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(54) Titre : PROTEINE DE LIAISON A IL-13
(54) Title: IL-13 BINDING PROTEIN

(57) **Abrégé/Abstract:**

The present invention relates to antigen binding proteins to human IL-13, including anti-IL-13 antibodies and anti-IL-3/anti-IL-4 mAbdAbs, pharmaceutical formulations containing them and to the use of such antigen binding proteins in the treatment and/or prophylaxis of inflammatory diseases such as asthma or IPF.



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(54) **Title:** IL-13 BINDING PROTEIN

(57) **Abstract:** The present invention relates to antigen binding proteins to human IL-13, including anti-IL-13 antibodies and anti-IL-3/anti-IL-4 mAbdAbs, pharmaceutical formulations containing them and to the use of such antigen binding proteins in the treatment and/or prophylaxis of inflammatory diseases such as asthma or IPF.



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IL-13 BINDING PROTEIN

Field of the Invention

5 The present invention relates to antigen binding proteins, particularly antibodies
that bind to interleukin 13 (IL-13) and neutralise the activity thereof, polynucleotides
encoding such antigen binding proteins, pharmaceutical formulations containing said
antigen binding proteins and to the use of such antigen binding proteins in the treatment
and/or prophylaxis of diseases associated with inflammation, such as asthma. Other
aspects, objects and advantages of the present invention will become apparent from the
10 description below.

Background of the Invention**Interleukin-13 (IL-13)**

15 IL-13 is a 12kDa secreted cytokine originally described as a T cell-derived cytokine that
inhibits inflammatory cytokine production. Structural studies indicate that it has a four-
helical bundle arrangement held by two disulphide bonds. Although IL-13 has four
potential glycosylation sites, analysis of native IL-13 from rat lung has indicated that it is
20 produced as an unglycosylated molecule. Expression of human IL-13 from NSO and
COS-7 cells confirms this observation (Eisenmesser et al, J. Mol. Biol. 2001 310(1):231-
241; Moy et al, J. Mol. Biol 2001 310(1):219-230; Cannon-Carlson et al, Protein
Expression and Purification 1998 12(2):239-248).

25 IL-13 has been implicated in asthma, Chronic Obstructive Pulmonary Disease (COPD),
Allergic disease including atopic dermatitis and allergic rhinitis, Esophagal eosinophilia,
Oncology Indications, e.g. B-cell chronic lymphocytic leukemia (B-CLL) and Hodgkin's
disease, Inflammatory Bowel Diseases e.g. ulcerative colitis, Crohn's disease and
indeterminate colitis, Psoriasis and Psoriatic Arthritis, Acute graft-versus-host disease,
30 Diabetic nephropathy, Fibrotic Conditions such as Pulmonary fibrosis e.g. Idiopathic
Pulmonary Fibrosis (IPF).

Summary of Invention

35 The invention provides antigen binding proteins which bind to IL-13, for example IL-13
antibodies, and to the combination of such IL-13 antibodies with an IL-4 antagonist
and/or an IL-5 antagonist. The IL-13 antibodies of the present invention are related to, or
derived from, a murine mAb 6A1, wherein the CDRH3 is mutated. The 6A1 murine
heavy chain variable region amino acid sequence is provided as SEQ ID NO: 58. The
40 6A1 murine light chain variable region amino acid sequence is provided as SEQ ID NO
59.

The heavy chain variable regions (VH) of the present invention comprise the
following CDRs (as defined by Kabat (*Kabat et al; Sequences of proteins of
Immunological Interest* NIH, 1987)):

The CDRs of the heavy chain variable regions of the present invention may comprise the following CDRs:

CDR	According to Kabat
H1	DTYMH (SEQ ID NO:1)
H2	TIDPANGNTKYVPKFQG (SEQ ID NO:2)
H3	WIYDDYHYDDYYAMDY (SEQ ID NO: 4); or SVYDDYHYDDYYAMDY (SEQ ID NO: 5); or SIFDDYHYDDYYAMDY (SEQ ID NO: 6); or SIYEDYHYDDYYAMDY (SEQ ID NO: 7); or SIYDDYAYDDYYAMDY (SEQ ID NO: 8); or SIYDDYFYDDYYAMDY (SEQ ID NO: 9); or SIYDDYQYDDYYAMDY (SEQ ID NO: 10); or SIYDDYRYDDYYAMDY (SEQ ID NO: 11); or SIYDDYSYDDYYAMDY (SEQ ID NO: 12); or SIYDDYTYDDYYAMDY (SEQ ID NO: 13) or SIYDDYVYDDYYAMDY (SEQ ID NO: 14); or SIYDDYHADDYYAMDY (SEQ ID NO: 15); or SIYDDYHIDDYYAMDY (SEQ ID NO: 16); or SIYDDYHWDDYYAMDY (SEQ ID NO: 17); or SIYDDYHVDDYYAMDY (SEQ ID NO: 18)

- 5 The light chain variable regions of the present invention comprise the following CDRs (as defined by Kabat):

CDR	According to Kabat
L1	RSSQNIVHINGNTYLE (SEQ ID NO:19)
L2	KISDRFS (SEQ ID NO:20)
L3	FQGSHPVPT (SEQ ID NO:21)

- 10 The CDR sequences of antibodies can be determined by the Kabat numbering system (Kabat *et al*; *Sequences of proteins of Immunological Interest* NIH, 1987), as set out in the tables above, alternatively they can be determined using the Chothia numbering system (Al-Lazikani *et al.*, (1997) JMB **273**,927-948), the contact definition method (MacCallum R.M., and Martin A.C.R. and Thornton J.M, (1996), Journal of Molecular Biology, 262 (5), 732-745) or any other established method for numbering the residues in an antibody and determining CDRs known to the skilled man in the art.
- 15 The CDRs of the invention described herein may be defined by any of these methods, or by using a combination of Chothia and Kabat numbering, for example CDRH1 may be defined as comprising FYIKDTYMH (SEQ ID NO 60) or GFYIKDTYMH (SEQ ID NO 61).

