis.

Embodiment 21. Use of an effective amount of the antibody molecule of any one of embodiments 1 to 15 or the pharmaceutical composition of embodiment 16 in the treatment of eosinophilic asthma, hypereosinophilic syndrome, nasal polyposis with eosinophilic involvement, eosinophilic granulomatosis with polyangiitis, atopic dermatitis, or eosinophilic esophagitis.

Embodiment 22. Use of the antibody molecule of any one of embodiments 1 to 15 or the pharmaceutical composition of embodiment 16 in the manufacture of a medicament for the treatment of eosinophilic asthma, hypereosinophilic syndrome, nasal polyposis with eosinophilic involvement, eosinophilic granulomatosis with polyangiitis, atopic dermatitis or eosinophilic esophagitis

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

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

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What is Claimed:

1. A human antibody molecule that immunospecifically binds to human IL-5 , wherein the antibody molecule comprises a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 4, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 6, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 8, and
   a. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 5, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 15;
   b. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 21, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 15;
   c. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 24, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 15;
   d. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 27, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 15;
   e. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 30, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 15;
   f. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 33, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 15;
   g. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 36, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 15;
   h. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 39, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 15;
   i. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 66, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 15;

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j. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 5, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 42, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 15;

k. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 5, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 45, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 15;

l. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 5, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 48;

m. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 5, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 51;

n. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 5, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 54;

o. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 5, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 57;

p. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 5, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 60; or

q. a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 5, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 63;

wherein the position of the amino acid residues of the CDR is determined according to AbM.

2. The antibody molecule of claim 1, wherein the antibody molecule comprises a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 4, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 6, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 8, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 5, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 7, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 15.

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3. The antibody molecule of claim 1 or claim 2 any one of the previous claims, wherein the antibody molecule comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 16 and
   a. a light chain variable region comprising the amino acid sequence of SEQ ID NO: 17;
   b. a light chain variable region comprising the amino acid sequence of SEQ ID NO: 22;
   c. a light chain variable region comprising the amino acid sequence of SEQ ID NO: 25;
   d. a light chain variable region comprising the amino acid sequence of SEQ ID NO: 28;
   e. a light chain variable region comprising the amino acid sequence of SEQ ID NO: 31;
   f. a light chain variable region comprising the amino acid sequence of SEQ ID NO: 34;
   g. a light chain variable region comprising the amino acid sequence of SEQ ID NO: 37;
   h. a light chain variable region comprising the amino acid sequence of SEQ ID NO: 40;
   i. a light chain variable region comprising the amino acid sequence of SEQ ID NO: 43;
   j. a light chain variable region comprising the amino acid sequence of SEQ ID NO: 46;
   k. a light chain variable region comprising the amino acid sequence of SEQ ID NO: 49;
   l. a light chain variable region comprising the amino acid sequence of SEQ ID NO: 52;
   m. a light chain variable region comprising the amino acid sequence of SEQ ID NO: 55;
   n. a light chain variable region comprising the amino acid sequence of SEQ ID NO: 58;
   o. a light chain variable region comprising the amino acid sequence of SEQ ID NO: 61;

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p. a light chain variable region comprising the amino acid sequence of SEQ ID NO: 64; or

q. a light chain variable region comprising the amino acid sequence of SEQ ID NO: 67.

4. The antibody molecule of any one of the previous claims, wherein the antibody molecule comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 16 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 17.

5. The antibody molecule of any one of the previous claims, wherein the antibody molecule comprises:
   a. a S228P mutation;
   b. a M252Y mutation, a S254T mutation, and a T256E mutation;
   c. a deletion of a heavy chain C-terminal lysine residue; or
   d. any combination of a to c.

6. The antibody molecule of claim 5, wherein the antibody molecule comprises a S228P mutation and a deletion of a heavy chain C-terminal lysine residue.

7. The antibody molecule of claim 5, wherein the antibody molecule comprises a S228P mutation, a M252Y mutation, a S254T mutation, a T256E mutation, and a deletion of a heavy chain C-terminal lysine residue.

8. The antibody molecule of any one of the previous claims, wherein the antibody molecule comprises an IgG4 heavy chain constant region and a lambda light chain constant region.

9. The antibody molecule of any one of the previous claims, wherein the antibody molecule comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 18 and
   a. a light chain comprising the amino acid sequence of SEQ ID NO: 19;
   b. a light chain comprising the amino acid sequence of SEQ ID NO: 23;
   c. a light chain comprising the amino acid sequence of SEQ ID NO: 26;

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d. a light chain comprising the amino acid sequence of SEQ ID NO: 29;
e. a light chain comprising the amino acid sequence of SEQ ID NO: 32;
f. a light chain comprising the amino acid sequence of SEQ ID NO: 35;
g. a light chain comprising the amino acid sequence of SEQ ID NO: 38;
h. a light chain comprising the amino acid sequence of SEQ ID NO: 41;
i. a light chain comprising the amino acid sequence of SEQ ID NO: 44;
j. a light chain comprising the amino acid sequence of SEQ ID NO: 47;
k. a light chain comprising the amino acid sequence of SEQ ID NO: 50;
l. a light chain comprising the amino acid sequence of SEQ ID NO: 53;
m. a light chain comprising the amino acid sequence of SEQ ID NO: 56;
n. a light chain comprising the amino acid sequence of SEQ ID NO: 59;
o. a light chain comprising the amino acid sequence of SEQ ID NO: 62;
p. a light chain comprising the amino acid sequence of SEQ ID NO: 65; or
q. a light chain comprising the amino acid sequence of SEQ ID NO: 68.

10. The antibody molecule of any one of claims 1-8, wherein the antibody molecule comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 20 and a light chain comprising the amino acid sequence of SEQ ID NO: 19.

11. The antibody molecule of claim 1, wherein the antibody molecule is a Fab fragment, a Fab2 fragment, or a single chain antibody.

12. The antibody molecule of any one of the previous claims, wherein the antibody molecule has one or more of the following properties:
    a. reduces binding of IL-5 to the IL-5 receptor;
    b. has a serum half-life of at least about 20 days; or
    c. binds human and cynomolgus monkey IL-5 but not mouse, rat, or guinea pig IL-5.

13. The antibody molecule of any one of the previous claims, wherein the antibody molecule binds to human IL-5 with an equilibrium affinity constant (K_D) of at least about 40 pM as determined by surface plasmon resonance.

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14. A pharmaceutical composition comprising the antibody molecule of any one of claims 1 to 13.

15. A nucleic acid molecule encoding the antibody molecule of any one of claims 1 to 13.

16. A vector comprising the nucleic acid molecule of claim 15.

17. A cell transformed to express the antibody molecule of any one of claims 1 to 13.

18. A method of treating a subject having eosinophilic asthma, hypereosinophilic syndrome, nasal polyposis with eosinophilic involvement, eosinophilic granulomatosis with polyangiitis, atopic dermatitis or eosinophilic esophagitis comprising:

administering to the subject a therapeutically effective amount of the antibody molecule of any one of claims 1 to 13 or the pharmaceutical composition of claim 14 to treat the eosinophilic asthma, hypereosinophilic syndrome, nasal polyposis with eosinophilic involvement, eosinophilic granulomatosis with polyangiitis, atopic dermatitis or eosinophilic esophagitis.

19. Use of an effective amount of the antibody molecule of any one of claims 1 to 13 or the pharmaceutical composition of claim 14 in the treatment of eosinophilic asthma, hypereosinophilic syndrome, nasal polyposis with eosinophilic involvement, eosinophilic granulomatosis with polyangiitis, atopic dermatitis, or eosinophilic esophagitis.

20. Use of the antibody molecule of any one of claims 1 to 13 or the pharmaceutical composition of claim 14in the manufacture of a medicament for the treatment of eosinophilic asthma, hypereosinophilic syndrome, nasal polyposis with eosinophilic involvement, eosinophilic granulomatosis with polyangiitis, atopic dermatitis or eosinophilic esophagitis.

FIG. 1

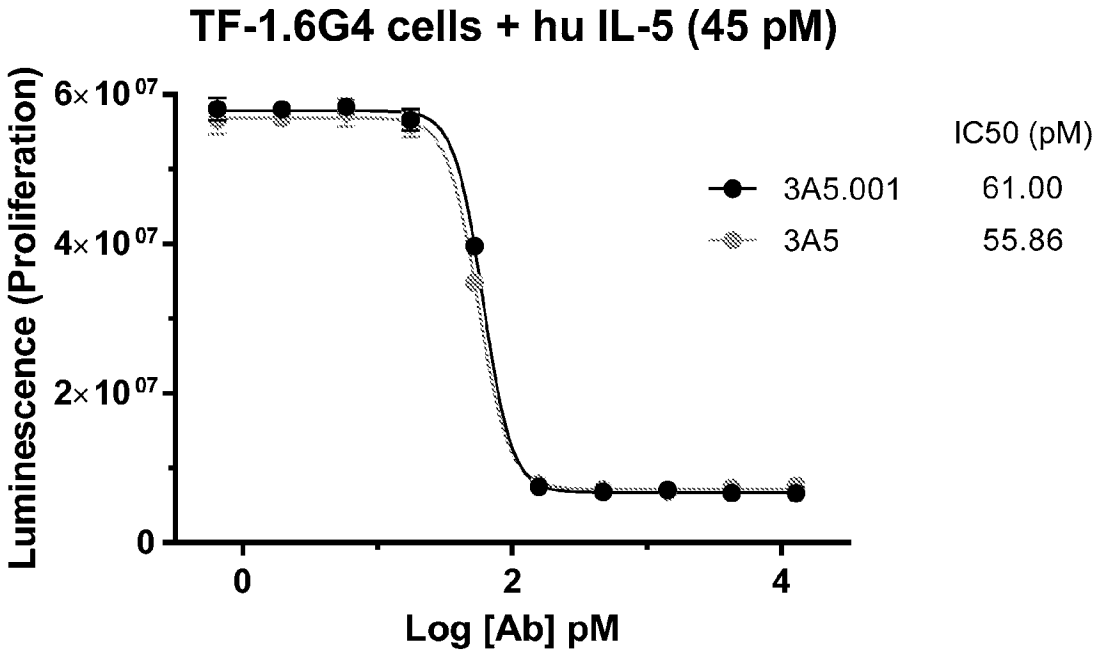
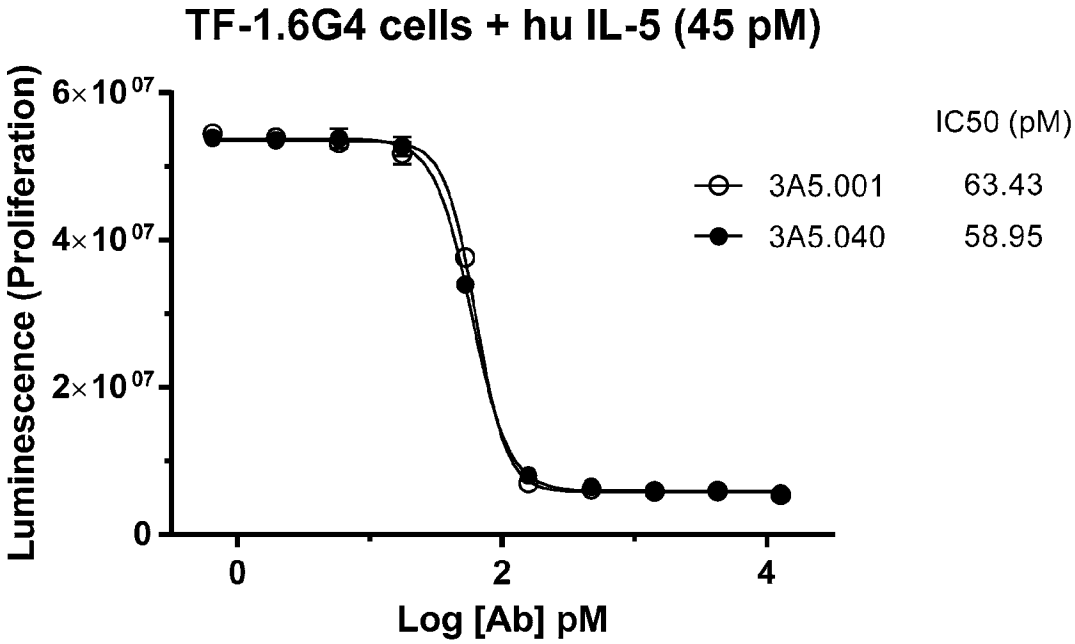