The present invention also provides an antigen-binding protein comprising the IL-13 antibody of the present invention which is linked to one or more epitope-binding domains, for example an antigen-binding protein comprising the IL-13 antibody of the present invention linked to an epitope-binding domain which is capable of binding to IL-4, or an antigen-binding protein comprising the IL-13 antibody of the present invention linked to an epitope-binding domain which is capable of binding to IL-5, or an antigen-binding protein comprising the IL-13 antibody of the present invention linked to a first epitope-binding domain which is capable of binding to IL-4 and a second epitope-binding domain which is capable of binding to IL-5.

The present invention also provides a method of decreasing the aggregation propensity of an immunoglobulin single variable domain, for example a human dAb, for example human VK domain antibody, by mutation of residue 89 (kabat numbering) to a residue selected from 'Q' (glutamine), 'G' (glycine), 'S' (serine), 'M' (methionine), 'A' (alanine), 'T' (threonine) and 'E' (glutamic acid). In one embodiment, the method involves mutation of residue 89 (kabat numbering) to a residue selected from 'Q' (glutamine), 'G' (glycine), 'S' (serine), 'M' (methionine) and 'E' (glutamic acid). In a further embodiment the method involves mutation of residue 89 (kabat numbering) to 'Q' (glutamine).

In one embodiment this method can be applied to the anti-IL-4 domain antibody of SEQ ID NO: 80, resulting in a mutated dAb sequence, for example SEQ ID NO:94. Such mutated dAbs may be alone or as part of a larger sequence, for example part of a mAbdAb sequence, resulting in for example, a dAb comprising a sequence selected from SEQ ID NO: 117-134.

The invention also provides human VK dAbs which have improved aggregation profiles, for example a human VK dAb derived from a germline framework selected from IGKV1-17, IGKV1D-17, IGKV1/OR2-108, IGKV1-6, IGKV5-2, IGKV1D-42, IGKV2-24, IGKV2-28, IGKV2-30, IGKV2-40, IGKV2D-29, IGKV2D-30, IGKV2D-24 and IGKV6-21 wherein residue 89 (kabat numbering) of the VK dAb is 'Q' (glutamine). In one such embodiment the VK dAb comprises germline framework regions selected from the germline frameworks of IGKV1-17, IGKV1D-17, IGKV1/OR2-108, IGKV1-6, IGKV5-2, IGKV1D-42, IGKV2-24, IGKV2-28, IGKV2-30, IGKV2-40, IGKV2D-29, IGKV2D-30, IGKV2D-24 and IGKV6-21 wherein residue 89 (kabat numbering) of the VK dAb is 'Q' (glutamine).

In one embodiment, the invention provides a human dAb comprising the sequence of SEQ ID NO: 80 which comprises a mutation at position 89 (kabat numbering) wherein the mutated position 89 is selected from 'Q' (glutamine), 'G' (glycine), 'S' (serine), 'M' (methionine), 'A' (alanine), 'T' (threonine) and 'E' (glutamic acid). For example the invention provides a human dab comprising the sequence of SEQ ID NO:80 wherein position 89 (kabat numbering) is mutated to a residue selected from 'Q' (glutamine), 'G' (glycine), 'S' (serine), 'M' (methionine) and 'E' (glutamic acid).

In one embodiment the invention provides a human dAb comprising the sequence of SEQ ID NO: 94

The invention also provides a polynucleotide sequence encoding a heavy chain of any of the antigen-binding proteins described herein, and a polynucleotide encoding a light chain of any of the antigen-binding proteins described herein. Such polynucleotides represent the coding sequence which corresponds to the equivalent polypeptide sequences, however it will be understood that such polynucleotide sequences could be cloned into an expression vector along with a start codon, an appropriate signal sequence and a stop codon.

The invention also provides a recombinant transformed or transfected host cell comprising one or more polynucleotides encoding a heavy chain and a light chain of any of the antigen-binding proteins described herein.

The invention further provides a method for the production of any of the antigen-binding proteins described herein which method comprises the step of culturing a host cell comprising a first and second vector, said first vector comprising a polynucleotide encoding a heavy chain of any of the antigen-binding proteins described herein and said second vector comprising a polynucleotide encoding a light chain of any of the antigen-binding proteins described herein, in a suitable culture media, for example serum-free culture media.

The invention further provides a pharmaceutical composition comprising an antigen-binding protein as described herein a pharmaceutically acceptable carrier.

In a further aspect, the present invention provides a method of treatment or prophylaxis of diseases or disorders associated with atopic diseases/ disorders and chronic inflammatory diseases/disorders by administration of the antigen binding protein of the present invention. Of particular interest is their use in the treatment of asthma, such as allergic asthma, particularly severe asthma (that is asthma that is unresponsive to current treatment, including systemically administered corticosteroids; see Busse WW et al, J Allergy Clin. Immunol 2000, 106: 1033-1042), "difficult" asthma (defined as the asthmatic phenotype characterised by failure to achieve control despite maximally recommended doses of prescribed inhaled steroids, see Barnes PJ (1998), Eur Respir J 12:1208-1218), "brittle" asthma (defines a subgroup of patients with severe, unstable asthma who maintain a wide peak expiratory flow (PEF) variability despite high doses of inhaled steroids, see Ayres JG et al (1998) Thorax 58:315-321), nocturnal asthma, premenstrual asthma, steroid resistant asthma (see Woodcock AJ (1993) Eur Respir J 6:743-747), steroid dependent asthma (defined as asthma that can be controlled only with high doses of oral steroids), aspirin induced asthma, adult-onset asthma, paediatric asthma. Antibodies of the invention maybe used to prevent, reduce the frequency of, or mitigate the effects of acute, asthmatic episodes (*status asthmaticus*). Antibodies of the invention may also be used to reduce the dosing required (either in terms of amount administered or frequency of dosing) of other medicaments used in the treatment of asthma. For example, antibodies of the invention may be used to reduce the dosing

required for steroid treatment of asthma such as corticosteroid treatment ("steroid sparing"). Other diseases or disorders that may be treated with antibodies of the invention include atopic dermatitis, allergic rhinitis, Crohn's disease, chronic obstructive pulmonary disease (COPD), eosinophilic esophagitis, fibrotic diseases or disorders such as idiopathic pulmonary fibrosis, progressive systemic sclerosis (scleroderma), hepatic fibrosis, hepatic granulomas, schistosomiasis, leishmaniasis, and diseases of cell cycle regulation, e.g. Hodgkins disease, B cell chronic lymphocytic leukaemia.

In another aspect, the invention provides the use of an antigen binding protein of the invention in the preparation of a medicament for treatment or prophylaxis of atopic diseases/ disorders and chronic inflammatory diseases/disorders. Of particular interest is their use in the treatment of asthma, such as allergic asthma, particularly severe asthma (that is asthma that is unresponsive to current treatment, including systemically administered corticosteroids; see Busse WW et al, J Allergy Clin. Immunol 2000, 106: 1033-1042), "difficult" asthma (defined as the asthmatic phenotype characterised by failure to achieve control despite maximally recommended doses of prescribed inhaled steroids, see Barnes PJ (1998), Eur Respir J 12:1208-1218), "brittle" asthma (defines a subgroup of patients with severe, unstable asthma who maintain a wide peak expiratory flow (PEF) variability despite high doses of inhaled steroids, see Ayres JG et al (1998) Thorax 58:315-321), nocturnal asthma, premenstrual asthma, steroid resistant asthma (see Woodcock AJ (1993) Eur Respir J 6:743-747), steroid dependent asthma (defined as asthma that can be controlled only with high doses of oral steroids), aspirin induced asthma, adult-onset asthma, paediatric asthma . Antibodies of the invention maybe used to prevent, reduce the frequency of, or mitigate the effects of acute, asthmatic episodes (*status asthmaticus*). Antibodies of the invention may also be used to reduce the dosing required (either in terms of amount administered or frequency of dosing) of other medicaments used in the treatment of asthma. For example, antibodies of the invention may be used to reduce the dosing required for steroid treatment of asthma such as corticosteroid treatment ("steroid sparing"). Other diseases or disorders that may be treated with antibodies of the invention include atopic dermatitis, allergic rhinitis, Crohn's disease, chronic obstructive pulmonary disease (COPD), eosinophilic esophagitis, fibrotic diseases or disorders such as idiopathic pulmonary fibrosis, progressive systemic sclerosis (scleroderma), hepatic fibrosis, hepatic granulomas, schistosomiasis, leishmaniasis, and diseases of cell cycle regulation, e.g. Hodgkins disease, B cell chronic lymphocytic leukaemia.

Other aspects and advantages of the present invention are described further in the detailed description and the embodiments thereof.

Definitions

The term "binds to human IL-13" as used throughout the present specification in relation to antigen binding proteins thereof of the invention means that the antigen binding protein binds human IL-13 (hereinafter referred to as hIL-13) with no or insignificant

binding to other human proteins such as IL-4. In particular the antigen binding proteins of the present invention bind to human IL-13 in that they can be seen to bind to human IL-13 in a Biacore assay (for example the Biacore assay described in example 3). The term however does not exclude the fact that certain antigen binding proteins of the invention may also be cross-reactive with IL-13 from other species, for example cynomolgus IL-13.

The term "antigen binding protein" as used herein refers to antibodies, antibody fragments and other protein constructs which are capable of binding to and neutralising human IL-13.

The terms Fv, Fc, Fd, Fab, or F(ab)₂ are used with their standard meanings (see, e.g., Harlow et al., Antibodies A Laboratory Manual, Cold Spring Harbor Laboratory, (1988)).

A "chimeric antibody" refers to a type of engineered antibody which contains a naturally-occurring variable region (light chain and heavy chains) derived from a donor antibody in association with light and heavy chain constant regions derived from an acceptor antibody.