TF-1.6G4 cells + hu IL-5 (45 pM)
Luminescence (Proliferation)
6×10^07
4×10^07
2×10^07
0
0
2
4
Log [Ab] pM
IC50 (pM)
3A5.001 61.00
3A5 55.86

FIG. 2


TF-1.6G4 cells + hu IL-5 (45 pM)
Luminescence (Proliferation)
6×10^07
4×10^07
2×10^07
0
0
2
4
Log [Ab] pM
IC50 (pM)
3A5.001 63.43
3A5.040 58.95

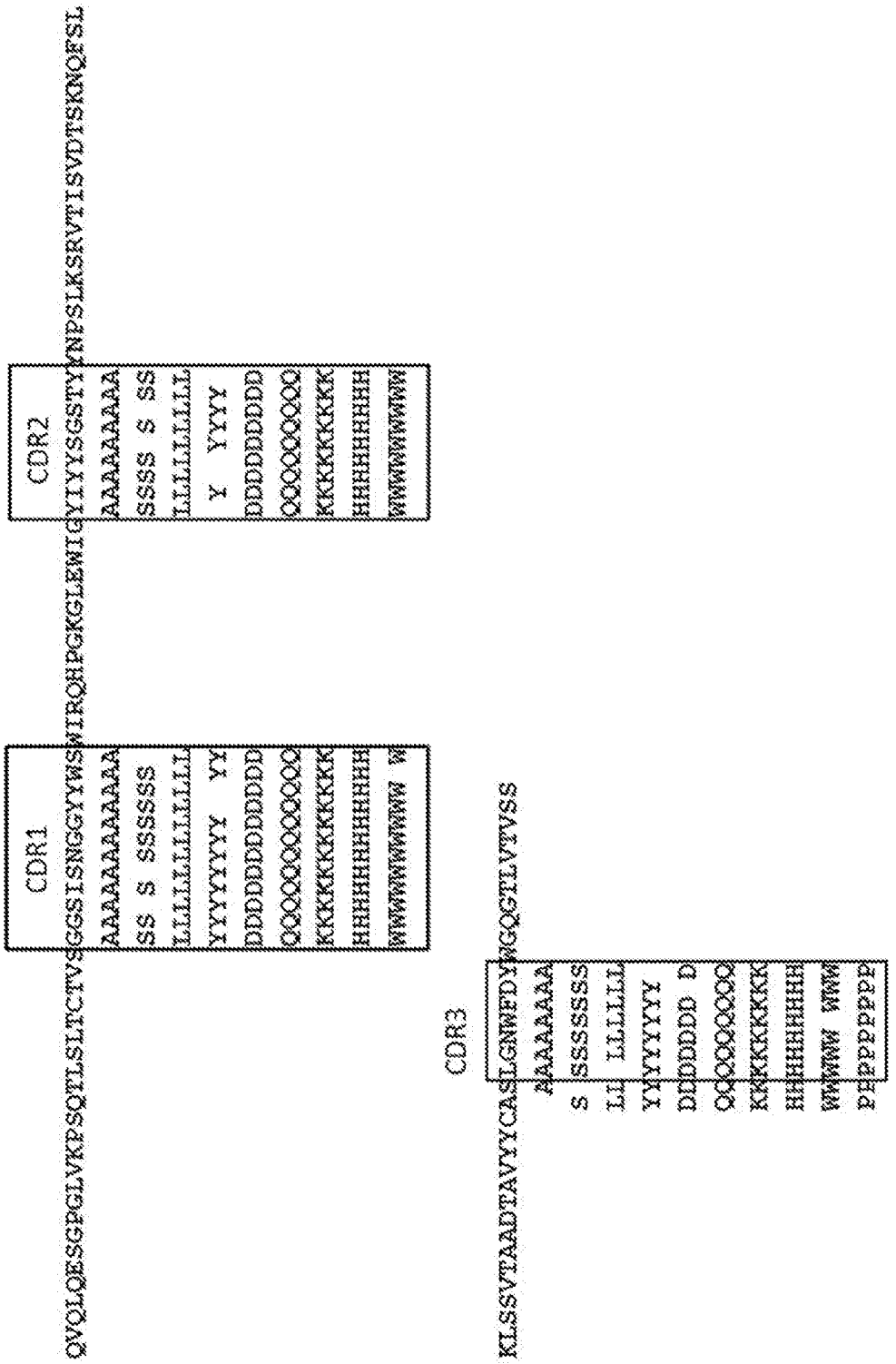

CDR1
CDR2
CDR3
QVQLQESGPGLVKPSQTLSLTCTVSGGSISNGGYYWSWIRQHPGKGLEWIGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSL
KLSSVTAADTAVYYCASLGNWFDYWGQGTLVTVSS

FIG. 3

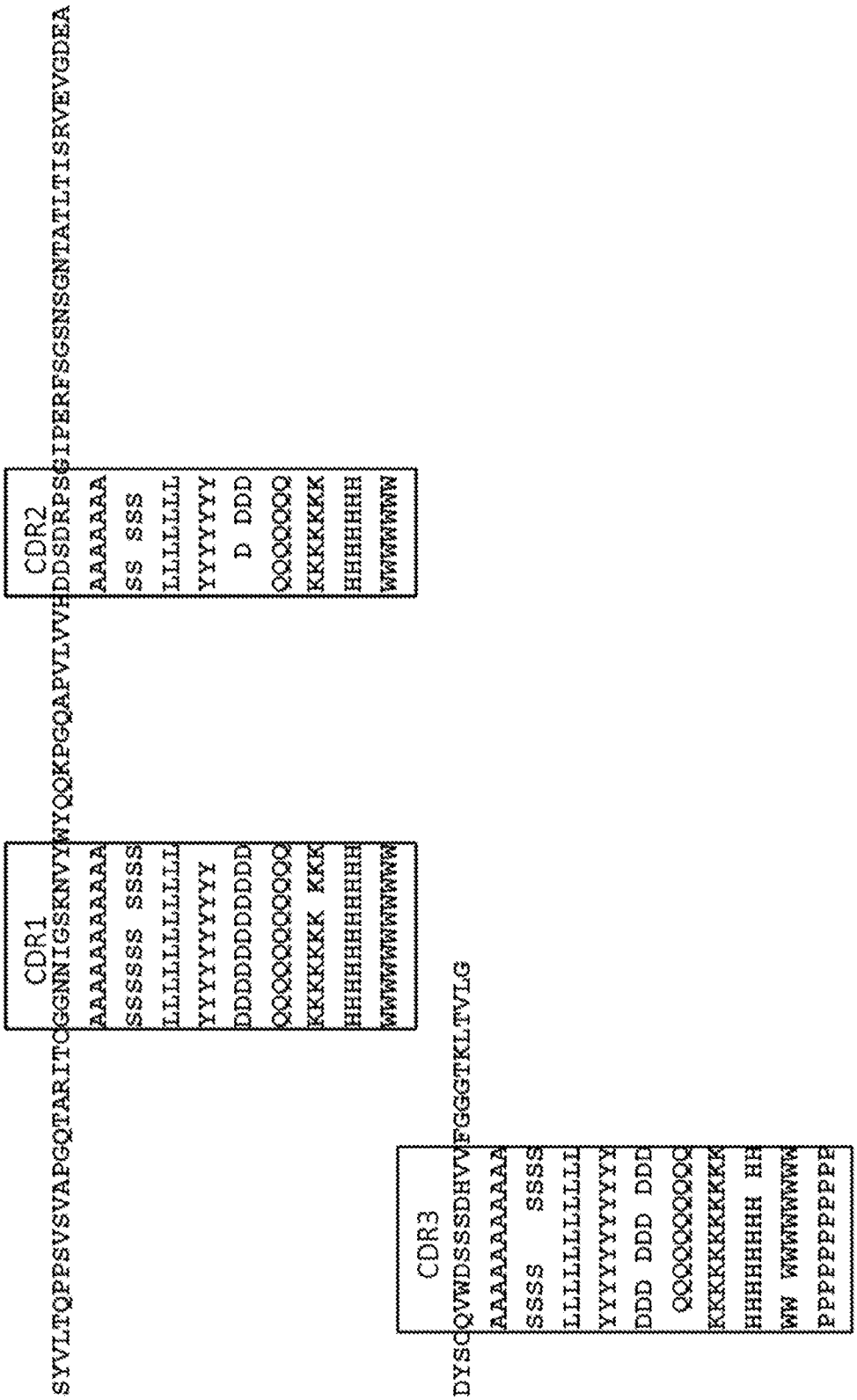

CDR1
SYVLTQPPSVSVAPGQTARITCGGNNIGSKNVYWYQQKPGQAPVLVVH
AAAAAAAAAA
SSSSSS SSSS
LLLLLLLLLL
YYYYYYYYYY
DDDDDDDDDD
QQQQQQQQQQ
KKKKKK KKK
HHHHHHHHHH
WWWWWWWWW
CDR2
DDSDRPSGIPERFSGSNSGNTATLTISRVEVGDEA
AAAAAAA
SS SSS
LLLLLLL
YYYYYYY
D DDD
QQQQQQQ
KKKKKKK
HHHHHHH
WWWWWWW
CDR3
DYSCQVWDSSSDHVVFGGGTKLTVLG
AAAAAAAAAA
SSSS SSSS
LLLLLLLLLL
YYYYYYYYYY
DDD DDD DDD
QQQQQQQQQQ
KKKKKKKKKK
HHHHHHHH HH
WW WWWWWWW
PPPPPPPPPP

FIG. 4

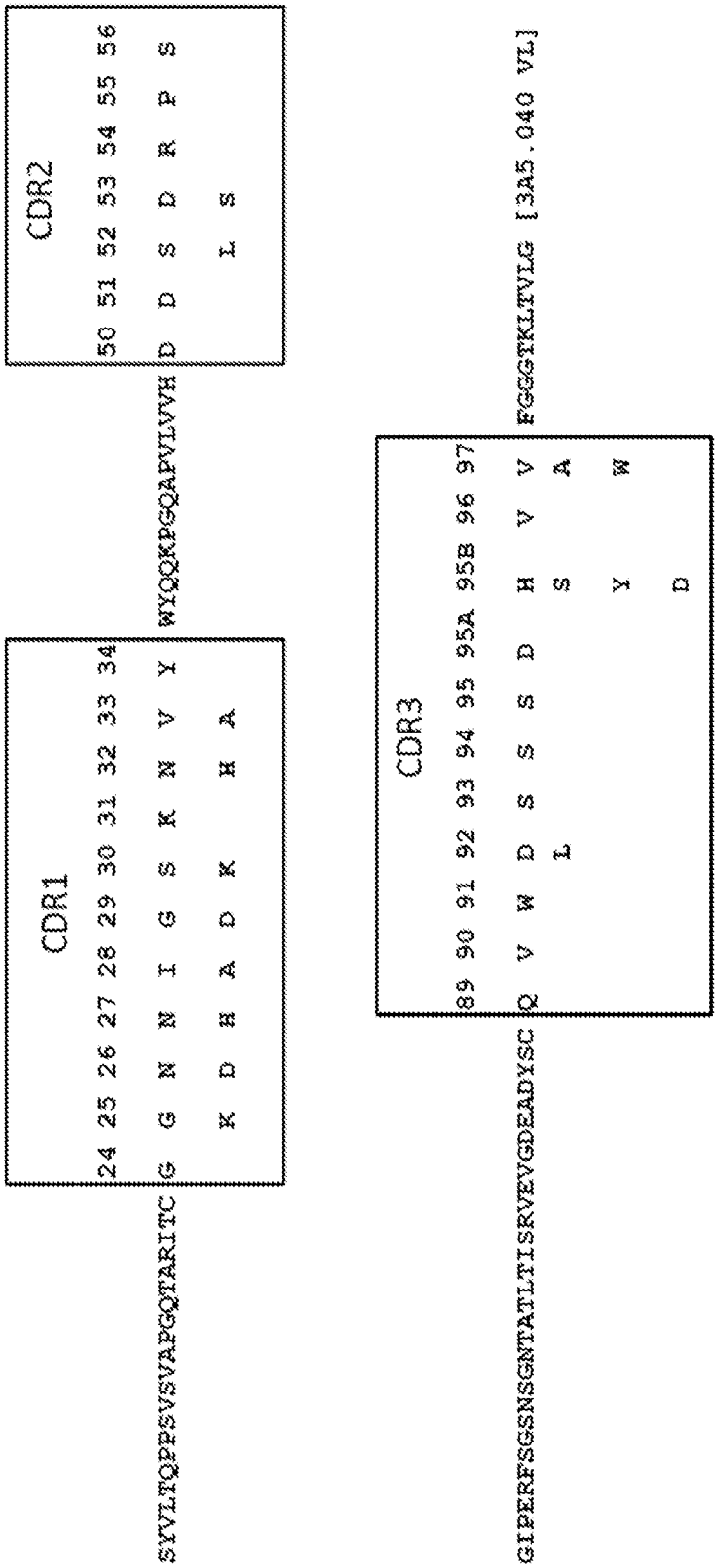

CDR1
24 25 26 27 28 29 30 31 32 33 34
G N N I G S K N V Y
K D H A D K H A
SYVLTQPPSVSVAPGQTARITC
CDR2
50 51 52 53 54 55 56
D D S D R P S
L S
WYQQKPGQAPVLVVH
CDR3
89 90 91 92 93 94 95 95A 95B 96 97
Q V W D S S S D H V V
L S A
Y W
D
GIPERFSGSNSGNTATLTISRVEVGDEADYSC
FGGGTKLTVLG [3A5.040 VL]