A "humanised antibody" refers to a type of engineered antibody having its CDRs derived from a non-human donor immunoglobulin, the remaining immunoglobulin-derived parts of the molecule being derived from one (or more) human immunoglobulin(s). In addition, framework support residues may be altered to preserve binding affinity (see, e.g., Queen et al., Proc. Natl Acad Sci USA, 86:10029-10032 (1989), Hodgson et al., Bio/Technology, 9:421 (1991)). A suitable human acceptor antibody may be one selected from a conventional database, e.g., the KABAT® database, Los Alamos database, and Swiss Protein database, by homology to the nucleotide and amino acid sequences of the donor antibody. A human antibody characterized by a homology to the framework regions of the donor antibody (on an amino acid basis) may be suitable to provide a heavy chain constant region and/or a heavy chain variable framework region for insertion of the donor CDRs. A suitable acceptor antibody capable of donating light chain constant or variable framework regions may be selected in a similar manner. It should be noted that the acceptor antibody heavy and light chains are not required to originate from the same acceptor antibody. The prior art describes several ways of producing such humanised antibodies – see for example EP-A-0239400 and EP-A-054951

The term "donor antibody" refers to an antibody (monoclonal, and/or recombinant) which contributes the amino acid sequences of its variable regions, CDRs, or other functional fragments or analogs thereof to a first immunoglobulin partner, so as to provide the altered immunoglobulin coding region and resulting expressed altered antibody with the antigenic specificity and neutralizing activity characteristic of the donor antibody.

The term "acceptor antibody" refers to an antibody (monoclonal and/or recombinant) heterologous to the donor antibody, which contributes all (or any portion, but in some embodiments all) of the amino acid sequences encoding its heavy and/or light chain

framework regions and/or its heavy and/or light chain constant regions to the first immunoglobulin partner. In certain embodiments a human antibody is the acceptor antibody.

- 5 "CDRs" are defined as the complementarity determining region amino acid sequences of an antibody which are the hypervariable regions of immunoglobulin heavy and light chains. See, e.g., Kabat et al., Sequences of Proteins of Immunological Interest, 4th Ed., U.S. Department of Health and Human Services, National Institutes of Health
 10 (1987). There are three heavy chain and three light chain CDRs (or CDR regions) in the variable portion of an immunoglobulin. Thus, "CDRs" as used herein refers to all three heavy chain CDRs, or all three light chain CDRs (or both all heavy and all light chain CDRs, if appropriate). The structure and protein folding of the antibody may mean that other residues are considered part of the antigen binding region and would be understood to be so by a skilled person. See for example Chothia et al., (1989)
 15 Conformations of immunoglobulin hypervariable regions; Nature 342, p877-883.

As used herein the term "domain" refers to a folded protein structure which has tertiary structure independent of the rest of the protein. Generally, domains are responsible for discrete functional properties of proteins and in many cases may be added, removed or
 20 transferred to other proteins without loss of function of the remainder of the protein and/or of the domain. An "antibody single variable domain" is a folded polypeptide domain comprising sequences characteristic of antibody variable domains. It therefore includes complete antibody variable domains and modified variable domains, for example, in which one or more loops have been replaced by sequences which are not
 25 characteristic of antibody variable domains, or antibody variable domains which have been truncated or comprise N- or C-terminal extensions, as well as folded fragments of variable domains which retain at least the binding activity and specificity of the full-length domain.

30 The phrase "immunoglobulin single variable domain" refers to an antibody variable domain (V_H , V_{HH} , V_L) that specifically binds an antigen or epitope independently of a different V region or domain. An immunoglobulin single variable domain can be present in a format (e.g., homo- or hetero-multimer) with other, different variable regions or variable domains where the other regions or domains are not required for antigen
 35 binding by the single immunoglobulin variable domain (i.e., where the immunoglobulin single variable domain binds antigen independently of the additional variable domains). A "domain antibody" or "dAb" is the same as an "immunoglobulin single variable domain" which is capable of binding to an antigen as the term is used herein. An immunoglobulin single variable domain may be a human antibody variable domain, but also includes
 40 single antibody variable domains from other species such as rodent (for example, as disclosed in WO 00/29004), nurse shark and *Camelid* V_{HH} dAbs (nanobodies). Camelid V_{HH} are immunoglobulin single variable domain polypeptides that are derived from species including camel, llama, alpaca, dromedary, and guanaco, which produce heavy chain antibodies naturally devoid of light chains. Such V_{HH} domains may be humanised
 45 according to standard techniques available in the art, and such domains are still

considered to be “domain antibodies” according to the invention. As used herein “V_H includes camelid V_{HH} domains. NARV are another type of immunoglobulin single variable domain which were identified in cartilaginous fish including the nurse shark. These domains are also known as Novel Antigen Receptor variable region (commonly abbreviated to V(NAR) or NARV). For further details see Mol. Immunol. **44**, 656-665 (2006) and US20050043519A.

The term “Epitope-binding domain” refers to a domain that specifically binds an antigen or epitope independently of a different V region or domain, this may be a domain antibody (dAb), for example a human, camelid or shark immunoglobulin single variable domain or it may be a domain which is a derivative of a non-Immunoglobulin scaffold, for example a non-immunoglobulin scaffold selected from the group consisting of CTLA-4 (Evibody); lipocalin; Protein A derived molecules such as Z-domain of Protein A (Affibody, SpA), A-domain (Avimer/Maxibody); Heat shock proteins such as GroEI and GroES; transferrin (trans-body); ankyrin repeat protein (DARPin); peptide aptamer; C-type lectin domain (Tetranectin); human γ -crystallin and human ubiquitin (affilins); PDZ domains; scorpion toxin/kunitz type domains of human protease inhibitors; and fibronectin (adnectin); which has been subjected to protein engineering in order to obtain binding to a ligand other than the natural ligand.

CTLA-4 (Cytotoxic T Lymphocyte-associated Antigen 4) is a CD28-family receptor expressed on mainly CD4+ T-cells. Its extracellular domain has a variable domain-like Ig fold. Loops corresponding to CDRs of antibodies can be substituted with heterologous sequence to confer different binding properties. CTLA-4 molecules engineered to have different binding specificities are also known as Evibodies. For further details see Journal of Immunological Methods **248 (1-2)**, 31-45 (2001)

Lipocalins are a family of extracellular proteins which transport small hydrophobic molecules such as steroids, bilins, retinoids and lipids. They have a rigid β -sheet secondary structure with a number of loops at the open end of the conical structure which can be engineered to bind to different target antigens. Anticalins are between 160-180 amino acids in size, and are derived from lipocalins. For further details see Biochim Biophys Acta **1482**: 337-350 (2000), US7250297B1 and US20070224633

An affibody is a scaffold derived from Protein A of *Staphylococcus aureus* which can be engineered to bind to antigen. The domain consists of a three-helical bundle of approximately 58 amino acids. Libraries have been generated by randomisation of surface residues. For further details see Protein Eng. Des. Sel. **17**, 455-462 (2004) and EP1641818A1

Avimers are multidomain proteins derived from the A-domain scaffold family. The native domains of approximately 35 amino acids adopt a defined disulphide bonded structure. Diversity is generated by shuffling of the natural variation exhibited by the family of A-domains. For further details see Nature Biotechnology **23(12)**, 1556 - 1561 (2005) and Expert Opinion on Investigational Drugs **16(6)**, 909-917 (June 2007)

5 A transferrin is a monomeric serum transport glycoprotein. Transferrins can be engineered to bind different target antigens by insertion of peptide sequences in a permissive surface loop. Examples of engineered transferrin scaffolds include the Trans-body. For further details see J. Biol. Chem **274**, 24066-24073 (1999).

10 Designed Ankyrin Repeat Proteins (DARPin)s are derived from Ankyrin which is a family of proteins that mediate attachment of integral membrane proteins to the cytoskeleton. A single ankyrin repeat is a 33 residue motif consisting of two α -helices and a β -turn. They can be engineered to bind different target antigens by randomising residues in the first α -helix and a β -turn of each repeat. Their binding interface can be increased by increasing the number of modules (a method of affinity maturation). For further details see J. Mol. Biol. **332**, 489-503 (2003), PNAS **100(4)**, 1700-1705 (2003) and J. Mol. Biol. 369, 1015-1028 (2007) and US20040132028A1.

15 Fibronectin is a scaffold which can be engineered to bind to antigen. Adnectins consists of a backbone of the natural amino acid sequence of the 10th domain of the 15 repeating units of human fibronectin type III (FN3). Three loops at one end of the β -sandwich can be engineered to enable an Adnectin to specifically recognize a therapeutic target of interest. For further details see Protein Eng. Des. Sel. **18**, 435-444 (2005),
20 US20080139791, WO2005056764 and US6818418B1.

25 Peptide aptamers are combinatorial recognition molecules that consist of a constant scaffold protein, typically thioredoxin (TrxA) which contains a constrained variable peptide loop inserted at the active site. For further details see Expert Opin. Biol. Ther. 5, 783-797 (2005).

30 Microbodies are derived from naturally occurring microproteins of 25-50 amino acids in length which contain 3-4 cysteine bridges – examples of microproteins include KalataB1 and conotoxin and knottins. The microproteins have a loop which can be engineered to include upto 25 amino acids without affecting the overall fold of the microprotein. For further details of engineered knottin domains, see WO2008098796.

35 Other epitope binding domains include proteins which have been used as a scaffold to engineer different target antigen binding properties include human γ -crystallin and human ubiquitin (affilins), kunitz type domains of human protease inhibitors, PDZ-domains of the Ras-binding protein AF-6, scorpion toxins (charybdotoxin), C-type lectin domain (tetranectins) are reviewed in Chapter 7 – Non-Antibody Scaffolds from Handbook of Therapeutic Antibodies (2007, edited by Stefan Dubel) and Protein Science
40 15:14-27 (2006). Epitope binding domains of the present invention could be derived from any of these alternative protein domains.

45 As used herein, the term “antigen-binding site” refers to a site on a protein which is capable of specifically binding to antigen, this may be a single domain, for example an epitope-binding domain, or it may be paired VH/VL domains as can be found on a

standard antibody. In some aspects of the invention single-chain Fv (ScFv) domains can provide antigen-binding sites.

5 The terms “mAbdAb” and dAbmAb” are used herein to refer to antigen-binding proteins of the present invention. The two terms can be used interchangeably, and are intended to have the same meaning as used herein.