FIG. 5

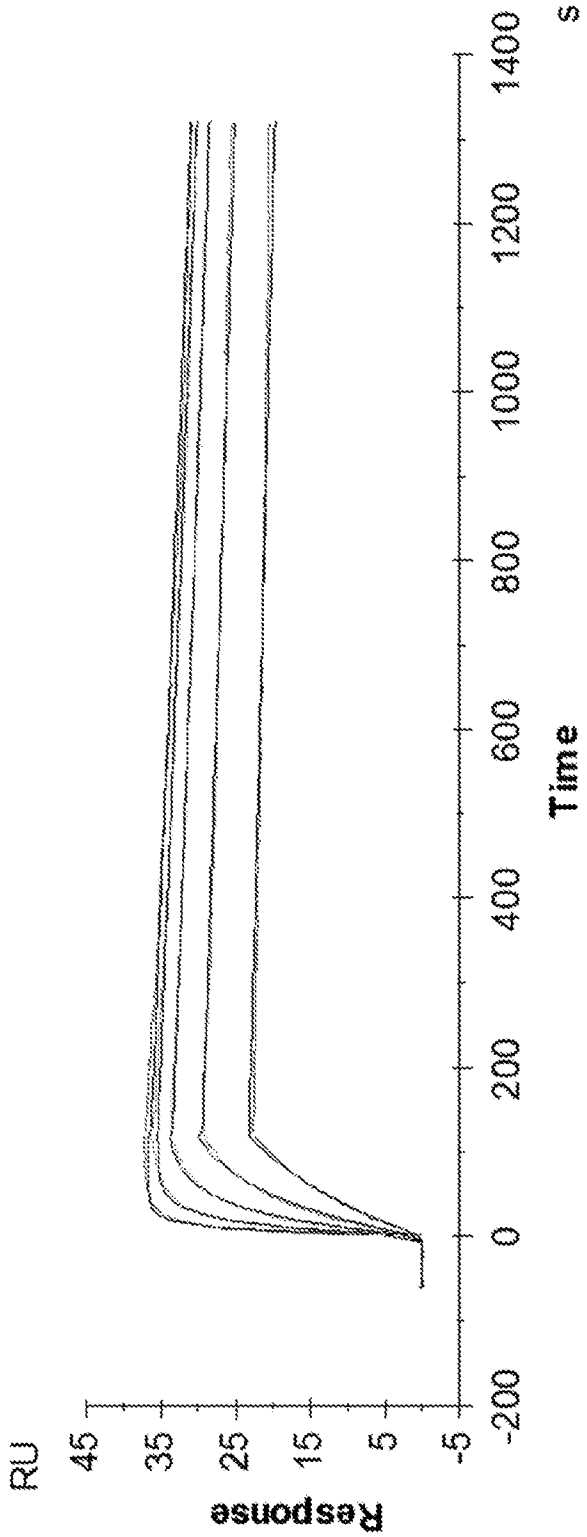

RU
45
35
25
15
5
-5
Response
-200
0
200
400
600
800
1000
1200
1400
s
Time

FIG. 6

FIG. 7A

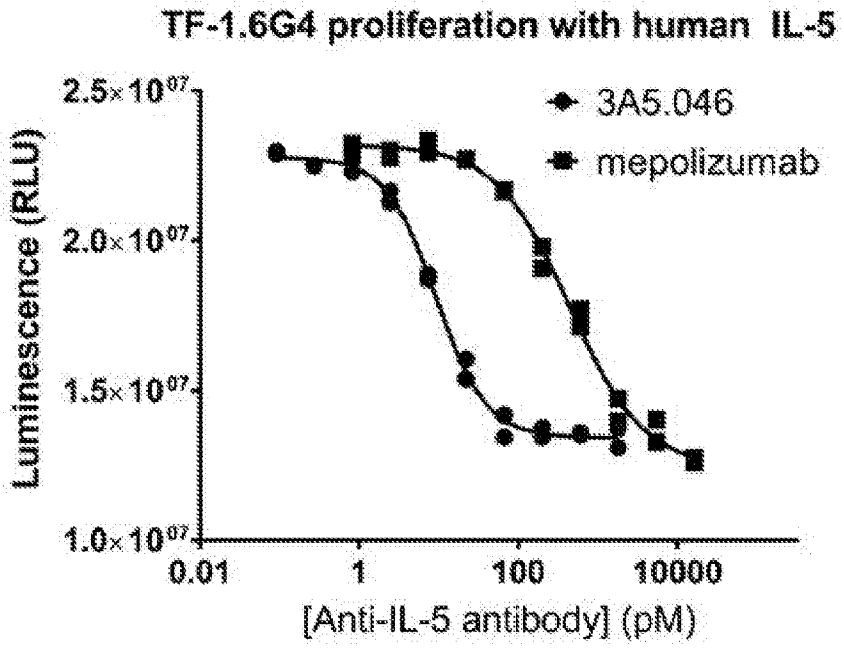

TF-1.6G4 proliferation with human IL-5
Luminescence (RLU)
2.5×10^07
2.0×10^07
1.5×10^07
1.0×10^07
0.01
1
100
10000
[Anti-IL-5 antibody] (pM)
3A5.046
mepolizumab

FIG. 7B

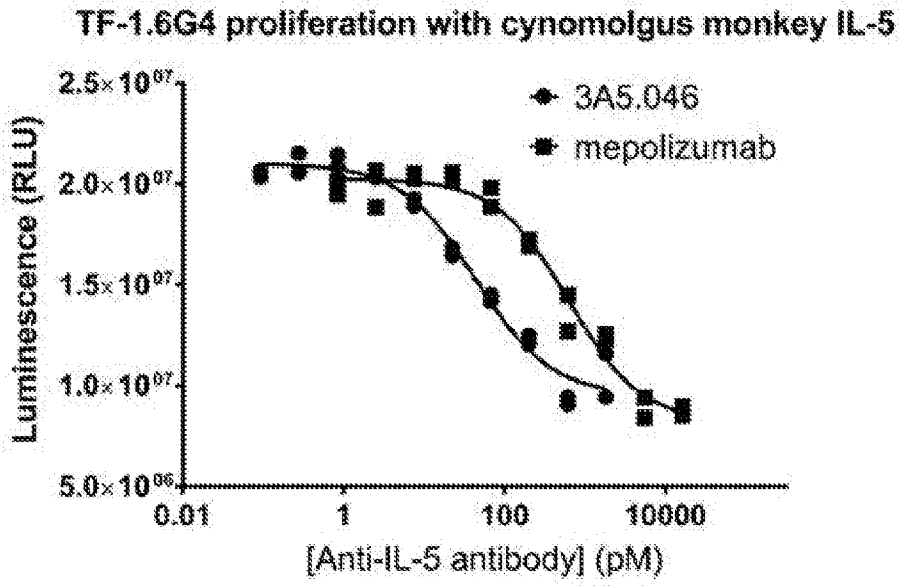

TF-1.6G4 proliferation with cynomolgus monkey IL-5
Luminescence (RLU)
2.5×10^07
2.0×10^07
1.5×10^07
1.0×10^07
5.0×10^06
0.01
1
100
10000
[Anti-IL-5 antibody] (pM)
3A5.046
mepolizumab

FIG. 8A

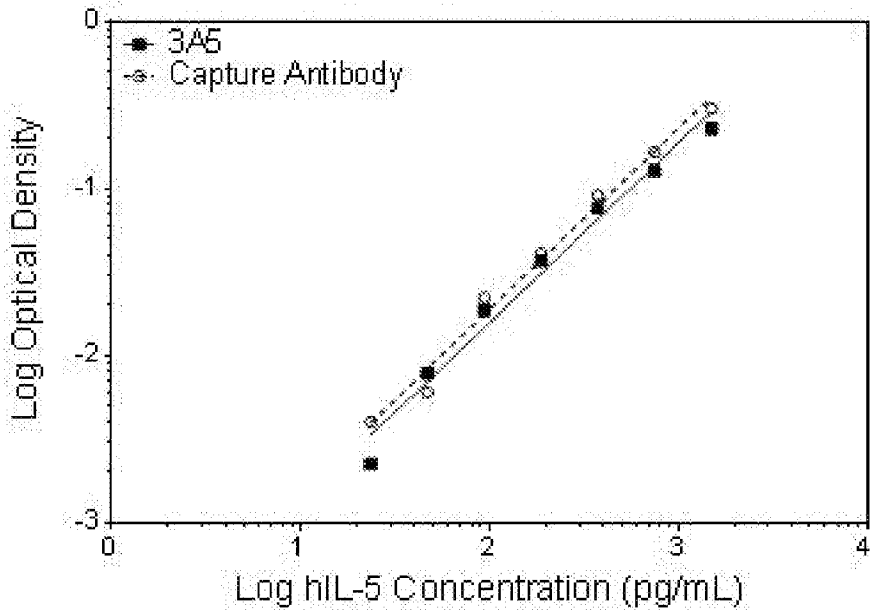

3A5
Capture Antibody
Log Optical Density
Log hIL-5 Concentration (pg/mL)
0
-1
-2
-3
0
1
2
3
4

FIG. 8B

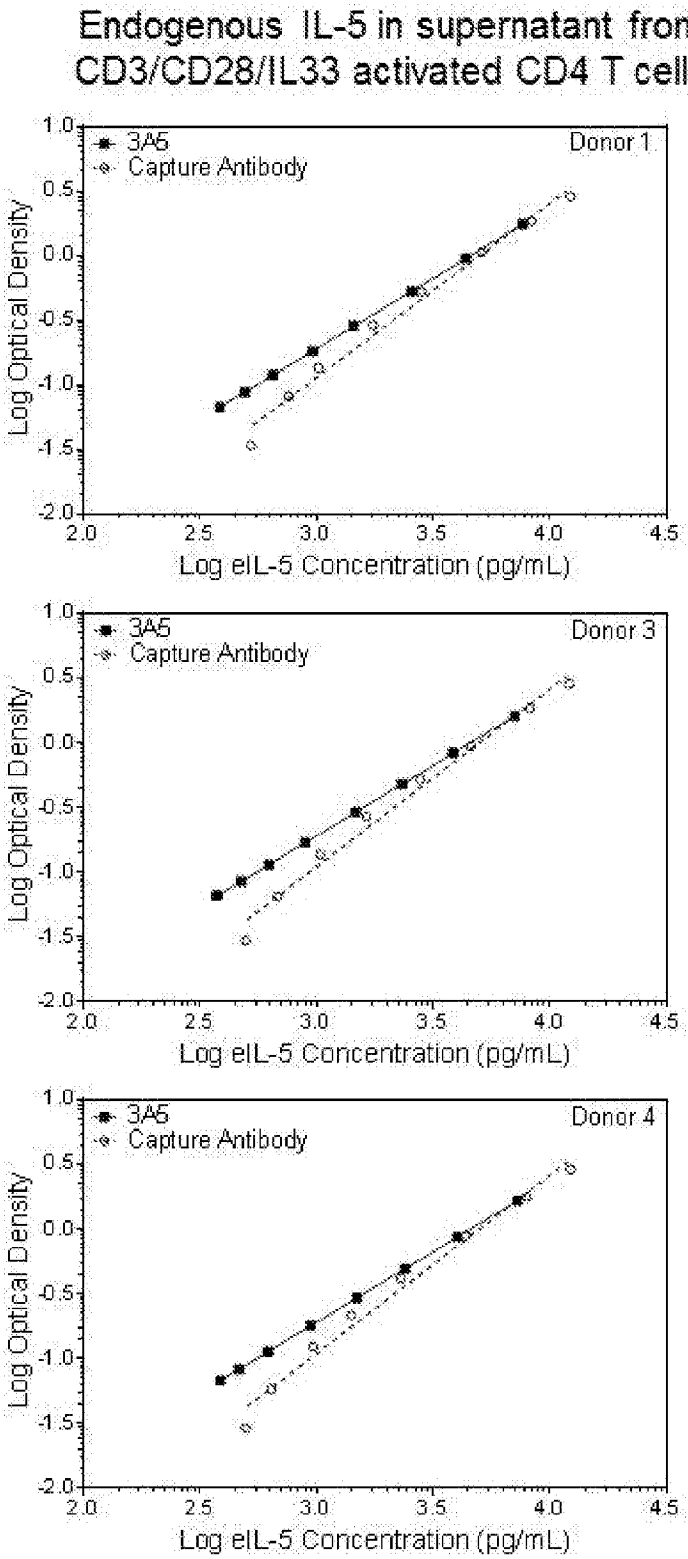

Endogenous IL-5 in supernatant from CD3/CD28/IL33 activated CD4 T cells
3A5
Capture Antibody
Donor 1
Donor 3
Donor 4
Log Optical Density
Log eIL-5 Concentration (pg/mL)
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
2.0
2.5
3.0
3.5
4.0
4.5