10 The term “antigen binding protein” as used herein refers to antibodies, antibody fragments, for example a domain antibody (dAb), ScFv, FAb, FAb₂, and other protein constructs which are capable of binding to IL-13. Antigen binding molecules may comprise at least one Ig variable domain, for example antibodies, domain antibodies, Fab, Fab', F(ab')₂, Fv, ScFv, diabodies, mAbdAbs, affibodies, heteroconjugate antibodies or bispecifics. In one embodiment the antigen binding molecule is an antibody. In another embodiment the antigen binding molecule is a dAb, i.e. an

15 immunoglobulin single variable domain such as a VH, VHH or VL that specifically binds an antigen or epitope independently of a different V region or domain. Antigen binding molecules may be capable of binding to two targets, i.e. they may be dual targeting proteins. Antigen binding molecules may be a combination of antibodies and antigen binding fragments such as for example, one or more domain antibodies and/or one or

20 more ScFvs linked to a monoclonal antibody. Antigen binding molecules may also comprise a non-Ig domain for example a domain which is a derivative of a scaffold selected from the group consisting of CTLA-4 (Evibody); lipocalin; Protein A derived molecules such as Z-domain of Protein A (Affibody, SpA), A-domain (Avimer/Maxibody); Heat shock proteins such as GroEl and GroES; transferrin (trans-body); ankyrin repeat protein (DARPin); peptide aptamer; C-type lectin domain (Tetranectin); human γ -

25 crystallin and human ubiquitin (affilins); PDZ domains; scorpion toxin/kunitz type domains of human protease inhibitors; and fibronectin (adnectin); which has been subjected to protein engineering in order to obtain binding to IL-13. As used herein “antigen binding protein” will be capable of antagonising and/or neutralising human IL-13. In addition, an

30 antigen binding protein may block IL-13 activity by binding to IL-13 and preventing a natural ligand from binding and/or activating the receptor.

35 As used herein “IL-13 antagonist” includes any compound capable of reducing and or eliminating at least one activity of IL-13. By way of example, an IL-13 antagonist may bind to IL-13 and that binding may directly reduce or eliminate IL-13 activity or it may work indirectly by blocking at least one ligand from binding the receptor.

40 As used herein “IL-4 antagonist” includes any compound capable of reducing and or eliminating at least one activity of IL-4. By way of example, an IL-4 antagonist may bind to IL-4 and that binding may directly reduce or eliminate IL-4 activity or it may work indirectly by blocking at least one ligand from binding the receptor.

As used herein “IL-5 antagonist” includes any compound capable of reducing and or eliminating at least one activity of IL-5. By way of example, an IL-5 antagonist may bind

to IL-5 and that binding may directly reduce or eliminate IL-5 activity or it may work indirectly by blocking at least one ligand from binding the receptor.

5 **Detailed Description of the Invention**

In one embodiment the antigen binding proteins of the present invention comprise a heavy chain variable region containing a CDRH3 selected from the list consisting of SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO:8 and SEQ ID NO: 10 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO:14 and SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17 and SEQ ID NO: 18 and a suitable CDRH1 and CDRH2, paired with a light chain variable region containing a suitable CDRL1, CDRL2 and CDRL3 to form an antigen binding Fv unit which binds to human IL-13. In one embodiment the antigen binding proteins of the present invention neutralise 15 the activity of human IL-13

In one aspect of this embodiment the CDRH1 as set out in SEQ ID NO: 1 or SEQ ID NO: 60, or SEQ ID NO:61 and CDRH2 as set out in SEQ ID NO: 2 are also present in the heavy chain variable region. In a further aspect of this embodiment the CDRHL1 as set 20 out in SEQ ID NO: 19, CDRL2 as set out in SEQ ID NO:20 and CDRL3 as set out in SEQ ID NO: 21 are also present in the light chain variable region.

In another aspect the antigen binding protein binds to human IL-13 with high affinity as measured by Biacore of 10nM or less, and more particularly 2nM or less, for example 25 between about 0.8nM and 2nM, 1nM or less, or 100pM or less, for example between about 20pM and about 100pM or between about 20pM and about 80pM, or between about 20pM and about 60pM. In one such embodiment, this is measured by Biacore with the antigen binding protein being captured on the biosensor chip, for example as set out in Example 3.

30 The heavy chain variable regions of the present invention may be formatted together with light chain variable regions to allow binding to human IL-13, in the conventional immunoglobulin manner (for example, human IgG, IgA, IgM etc.) or in any other “antibody-like” format that binds to human IL-13 (for example, single chain Fv, diabodies, 35 Tandabs™ etc (for a summary of alternative “antibody” formats see Holliger and Hudson, Nature Biotechnology, 2005, Vol 23, No. 9, 1126-1136)).

The antigen binding proteins of the present invention are derived from the murine antibody having the variable regions as described in SEQ ID NO:58 and SEQ ID NO:59 40 or non-murine equivalents thereof, such as rat, human, chimeric or humanised variants thereof, for example they are derived from the humanised antibody having the heavy and light chains as described in SEQ ID NO:22 and SEQ ID NO:24.

In one aspect of the invention there is provided an antigen binding protein, for example 45 an antibody which binds human IL-13 and which comprises variants of the CDRH3

SIYDDYHYDDYYAMDY (SEQ ID NO: 3), wherein CDRH3 is substituted by the alternative amino acids set out below at one or more of the following positions (using Kabat numbering):

- a) S95 in position 1 is substituted for tryptophan (W)
- 5 b) I96 in position 2 is substituted for valine (V)
- c) Y97 in position 3 is substituted for phenylalanine (F)
- d) D98 in position 4 is substituted for glutamine (E)
- e) H100A in position 7 is substituted for alanine (A), glutamic acid (E), glutamine (Q), Arginine (R), Serine (S), threonine (T) or valine (V), and
- 10 f) Y100B in position 8 is substituted for alanine (A), isoleucine, (I), tryptophan (W) or valine (V).

In another aspect of the invention there is provided an antigen binding protein, for example an antibody which binds human IL-13 and which comprises the CDRH3 set out
15 in SEQ ID NO: 3, wherein CDRH3 comprises one or more of the following substitutions: S95W, I96V, Y97F, D98E, H100A_A, H100A_E, H100A_Q, H100A_R, H100A_S, H100A_T, H100A_V, Y100B_A, Y100B_I, Y100B_W, and Y100B_V.