FIG. 9

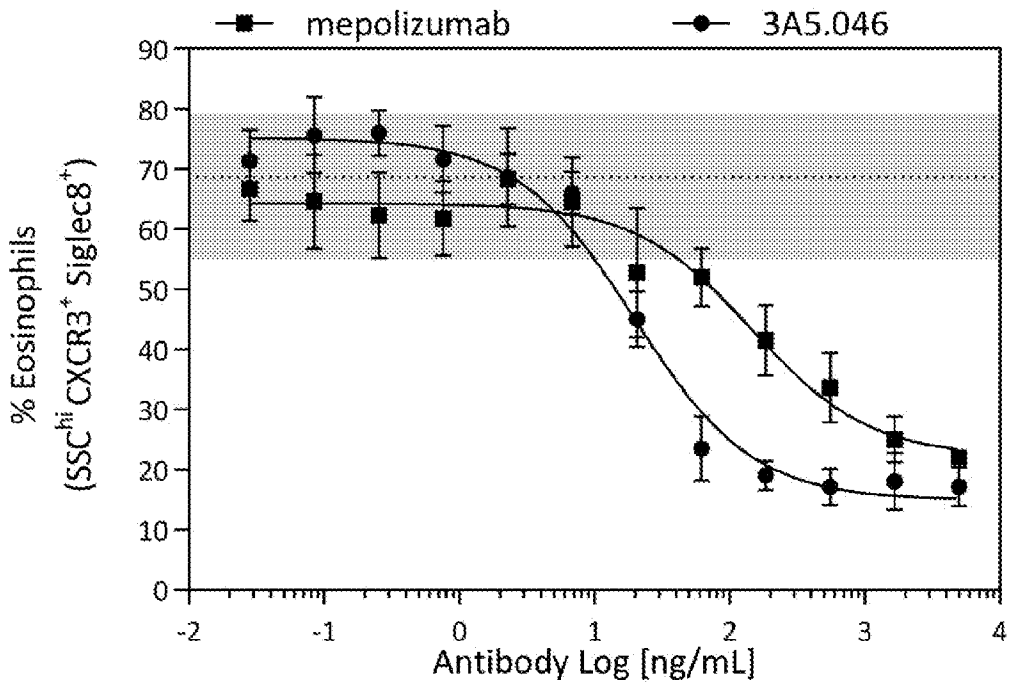

mepolizumab
3A5.046
% Eosinophils
(SSC^hi CXCR3^+ Siglec8^+)
90
80
70
60
50
40
30
20
10
0
-2
-1
0
1
2
3
4
Antibody Log [ng/mL]

FIG. 10A

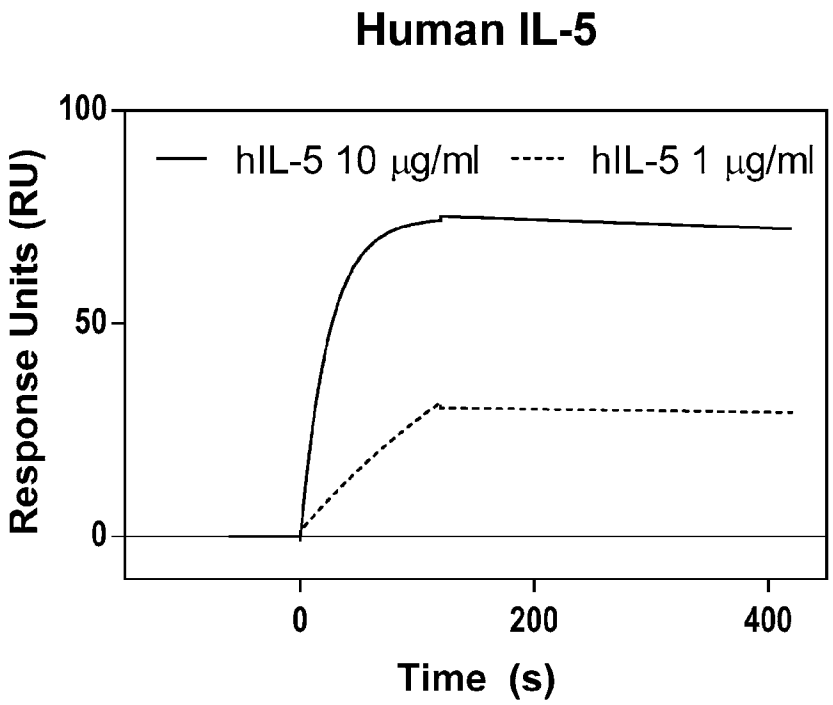


FIG. 10B

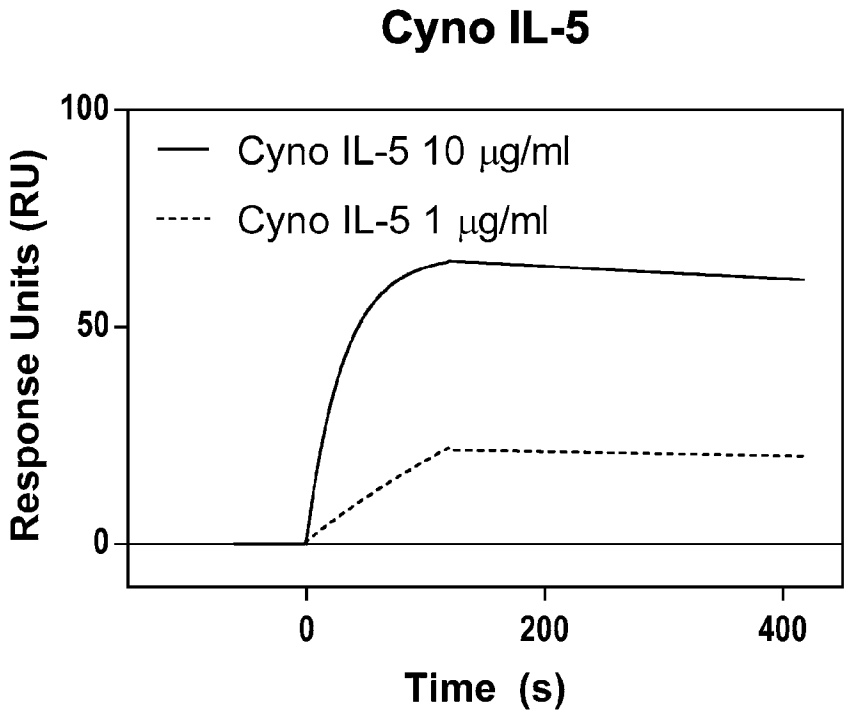


FIG. 10C

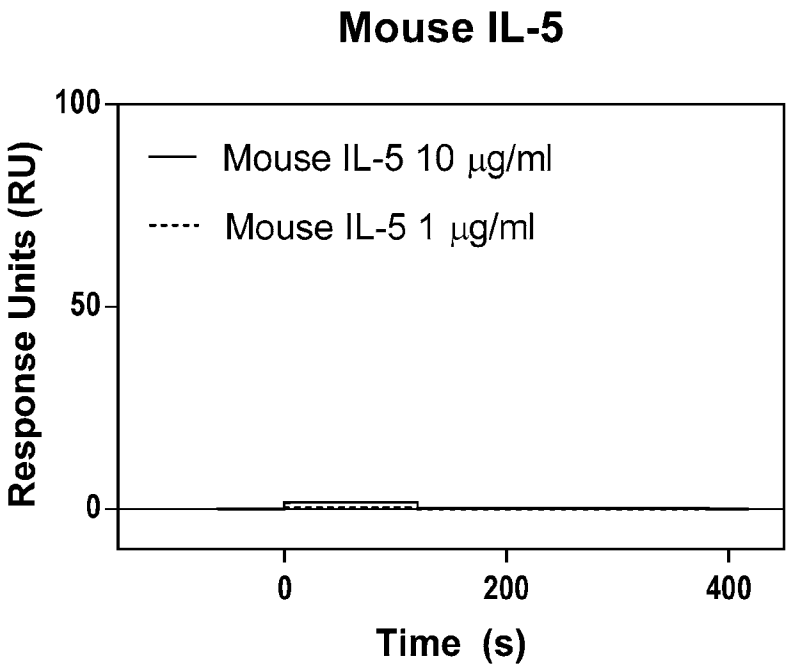


FIG. 10D

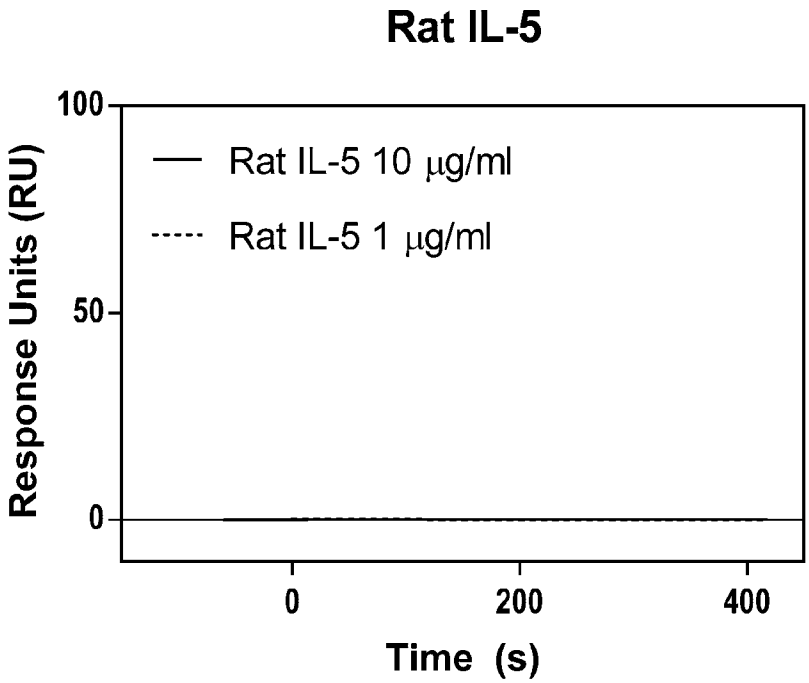


FIG. 10E

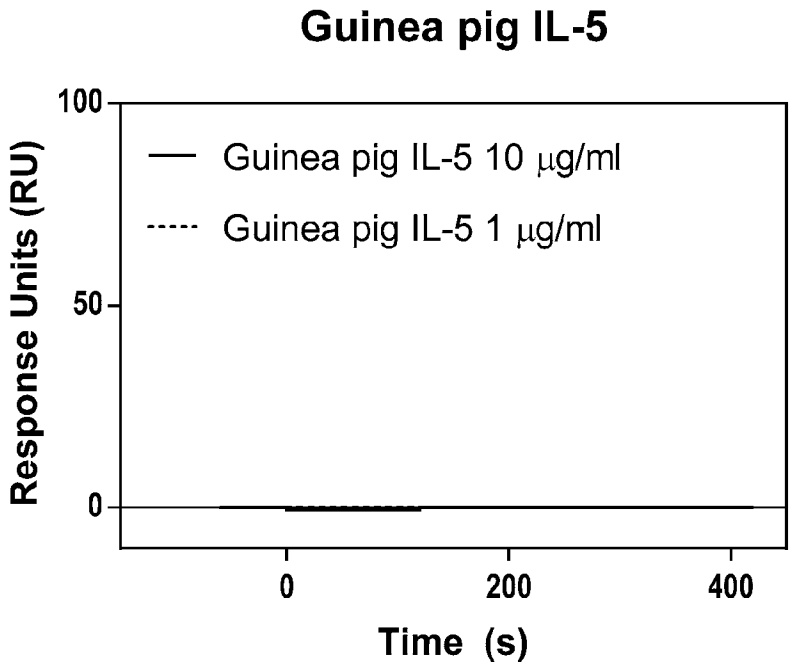

Guinea pig IL-5
Response Units (RU)
100
50
0
Guinea pig IL-5 10 μg/ml
Guinea pig IL-5 1 μg/ml
0
200
400
Time (s)