In one aspect the antigen binding protein of the present invention, for example the
20 antibody of the present invention, comprises a CDRH3 sequence selected from those set out in SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8 and SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14 and SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17 and SEQ ID NO: 18. Such antigen binding proteins may further comprise the following CDR sequences:
25 CDRH1: selected from SEQ ID NO: 1, 60 and 61,
CDRH2: SEQ ID NO: 2;
CDRL1: SEQ ID NO: 19;
CDRL2: SEQ ID NO: 20; and
CDRL3: SEQ ID NO: 21.

30 In one embodiment the antigen binding protein comprises the following CDRs:
CDRH1: SEQ ID NO: 1,
CDRH2: SEQ ID NO: 2;
CDRH3: SEQ ID NO: 18
35 CDRL1: SEQ ID NO: 19;
CDRL2: SEQ ID NO: 20; and
CDRL3: SEQ ID NO: 21.

In another embodiment the antigen binding protein comprises the following CDRs:
40 CDRH1: SEQ ID NO: 1,
CDRH2: SEQ ID NO: 2;
CDRH3: SEQ ID NO: 17
CDRL1: SEQ ID NO: 19;
CDRL2: SEQ ID NO: 20; and
45 CDRL3: SEQ ID NO: 21.

In another embodiment the antigen binding protein comprises the following CDRs:

CDRH1: SEQ ID NO:1,
 CDRH2: SEQ ID NO:2;
 5 CDRH3: SEQ ID NO:16
 CDRL1: SEQ ID NO:19;
 CDRL2: SEQ ID NO:20; and
 CDRL3: SEQ ID NO:21.

10 In another embodiment the antigen binding protein comprises the following CDRs:

CDRH1: SEQ ID NO:1,
 CDRH2: SEQ ID NO:2;
 CDRH3: SEQ ID NO:15
 CDRL1: SEQ ID NO:19;
 15 CDRL2: SEQ ID NO:20; and
 CDRL3: SEQ ID NO:21.

Throughout this specification, amino acid residues in antibody sequences are numbered according to the Kabat scheme. Similarly, the terms "CDR", "CDRL1",
 20 "CDRL2", "CDRL3", "CDRH1", "CDRH2", "CDRH3", unless otherwise indicated (e.g. CDRH3 as set out in SEQ ID NO:60 and 61), follow the Kabat numbering system as set forth in Kabat *et al*; "Sequences of proteins of Immunological Interest" NIH, 1987.

In another aspect of the invention there is provided an antigen binding protein, such as a
 25 humanised antibody or antigen binding fragment thereof, comprising a heavy chain having the sequence selected from SEQ ID NO: 26, SEQ ID NO: 28, SEQ ID NO: 30, SEQ ID NO: 32, SEQ ID NO: 34, SEQ ID NO: 36, SEQ ID NO: 38, SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 50, SEQ ID NO: 52, SEQ ID NO: 54, SEQ ID NO: 88, SEQ ID NO: 89, SEQ ID NO: 90 and SEQ ID
 30 NO: 91; and the light chain of SEQ ID NO:24.

The invention provides an antigen binding protein, such as a humanised antibody or antigen binding fragment thereof, comprising a heavy chain selected from SEQ ID NO: 26, SEQ ID NO: 28, SEQ ID NO: 30, SEQ ID NO: 32, SEQ ID NO: 34, SEQ ID NO: 36,
 35 SEQ ID NO: 38, SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 50, SEQ ID NO: 52, SEQ ID NO: 54, SEQ ID NO: 88, SEQ ID NO: 89, SEQ ID NO: 90.

The invention also provides an antigen binding protein, such as a humanised antibody or
 40 antigen binding fragment thereof, comprising a light chain selected from SEQ ID NO: 108, SEQ ID NO: 110, SEQ ID NO: 112 and SEQ ID NO: 114.

The invention further provides an antigen binding protein, such as a humanised antibody or antigen binding fragment thereof, comprising a heavy chain having the sequence
 45 selected from SEQ ID NO: 26, SEQ ID NO: 28, SEQ ID NO: 30, SEQ ID NO: 32, SEQ ID

NO: 34, SEQ ID NO: 36, SEQ ID NO: 38, SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 50, SEQ ID NO: 52, SEQ ID NO: 54, SEQ ID NO: 88, SEQ ID NO: 89, SEQ ID NO: 90 and SEQ ID NO: 91; and the light chain of SEQ ID NO: 108, SEQ ID NO: 110, SEQ ID NO: 112 and SEQ ID NO: 114.

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In one embodiment the antigen binding protein of the present invention comprises an antibody comprising a heavy chain selected from SEQ ID NO: 26, SEQ ID NO: 28, SEQ ID NO: 30, SEQ ID NO: 32, SEQ ID NO: 34, SEQ ID NO: 36, SEQ ID NO: 38, SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 50, SEQ ID NO: 52, SEQ ID NO: 54, SEQ ID NO: 88, SEQ ID NO: 89, SEQ ID NO: 90 and SEQ ID NO: 91 and a light chain selected from SEQ ID NO: 24, SEQ ID NO: 108, SEQ ID NO: 110, SEQ ID NO: 112 and SEQ ID NO: 114.