FIG. 11A

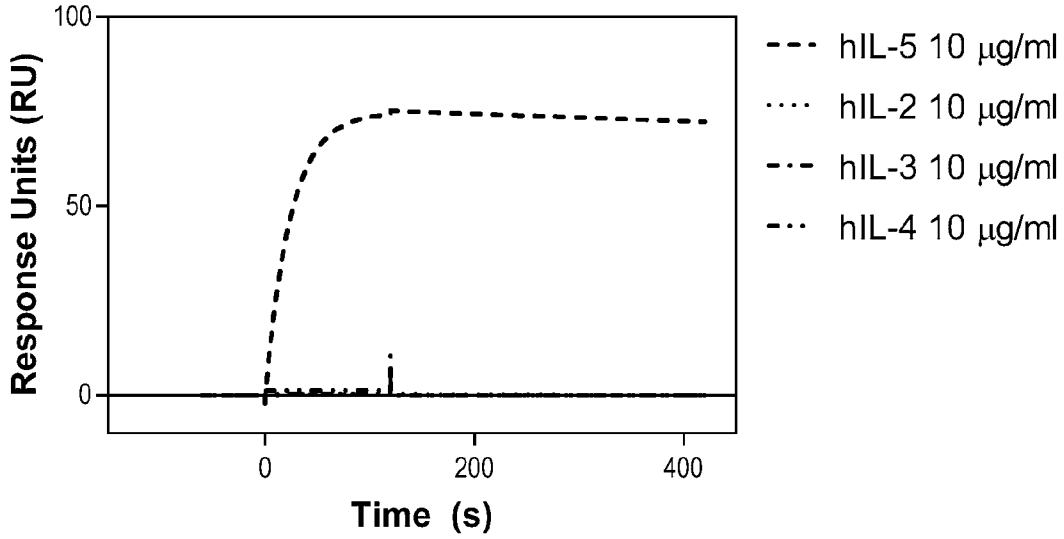


FIG. 11B

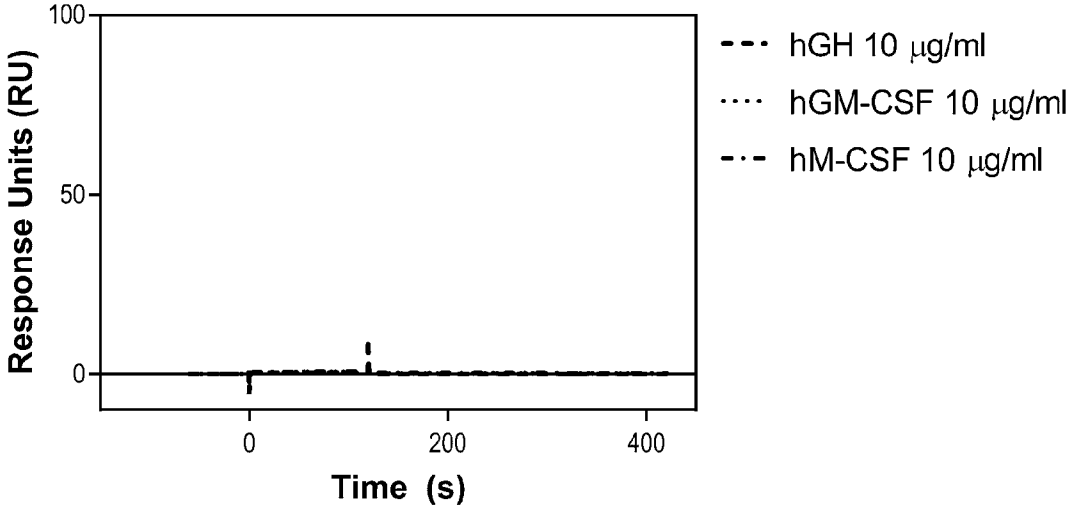


FIG. 11C

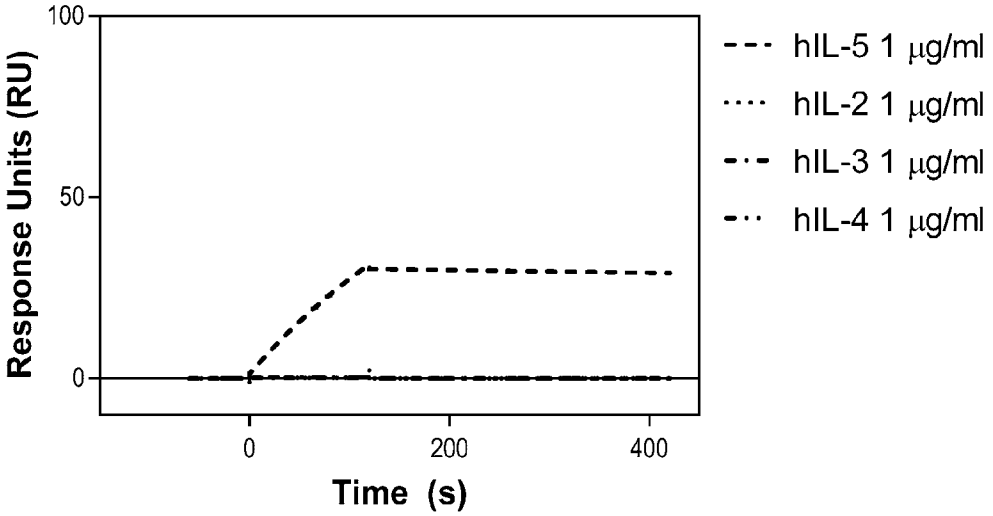


FIG. 11D

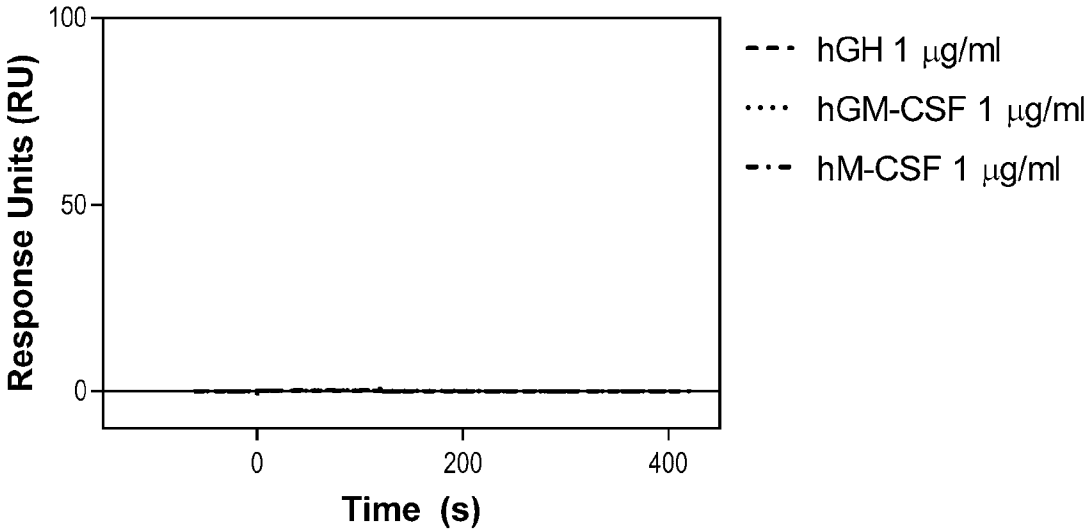


FIG. 12

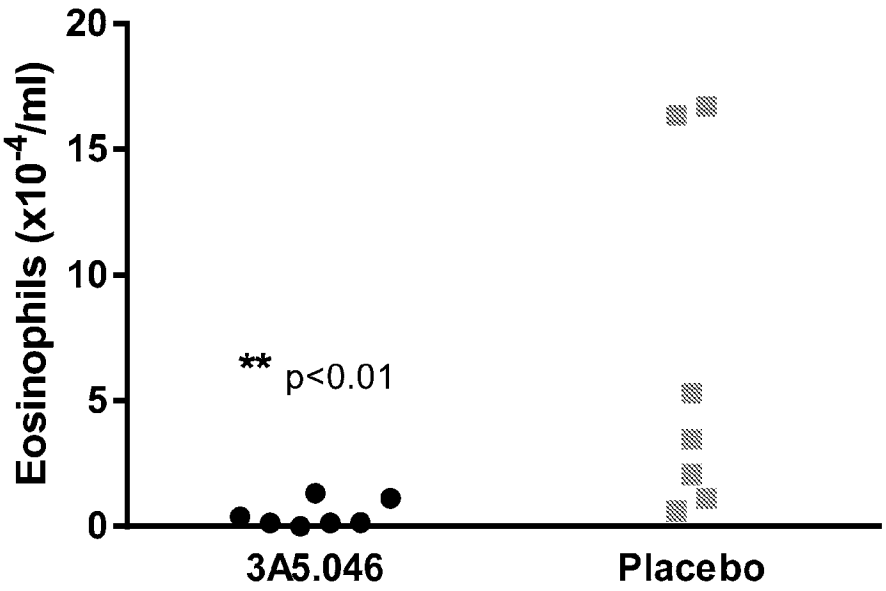


FIG. 13A

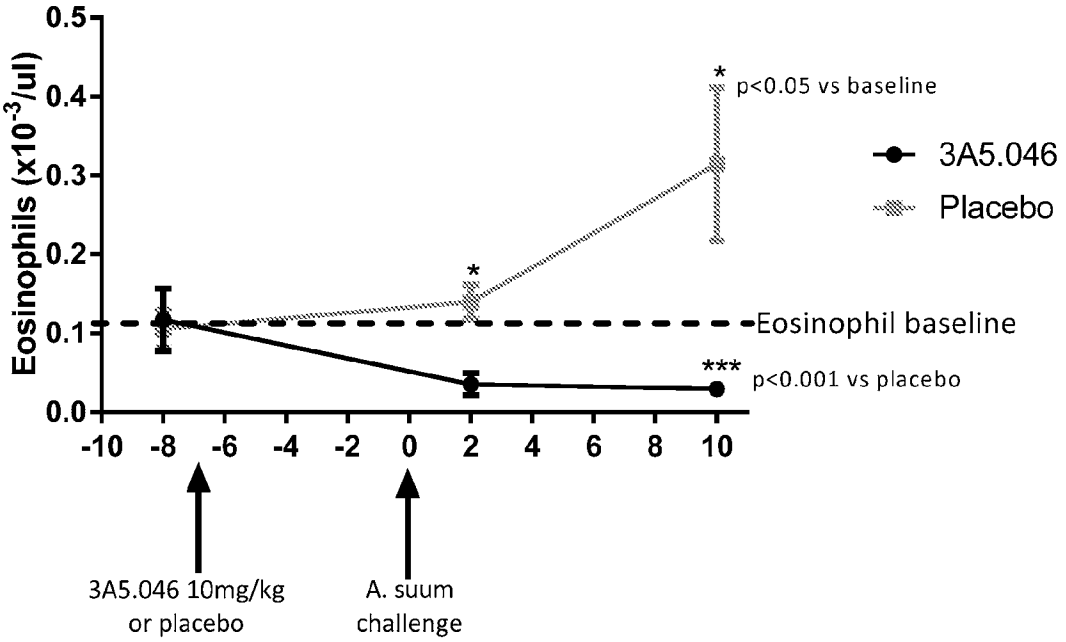


FIG. 13B

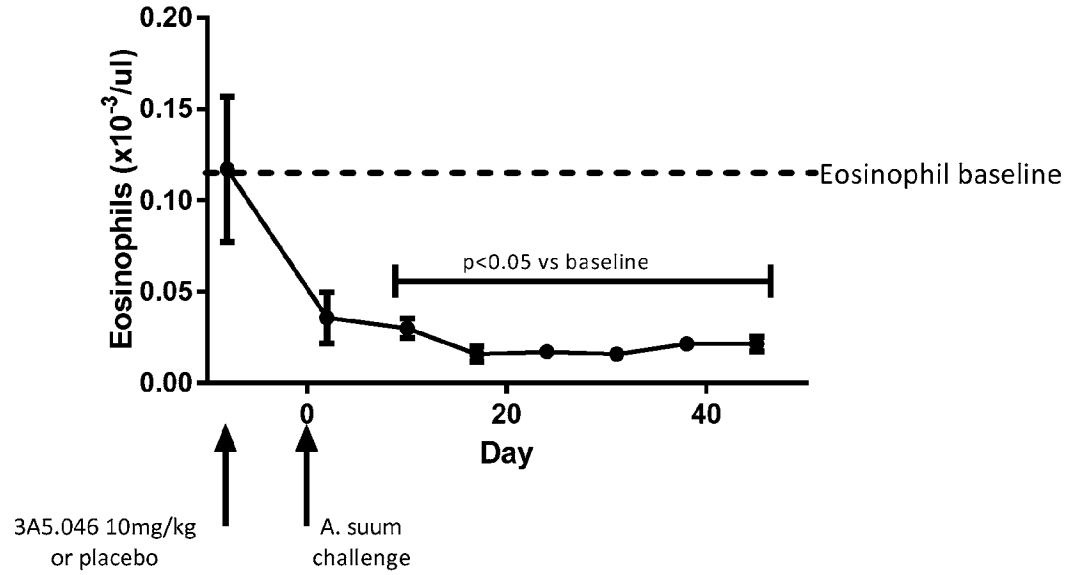
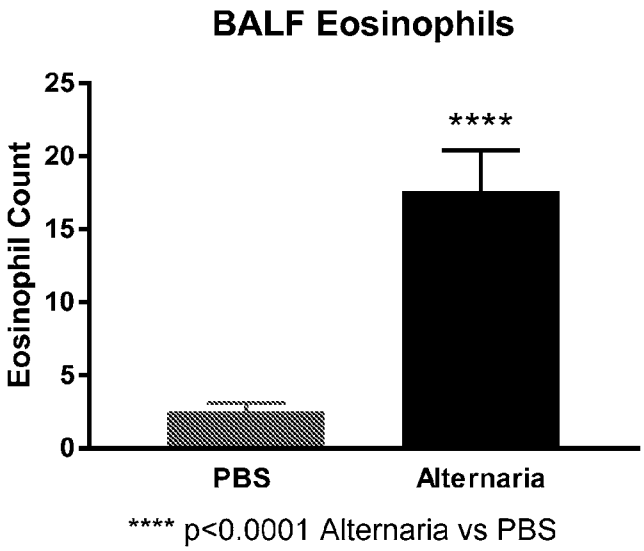


FIG. 14


BALF Eosinophils
Eosinophil Count
25
20
15
10
5
0
****
PBS
Alternaria
**** p<0.0001 Alternaria vs PBS

SEQUENCE LISTING

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<120> ANTI-IL-5 ANTIBODIES

<130> 102085.000906

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<223> Asn or Asp

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<223> Ile or Ala

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1   5   10

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      peptide

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Gln Val Trp Xaa Ser Ser Ser Asp Xaa Val Xaa
1 5 10

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1 5 10

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peptide

<400> 5
Gly Gly Asn Asn Ile Gly Ser Lys Asn Val Tyr
1 5 10

<210> 6
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Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr
1 5

<210> 7
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Asp Asp Ser Asp Arg Pro Ser
1 5

<210> 8
<211> 7
<212> PRT
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Leu Gly Asn Trp Phe Asp Tyr
1 5

<210> 9
<211> 11
<212> PRT
<213> Artificial Sequence

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<400> 9

Gln Val Trp Tyr Ser Ser Ser Asp His Val Val
1 5 10

<210> 10
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<400> 10
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Asn Gly
20 25 30

Gly Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
35 40 45

Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Arg Val Ser 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 Ser Leu Gly Asn Trp Phe Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 11
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Ser Ser Ile 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 Asn Val
            20                  25                  30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val His
        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 Val Gly
65                  70                  75                  80

Asp Glu Ala Asp Tyr Ser Cys Gln Val Trp Tyr Ser Ser Ser Asp His
                85                  90                  95

Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105
```

<210> 12
<211> 446
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 12

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Asn Gly
            20                  25                  30

Gly Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
        35                  40                  45
```

```
Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
    50                  55                  60

Leu Lys Ser Arg Val Ser 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 Ser Leu Gly Asn Trp Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

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

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
    130                 135                 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145                 150                 155                 160

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

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

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
        195                 200                 205

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His
    210                 215                 220

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

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

```
Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
            260                 265                 270

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

Thr Lys Pro Arg Glu Glu Gln Tyr 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 Ala Leu Pro Ala Pro 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 Arg Asp Glu Leu 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 Lys Leu Thr Val Asp Lys Ser Arg
                405                 410                 415

Trp Gln Gln 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 Pro Gly
        435                 440                 445
```

<210> 13
<211> 214

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 13

```
Ser Ser Ile 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 Asn Val
            20                  25                  30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val His
        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 Val Gly
65                  70                  75                  80

Asp Glu Ala Asp Tyr Ser Cys Gln Val Trp Tyr Ser Ser Ser Asp His
                85                  90                  95

Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
            100                 105                 110

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
        115                 120                 125

Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
    130                 135                 140

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145                 150                 155                 160

Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
                165                 170                 175
```

Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
180 185 190

Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195 200 205

Ala Pro Thr Glu Cys Ser
210

<210> 14
<211> 443
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 14
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Asn Gly
20 25 30

Gly Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
35 40 45

Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Arg Val Ser 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 Ser Leu Gly Asn Trp Phe Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

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

```
Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys
    130                 135                 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145                 150                 155                 160

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

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

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

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

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

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

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

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
        275                 280                 285

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

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

Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala
                325                 330                 335
```

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

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

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

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

Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu
                405                 410                 415

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

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
        435                 440
```

<210> 15
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 15
```
Gln Val Trp Asp Ser Ser Ser Asp His Val Val
1               5                   10
```

<210> 16
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 16
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Asn Gly
20 25 30

Gly Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
35 40 45

Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65 70 75 80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95

Cys Ala Ser Leu Gly Asn Trp Phe Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 17
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 17
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 Asn Val
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val His
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 Val Gly
65 70 75 80

Asp Glu Ala Asp Tyr Ser 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 Gly
100 105

<210> 18
<211> 443
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 18
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Asn Gly
20 25 30

Gly Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
35 40 45

Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65 70 75 80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95

```
Cys Ala Ser Leu Gly Asn Trp Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

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

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

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145                 150                 155                 160

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

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

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

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

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

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

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

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
        275                 280                 285

Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
    290                 295                 300
```

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


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


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


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


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


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


Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu
                405                 410                 415


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


Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
        435                 440


<210> 19
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 19
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 Asn Val
            20                  25                  30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val His
        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 Val Gly
65                  70                  75                  80

Asp Glu Ala Asp Tyr Ser 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 Gly Gln Pro Lys
            100                 105                 110

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
        115                 120                 125

Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
    130                 135                 140

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145                 150                 155                 160

Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
                165                 170                 175

Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
            180                 185                 190

Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
        195                 200                 205

Ala Pro Thr Glu Cys Ser
    210
```

<210> 20
<211> 443
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 20

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Asn Gly
            20                  25                  30

Gly Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
        35                  40                  45

Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
    50                  55                  60

Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65                  70                  75                  80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
                85                  90                  95

Cys Ala Ser Leu Gly Asn Trp Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

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

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

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145                 150                 155                 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
                165                 170                 175
```

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

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

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

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

Pro Pro Lys Pro Lys Asp Thr Leu Tyr Ile Thr Arg Glu Pro Glu Val
                245                 250                 255

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

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
        275                 280                 285

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

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

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

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

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

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

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

Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu
405 410 415

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

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
435 440

<210> 21
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 21
Gly Lys Asn Asn Ile Gly Ser Lys Asn Val Tyr
1 5 10

<210> 22
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 22
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 Lys Asn Asn Ile Gly Ser Lys Asn Val
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val His
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 Val Gly
65                  70                  75                  80

Asp Glu Ala Asp Tyr Ser 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 Gly
            100                 105
```

<210> 23
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 23

```
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 Lys Asn Asn Ile Gly Ser Lys Asn Val
            20                  25                  30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val His
        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 Val Gly
65                  70                  75                  80

Asp Glu Ala Asp Tyr Ser 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 Gly Gln Pro Lys
            100                 105                 110


Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
        115                 120                 125


Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
    130                 135                 140


Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145                 150                 155                 160


Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
                165                 170                 175


Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
            180                 185                 190


Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
        195                 200                 205


Ala Pro Thr Glu Cys Ser
    210


<210> 24
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 24
Gly Gly Asp Asn Ile Gly Ser Lys Asn Val Tyr
1               5                   10


<210> 25
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
```

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 25

```
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 Asp Asn Ile Gly Ser Lys Asn Val
            20                  25                  30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val His
        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 Val Gly
65                  70                  75                  80

Asp Glu Ala Asp Tyr Ser 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 Gly
            100                 105
```

<210> 26
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 26

```
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 Asp Asn Ile Gly Ser Lys Asn Val
            20                  25                  30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val His
        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 Val Gly
65                  70                  75                  80

Asp Glu Ala Asp Tyr Ser 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 Gly Gln Pro Lys
            100                 105                 110

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
        115                 120                 125

Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
    130                 135                 140

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145                 150                 155                 160

Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
                165                 170                 175

Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
            180                 185                 190

Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
        195                 200                 205

Ala Pro Thr Glu Cys Ser
    210
```

<210> 27
<211> 11
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
peptide

<400> 27
Gly Gly Asn His Ile Gly Ser Lys Asn Val Tyr
1 5 10

<210> 28
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 28
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 His Ile Gly Ser Lys Asn Val
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val His
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 Val Gly
65 70 75 80

Asp Glu Ala Asp Tyr Ser 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 Gly
100 105

<210> 29
<211> 214
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 29

```
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 His Ile Gly Ser Lys Asn Val
            20                  25                  30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val His
        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 Val Gly
65                  70                  75                  80

Asp Glu Ala Asp Tyr Ser 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 Gly Gln Pro Lys
            100                 105                 110

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
        115                 120                 125

Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
    130                 135                 140

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145                 150                 155                 160

Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
                165                 170                 175

Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
            180                 185                 190
```

Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195 200 205

Ala Pro Thr Glu Cys Ser
210

<210> 30
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 30
Gly Gly Asn Asn Ala Gly Ser Lys Asn Val Tyr
1 5 10

<210> 31
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 31
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 Ala Gly Ser Lys Asn Val
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val His
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 Val Gly
65 70 75 80

Asp Glu Ala Asp Tyr Ser 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 Gly
100 105

<210> 32
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 32
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 Ala Gly Ser Lys Asn Val
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val His
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 Val Gly
65 70 75 80

Asp Glu Ala Asp Tyr Ser 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 Gly Gln Pro Lys
100 105 110

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115 120 125

Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130 135 140

```
Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145                 150                 155                 160


Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
                165                 170                 175


Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
            180                 185                 190


Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
        195                 200                 205


Ala Pro Thr Glu Cys Ser
    210


<210> 33
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 33
Gly Gly Asn Asn Ile Gly Lys Lys Asn Val Tyr
1               5                   10


<210> 34
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 34
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 Lys Lys Asn Val
            20                  25                  30
```

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val His
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 Val Gly
65 70 75 80

Asp Glu Ala Asp Tyr Ser 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 Gly
100 105

<210> 35
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 35
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 Lys Lys Asn Val
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val His
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 Val Gly
65 70 75 80

```
Asp Glu Ala Asp Tyr Ser 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 Gly Gln Pro Lys
            100                 105                 110


Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
        115                 120                 125


Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
    130                 135                 140


Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145                 150                 155                 160


Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
                165                 170                 175


Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
            180                 185                 190


Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
        195                 200                 205


Ala Pro Thr Glu Cys Ser
    210


<210> 36
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 36
Gly Gly Asn Asn Ile Gly Ser Lys His Val Tyr
1               5                   10


<210> 37
<211> 109
```

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 37
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 His Val
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val His
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 Val Gly
65 70 75 80

Asp Glu Ala Asp Tyr Ser 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 Gly
100 105

<210> 38
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 38
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 His Val
20 25 30

```
Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val His
        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 Val Gly
65                  70                  75                  80

Asp Glu Ala Asp Tyr Ser 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 Gly Gln Pro Lys
            100                 105                 110

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
        115                 120                 125

Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
    130                 135                 140

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145                 150                 155                 160

Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
                165                 170                 175

Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
            180                 185                 190

Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
        195                 200                 205

Ala Pro Thr Glu Cys Ser
    210
```

<210> 39
<211> 11

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 39
Gly Gly Asn Asn Ile Gly Ser Lys Asn Ala Tyr
1 5 10

<210> 40
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 40
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 Asn Ala
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val His
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 Val Gly
65 70 75 80

Asp Glu Ala Asp Tyr Ser 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 Gly
100 105

<210> 41
<211> 214

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 41

```
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 Asn Ala
            20                  25                  30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val His
        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 Val Gly
65                  70                  75                  80

Asp Glu Ala Asp Tyr Ser 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 Gly Gln Pro Lys
            100                 105                 110

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
        115                 120                 125

Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
    130                 135                 140

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145                 150                 155                 160

Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
                165                 170                 175
```

Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
180 185 190

Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195 200 205

Ala Pro Thr Glu Cys Ser
210

<210> 42
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 42
Asp Asp Leu Asp Arg Pro Ser
1 5

<210> 43
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 43
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 Asn Val
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val His
35 40 45

Asp Asp Leu 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 Val Gly
65 70 75 80

Asp Glu Ala Asp Tyr Ser 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 Gly
100 105

<210> 44
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 44
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 Asn Val
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val His
35 40 45

Asp Asp Leu 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 Val Gly
65 70 75 80

Asp Glu Ala Asp Tyr Ser 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 Gly Gln Pro Lys
100 105 110

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115 120 125

```
Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
    130                 135                 140


Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145                 150                 155                 160


Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
                165                 170                 175


Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
            180                 185                 190


Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
        195                 200                 205


Ala Pro Thr Glu Cys Ser
    210


<210> 45
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 45
Asp Asp Ser Ser Arg Pro Ser
1               5


<210> 46
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 46
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 Asn Val
            20                  25                  30


Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val His
        35                  40                  45


Asp Asp Ser Ser 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 Val Gly
65                  70                  75                  80


Asp Glu Ala Asp Tyr Ser 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 Gly
            100                 105


<210> 47
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 47
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 Asn Val
            20                  25                  30


Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val His
        35                  40                  45


Asp Asp Ser Ser 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 Val Gly
65                  70                  75                  80


Asp Glu Ala Asp Tyr Ser 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 Gly Gln Pro Lys
            100                 105                 110


Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
        115                 120                 125


Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
    130                 135                 140


Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145                 150                 155                 160


Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
                165                 170                 175


Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
            180                 185                 190


Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
        195                 200                 205


Ala Pro Thr Glu Cys Ser
    210


<210> 48
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 48
Gln Val Trp Leu Ser Ser Ser Asp His Val Val
1               5                   10
```

<210> 49
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 49
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 Asn Val
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val His
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 Val Gly
65 70 75 80

Asp Glu Ala Asp Tyr Ser Cys Gln Val Trp Leu Ser Ser Ser Asp His
85 90 95

Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105

<210> 50
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 50
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 Asn Val
            20                  25                  30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val His
        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 Val Gly
65                  70                  75                  80

Asp Glu Ala Asp Tyr Ser Cys Gln Val Trp Leu Ser Ser Ser Asp His
                85                  90                  95

Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
            100                 105                 110

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
        115                 120                 125

Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
    130                 135                 140

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145                 150                 155                 160

Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
                165                 170                 175

Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
            180                 185                 190

Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
        195                 200                 205

Ala Pro Thr Glu Cys Ser
    210
```

<210> 51
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 51
Gln Val Trp Asp Ser Ser Ser Asp Ser Val Val
1 5 10

<210> 52
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 52
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 Asn Val
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val His
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 Val Gly
65 70 75 80

Asp Glu Ala Asp Tyr Ser Cys Gln Val Trp Asp Ser Ser Ser Asp Ser
85 90 95

Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105

<210> 53
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 53
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 Asn Val
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val His
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 Val Gly
65 70 75 80

Asp Glu Ala Asp Tyr Ser Cys Gln Val Trp Asp Ser Ser Ser Asp Ser
85 90 95

Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
100 105 110

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115 120 125

Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130 135 140

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145 150 155 160

```
Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
                165                 170                 175


Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
            180                 185                 190


Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
        195                 200                 205


Ala Pro Thr Glu Cys Ser
    210


<210> 54
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 54
Gln Val Trp Asp Ser Ser Ser Asp Tyr Val Val
1               5                   10


<210> 55
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 55
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 Asn Val
            20                  25                  30


Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val His
        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 Val Gly
65 70 75 80

Asp Glu Ala Asp Tyr Ser Cys Gln Val Trp Asp Ser Ser Ser Asp Tyr
85 90 95

Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105

<210> 56
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 56
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 Asn Val
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val His
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 Val Gly
65 70 75 80

Asp Glu Ala Asp Tyr Ser Cys Gln Val Trp Asp Ser Ser Ser Asp Tyr
85 90 95

Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
100 105 110

```
Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
        115                 120                 125


Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
    130                 135                 140


Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145                 150                 155                 160


Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
                165                 170                 175


Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
            180                 185                 190


Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
        195                 200                 205


Ala Pro Thr Glu Cys Ser
    210


<210> 57
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 57
Gln Val Trp Asp Ser Ser Ser Asp Asp Val Val
1               5                   10


<210> 58
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide
```

<400> 58
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 Asn Val
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val His
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 Val Gly
65 70 75 80

Asp Glu Ala Asp Tyr Ser Cys Gln Val Trp Asp Ser Ser Ser Asp Asp
85 90 95

Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105

<210> 59
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 59
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 Asn Val
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val His
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 Val Gly
65                  70                  75                  80

Asp Glu Ala Asp Tyr Ser Cys Gln Val Trp Asp Ser Ser Ser Asp Asp
                85                  90                  95

Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
            100                 105                 110

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
        115                 120                 125

Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
    130                 135                 140

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145                 150                 155                 160

Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
                165                 170                 175

Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
            180                 185                 190

Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
        195                 200                 205

Ala Pro Thr Glu Cys Ser
    210
```

<210> 60
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 60
Gln Val Trp Asp Ser Ser Ser Asp His Val Ala
1 5 10

<210> 61
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 61
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 Asn Val
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val His
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 Val Gly
65 70 75 80

Asp Glu Ala Asp Tyr Ser Cys Gln Val Trp Asp Ser Ser Ser Asp His
85 90 95

Val Ala Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105

<210> 62
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 62

```
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 Asn Val
            20                  25                  30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val His
        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 Val Gly
65                  70                  75                  80

Asp Glu Ala Asp Tyr Ser Cys Gln Val Trp Asp Ser Ser Ser Asp His
                85                  90                  95

Val Ala Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
            100                 105                 110

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
        115                 120                 125

Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
    130                 135                 140

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145                 150                 155                 160

Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
                165                 170                 175

Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
            180                 185                 190

Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
        195                 200                 205
```

Ala Pro Thr Glu Cys Ser
    210

<210> 63
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      peptide

<400> 63
Gln Val Trp Asp Ser Ser Ser Asp His Val Trp
1   5   10

<210> 64
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<400> 64
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 Asn Val
            20   25   30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val His
        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 Val Gly
65   70   75   80

Asp Glu Ala Asp Tyr Ser Cys Gln Val Trp Asp Ser Ser Ser Asp His
                85   90   95

Val Trp Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105

<210> 65
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 65
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 Asn Val
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val His
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 Val Gly
65 70 75 80

Asp Glu Ala Asp Tyr Ser Cys Gln Val Trp Asp Ser Ser Ser Asp His
85 90 95

Val Trp Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
100 105 110

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115 120 125

Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130 135 140

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145 150 155 160

Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
165 170 175

Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
180 185 190

Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195 200 205

Ala Pro Thr Glu Cys Ser
210

<210> 66
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 66
Gly Gly Asn Asn Ile Asp Ser Lys Asn Val Tyr
1 5 10

<210> 67
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 67
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 Asp Ser Lys Asn Val
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val His
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 Val Gly
65 70 75 80

Asp Glu Ala Asp Tyr Ser 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 Gly
100 105

<210> 68
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 68
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 Asp Ser Lys Asn Val
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val His
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 Val Gly
65 70 75 80

Asp Glu Ala Asp Tyr Ser Cys Gln Val Trp Asp Ser Ser Ser Asp His
85 90 95

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Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
            100                 105                 110


Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
        115                 120                 125


Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
    130                 135                 140


Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145                 150                 155                 160


Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
                165                 170                 175


Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
            180                 185                 190


Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
        195                 200                 205


Ala Pro Thr Glu Cys Ser
    210


<210> 69
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polynucleotide

<400> 69
caggtgcagc tgcaggaatc tggccctggc ctggtcaagc ccagccagac cctgagcctg       60

acctgtaccg tgtccggcgg cagcatcagc aacggcggct actactggtc ctggatcaga      120

cagcaccccg gcaagggcct ggaatggatc ggctacatct actacagcgg cagcacctac      180

tacaacccca gcctgaagtc cagagtgacc atcagcgtgg acaccagcaa gaaccagttc      240
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agcctgaagc tgagcagcgt gacagccgcc gacaccgccg tgtactactg cgccagcctg 300

ggcaattggt tcgactactg gggccagggc accctcgtga cagtgtcctc a 351

<210> 70
<211> 978
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 70
gctagcacca agggccccag cgtgttcccc ctggcccctt gtagcagaag caccagcgag 60

agcacagccg ccctgggctg cctggtgaaa gactacttcc ccgagcccgt caccgtgtcc 120

tggaacagcg gagccctgac cagcggcgtg cacacctttc cagccgtgct gcagagcagc 180

ggcctgtaca gcctgagcag cgtggtgaca gtgccctcca gcagcctggg caccaagacc 240

tacacctgta acgtggacca caagcccagc aacaccaagg tggacaagcg ggtggaatct 300

aagtacggcc caccctgccc cccctgccct gcccctgaat ttctgggcgg accctccgtg 360

ttcctgttcc ccccaaagcc caaggacacc ctgtatatca ctcgggagcc cgaagtgacc 420

tgcgtggtgg tggacgtgtc ccaggaagat cccgaggtcc agttcaattg gtacgtggac 480

ggcgtggaag tgcacaacgc caagaccaag cccagagagg aacagttcaa cagcacctac 540

cgggtggtgt ccgtgctgac cgtgctgcac caggactggc tgaacggcaa agagtacaag 600

tgcaaagtct ccaacaaggg cctgcccagc tccatcgaga aaaccatcag caaggccaag 660

ggccagcccc gcgagcctca ggtgtacaca ctgccccca gccaggaaga gatgaccaag 720

aaccaggtgt ccctgacctg tctggtgaaa ggcttctacc ccagcgatat cgccgtggaa 780

tgggagagca acggccagcc cgagaacaac tacaagacca ccccccctgt gctggacagc 840

gacggcagct tcttcctgta ctcccggctg accgtggaca agagccggtg gcaggaaggc 900

aacgtcttca gctgcagcgt gatgcacgag gccctgcaca accactacac ccagaagtcc 960

ctgagcctga gcctgggc 978

<210> 71
<211> 327

<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 71
agctacgtgc tgacccagcc tcctagcgtg tccgtggccc ctggccagac cgccagaatc 60

acctgtggcg gcaacaacat cggcagcaag aacgtgtact ggtatcagca gaagcccggc 120

caggcccccg tgctggtggt gcacgacgac agcgacagac ccagcggcat ccccgagcgg 180

ttcagcggca gcaacagcgg caataccgcc accctgacca tcagccgggt ggaagtgggc 240

gacgaggccg actacagctg ccaggtctgg gacagcagca gcgaccacgt ggtgttcggc 300

ggaggcacca agctgaccgt cctaggt 327

<210> 72
<211> 315
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 72
cagcccaagg ccgctcccag cgtgaccctg ttcccccaa gcagcgagga actgcaggcc 60

aacaaggcca ccctggtgtg cctgatcagc gacttctacc ctggggccgt gaccgtggcc 120

tggaaggccg atagcagccc tgtgaaggcc ggcgtggaaa ccaccacccc ctccaagcag 180

agcaacaaca aatacgccgc cagcagctac ctgtccctga cccccgagca gtggaagtcc 240

caccggtcct acagctgcca ggtgacacac gagggcagca ccgtggaaaa gaccgtggcc 300

cccaccgagt gcagc 315

<210> 73
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<220>
<221> MOD_RES
<222> (26)..(26)
<223> Gly, Ala, Ser, Leu, Tyr, Asp, Gln, Lys, His or Trp

<220>
<221> MOD_RES
<222> (27)..(27)
<223> Gly, Ala, Ser, Leu, Tyr, Asp, Gln, Lys, His or Trp

<220>
<221> MOD_RES
<222> (28)..(28)
<223> Ser, Ala, Leu, Tyr, Asp, Gln, Lys, His or Trp

<220>
<221> MOD_RES
<222> (29)..(29)
<223> Ile, Ala, Ser, Leu, Tyr, Asp, Gln, Lys, His or Trp

<220>
<221> MOD_RES
<222> (30)..(30)
<223> Ser, Ala, Leu, Tyr, Asp, Gln, Lys, His or Trp

<220>
<221> MOD_RES
<222> (31)..(31)
<223> Asn, Ala, Ser, Leu, Tyr, Asp, Gln, Lys, His or Trp

<220>
<221> MOD_RES
<222> (32)..(32)
<223> Gly, Ala, Ser, Leu, Tyr, Asp, Gln, Lys, His or Trp

<220>
<221> MOD_RES
<222> (33)..(33)
<223> Gly, Ala, Ser, Leu, Tyr, Asp, Gln, Lys, His or Trp

<220>
<221> MOD_RES
<222> (34)..(34)
<223> Tyr, Ala, Ser, Leu, Asp, Gln, Lys, His or Trp

<220>
<221> MOD_RES
<222> (35)..(35)
<223> Tyr, Ala, Ser, Leu, Asp, Gln, Lys, His or Trp

<220>
<221> MOD_RES
<222> (36)..(36)
<223> Trp, Ala, Ser, Leu, Tyr, Asp, Gln, Lys or His

<220>
<221> MOD_RES
<222> (37)..(37)
<223> Ser, Ala, Leu, Tyr, Asp, Gln, Lys, His or Trp

<220>
<221> MOD_RES
<222> (52)..(52)
<223> Tyr, Ala, Ser, Leu, Asp, Gln, Lys, His or Trp

<220>
<221> MOD_RES
<222> (53)..(53)
<223> Ile, Ala, Ser, Leu, Tyr, Asp, Gln, Lys, His or Trp

<220>
<221> MOD_RES
<222> (54)..(54)
<223> Tyr, Ala, Ser, Leu, Asp, Gln, Lys, His or Trp

<220>
<221> MOD_RES
<222> (55)..(55)
<223> Tyr, Ala, Ser, Leu, Asp, Gln, Lys, His or Trp

<220>
<221> MOD_RES
<222> (56)..(56)
<223> Ser, Ala, Leu, Asp, Gln, Lys, His or Trp

<220>
<221> MOD_RES
<222> (57)..(57)
<223> Gly, Ala, Ser, Leu, Tyr, Asp, Gln, Lys, His or Trp

<220>
<221> MOD_RES
<222> (58)..(58)
<223> Ser, Ala, Leu, Tyr, Asp, Gln, Lys, His or Trp

<220>
<221> MOD_RES
<222> (59)..(59)
<223> Thr, Ala, Ser, Leu, Tyr, Asp, Gln, Lys, His or Trp

<220>
<221> MOD_RES

<222> (60)..(60)
<223> Tyr, Ala, Ser, Leu, Asp, Gln, Lys, His or Trp

<220>
<221> MOD_RES
<222> (98)..(98)
<223> Ala, Ser, Leu, Tyr, Asp, Gln, Lys, His, Trp or Pro

<220>
<221> MOD_RES
<222> (99)..(99)
<223> Ser, Ala, Leu, Tyr, Asp, Gln, Lys, His, Trp or Pro

<220>
<221> MOD_RES
<222> (100)..(100)
<223> Leu, Ala, Ser, Tyr, Asp, Gln, Lys, His, Trp or Pro

<220>
<221> MOD_RES
<222> (101)..(101)
<223> Gly, Ala, Ser, Leu, Tyr, Asp, Gln, Lys, His, Trp or Pro

<220>
<221> MOD_RES
<222> (102)..(102)
<223> Asn, Ala, Ser, Leu, Tyr, Asp, Gln, Lys, His, Trp or Pro

<220>
<221> MOD_RES
<222> (103)..(103)
<223> Trp, Ala, Ser, Leu, Tyr, Asp, Gln, Lys, His or Pro

<220>
<221> MOD_RES
<222> (104)..(104)
<223> Phe, Ala, Ser, Leu, Tyr, Asp, Gln, Lys, His, Trp or Pro

<220>
<221> MOD_RES
<222> (105)..(105)
<223> Asp, Ala, Ser, Leu, Tyr, Gln, Lys, His, Trp or Pro

<220>
<221> MOD_RES
<222> (106)..(106)
<223> Tyr, Ala, Ser, Leu, Asp, Gln, Lys, His, Trp or Pro

<400> 73
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Xaa Xaa Xaa Xaa Xaa Xaa Xaa
            20   25   30

Xaa Xaa Xaa Xaa Xaa Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
        35   40   45

Trp Ile Gly Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa 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 Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Trp Gly Gln Gly Thr Leu
            100   105   110

Val Thr Val Ser Ser
        115

<210> 74
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
      polypeptide

<220>
<221> MOD_RES
<222> (23)..(23)
<223> Gly, Ala, Ser, Leu, Tyr, Asp, Gln, Lys, His or Trp

<220>
<221> MOD_RES
<222> (24)..(24)
<223> Gly, Ala, Ser, Leu, Tyr, Asp, Gln, Lys, His or Trp

<220>
<221> MOD_RES
<222> (25)..(25)

<223> Asn, Ala, Ser, Leu, Tyr, Asp, Gln, Lys, His or Trp

<220>
<221> MOD_RES
<222> (26)..(26)
<223> Asn, Ala, Ser, Leu, Tyr, Asp, Gln, Lys, His or Trp

<220>
<221> MOD_RES
<222> (27)..(27)
<223> Ile, Ala, Ser, Leu, Tyr, Asp, Gln, Lys, His or Trp

<220>
<221> MOD_RES
<222> (28)..(28)
<223> Gly, Ala, Ser, Leu, Tyr, Asp, Gln, Lys, His or Trp

<220>
<221> MOD_RES
<222> (29)..(29)
<223> Ser, Ala, Leu, Tyr, Asp, Gln, Lys, His or Trp

<220>
<221> MOD_RES
<222> (30)..(30)
<223> Lys, Ala, Ser, Leu, Tyr, Asp, Gln, His or Trp

<220>
<221> MOD_RES
<222> (31)..(31)
<223> Asn, Ala, Ser, Leu, Tyr, Asp, Gln, Lys, His or Trp

<220>
<221> MOD_RES
<222> (32)..(32)
<223> Val, Ala, Ser, Leu, Tyr, Asp, Gln, Lys, His or Trp

<220>
<221> MOD_RES
<222> (33)..(33)
<223> Tyr, Ala, Ser, Leu, Asp, Gln, Lys, His or Trp

<220>
<221> MOD_RES
<222> (49)..(49)
<223> Asp, Ala, Ser, Leu, Tyr, Gln, Lys, His or Trp

<220>
<221> MOD_RES
<222> (50)..(50)
<223> Asp, Ala, Ser, Leu, Tyr, Gln, Lys, His or Trp

<220>
<221> MOD_RES
<222> (51)..(51)
<223> Ser, Ala, Leu, Tyr, Asp, Gln, Lys, His or Trp

<220>
<221> MOD_RES
<222> (52)..(52)
<223> Asp, Ala, Ser, Leu, Tyr, Gln, Lys, His or Trp

<220>
<221> MOD_RES
<222> (53)..(53)
<223> Arg, Ala, Ser, Leu, Tyr, Asp, Gln, Lys, His or Trp

<220>
<221> MOD_RES
<222> (54)..(54)
<223> Pro, Ala, Ser, Leu, Tyr, Asp, Gln, Lys, His or Trp

<220>
<221> MOD_RES
<222> (55)..(55)
<223> Ser, Ala, Leu, Tyr, Asp, Gln, Lys, His or Trp

<220>
<221> MOD_RES
<222> (88)..(88)
<223> Gln, Ala, Ser, Leu, Tyr, Asp, Lys, His, Trp or Pro

<220>
<221> MOD_RES
<222> (89)..(89)
<223> Val, Ala, Ser, Leu, Tyr, Asp, Gln, Lys, His, Trp or Pro

<220>
<221> MOD_RES
<222> (90)..(90)
<223> Trp, Ala, Ser, Leu, Tyr, Asp, Gln, Lys, His or Pro

<220>
<221> MOD_RES
<222> (91)..(91)
<223> Asp, Ala, Ser, Leu, Tyr, Gln, Lys, His, Trp or Pro

<220>
<221> MOD_RES
<222> (92)..(92)
<223> Ser, Ala, Leu, Tyr, Asp, Gln, Lys, His, Trp or Pro

<220>
<221> MOD_RES

<222> (93)..(93)
<223> Ser, Ala, Leu, Tyr, Asp, Gln, Lys, His, Trp or Pro

<220>
<221> MOD_RES
<222> (94)..(94)
<223> Ser, Ala, Leu, Tyr, Asp, Gln, Lys, His, Trp or Pro

<220>
<221> MOD_RES
<222> (95)..(95)
<223> Asp, Ala, Ser, Leu, Tyr, Gln, Lys, His, Trp or Pro

<220>
<221> MOD_RES
<222> (96)..(96)
<223> His, Ala, Ser, Leu, Tyr, Asp, Gln, Lys, Trp or Pro

<220>
<221> MOD_RES
<222> (97)..(97)
<223> Val, Ala, Ser, Leu, Tyr, Asp, Gln, Lys, His, Trp or Pro

<220>
<221> MOD_RES
<222> (98)..(98)
<223> Val, Ala, Ser, Leu, Tyr, Asp, Gln, Lys, His, Trp or Pro

<400> 74
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 Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
            20   25   30

Xaa Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val His
        35   40   45

Xaa Xaa Xaa Xaa Xaa Xaa Xaa 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 Val Gly
65   70   75   80

Asp Glu Ala Asp Tyr Ser Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
                85   90   95

Xaa Xaa Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105

<210> 75
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<220>
<221> MOD_RES
<222> (24)..(24)
<223> Gly or Lys

<220>
<221> MOD_RES
<222> (25)..(25)
<223> Asn or Asp

<220>
<221> MOD_RES
<222> (26)..(26)
<223> Asn or His

<220>
<221> MOD_RES
<222> (27)..(27)
<223> Ile or Ala

<220>
<221> MOD_RES
<222> (28)..(28)
<223> Gly or Asp

<220>
<221> MOD_RES
<222> (29)..(29)
<223> Ser or Lys

<220>
<221> MOD_RES
<222> (31)..(31)
<223> Asn or His

<220>
<221> MOD_RES

<222> (32)..(32)
<223> Val or Ala

<220>
<221> MOD_RES
<222> (51)..(51)
<223> Ser or Leu

<220>
<221> MOD_RES
<222> (52)..(52)
<223> Asp or Ser

<220>
<221> MOD_RES
<222> (91)..(91)
<223> Asp or Leu

<220>
<221> MOD_RES
<222> (96)..(96)
<223> His, Ser, Tyr or Asp

<220>
<221> MOD_RES
<222> (98)..(98)
<223> Val, Ala or Trp

<400> 75

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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 Xaa Xaa Xaa Xaa Xaa Xaa Lys Xaa Xaa
            20                  25                  30


Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val His
        35                  40                  45


Asp Asp Xaa Xaa 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 Val Gly
65                  70                  75                  80


Asp Glu Ala Asp Tyr Ser Cys Gln Val Trp Xaa Ser Ser Ser Asp Xaa
                85                  90                  95
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Val Xaa Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105