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In one embodiment the antigen binding protein of the present invention comprises a heavy chain selected from SEQ ID NO: 48, SEQ ID NO: 50, SEQ ID NO: 52 and SEQ ID NO: 54; and a light chain selected from SEQ ID NO: 24, SEQ ID NO: 108, SEQ ID NO: 110, SEQ ID NO: 112 and SEQ ID NO: 114, for example the antigen binding protein comprises the heavy chain of SEQ ID NO: 48 and the light chain of SEQ ID NO: 24, or the heavy chain of SEQ ID NO: 50 and the light chain of SEQ ID NO: 24, or the heavy chain of SEQ ID NO: 52 and the light chain of SEQ ID NO: 24, or the heavy chain of SEQ ID NO: 54 and the light chain of SEQ ID NO: 24, or the heavy chain of SEQ ID NO: 88 and the light chain of SEQ ID NO: 24 or the heavy chain of SEQ ID NO: 89 and the light chain of SEQ ID NO: 24, or the heavy chain of SEQ ID NO: 90 and the light chain of SEQ ID NO: 24, or the heavy chain of SEQ ID NO: 91 and the light chain of SEQ ID NO: 24, or the heavy chain of SEQ ID NO: 48 and the light chain of SEQ ID NO: 108, or the heavy chain of SEQ ID NO: 50 and the light chain of SEQ ID NO: 108, or the heavy chain of SEQ ID NO: 52 and the light chain of SEQ ID NO: 108, or the heavy chain of SEQ ID NO: 54 and the light chain of SEQ ID NO: 108, or the heavy chain of SEQ ID NO: 88 and the light chain of SEQ ID NO: 108 or the heavy chain of SEQ ID NO: 89 and the light chain of SEQ ID NO: 108, or the heavy chain of SEQ ID NO: 90 and the light chain of SEQ ID NO: 108, or the heavy chain of SEQ ID NO: 91 and the light chain of SEQ ID NO: 108, or the heavy chain of SEQ ID NO: 48 and the light chain of SEQ ID NO: 110, or the heavy chain of SEQ ID NO: 50 and the light chain of SEQ ID NO: 110, or the heavy chain of SEQ ID NO: 52 and the light chain of SEQ ID NO: 110, or the heavy chain of SEQ ID NO: 54 and the light chain of SEQ ID NO: 110, or the heavy chain of SEQ ID NO: 88 and the light chain of SEQ ID NO: 110 or the heavy chain of SEQ ID NO: 89 and the light chain of SEQ ID NO: 110, or the heavy chain of SEQ ID NO: 90 and the light chain of SEQ ID NO: 110, or the heavy chain of SEQ ID NO: 91 and the light chain of SEQ ID NO: 110.

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In one such embodiment the antigen binding protein of the present invention comprises a heavy chain selected from SEQ ID NO: 48, SEQ ID NO: 50, SEQ ID NO: 52 and SEQ ID NO: 54; and a light chain selected from SEQ ID NO: 108 and SEQ ID NO: 110, for example the antigen binding protein comprises the heavy chain of SEQ ID NO: 48 and the light chain of SEQ ID NO: 108, or the antigen binding protein comprises the heavy chain of SEQ ID NO: 48 and the light chain of SEQ ID NO: 110, or the antigen binding

protein comprises the heavy chain of SEQ ID NO: 50 and the light chain of SEQ ID NO:108, or the antigen binding protein comprises the heavy chain of SEQ ID NO: 50 and the light chain of SEQ ID NO:110, or the antigen binding protein comprises the heavy chain of SEQ ID NO: 52 and the light chain of SEQ ID NO:108, or the antigen binding protein comprises the heavy chain of SEQ ID NO: 52 and the light chain of SEQ ID NO:110, or the antigen binding protein comprises the heavy chain of SEQ ID NO: 54 and the light chain of SEQ ID NO:108, or the antigen binding protein comprises the heavy chain of SEQ ID NO: 54 and the light chain of SEQ ID NO:110.

The IL-13 antibodies of the present invention may be combined with an IL-4 and/or an IL-5 antagonist, for example an IL-4 antibody or epitope binding domain, and/or an IL-5 antibody or epitope binding domain. These may be administered as a mixture of separate molecules which are administered at the same time i.e. co-administered, or are administered within 24 hours of each other, for example within 20 hours, or within 15 hours or within 12 hours, or within 10 hours, or within 8 hours, or within 6 hours, or within 4 hours, or within 2 hours, or within 1 hour, or within 30 minutes of each other.

In a further embodiment the antagonists are present as one molecule capable of binding to two or more antigens, for example the invention provides an antigen binding protein comprising the IL-13 antibody of the present invention which is capable of binding to IL-13 and which is also capable of binding to IL-4 or which is also capable of binding to IL-5, or which is also capable of binding to IL-4 and IL-5.

In one embodiment the antigen binding protein of the present invention may be a multi-specific antibody which comprises at least CDRH3, and optionally one or more of CDRH1, CDRH2, CDRL1, CDRL2, and CDRL3 of the present invention, which is capable of binding to IL-13 and which is also capable of binding to one or more of IL-4 or IL-5. In one such embodiment, a multi-specific antibody is provided which comprises a CDRH3, or an antigen binding protein as defined herein, and which comprises a further antigen binding site which is capable of binding to IL-4, or IL-5.

One example of an antigen binding protein of the present invention is an antibody specific for IL-13 comprising CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 as defined herein, linked to one or more epitope-binding domains which have specificity for IL-4 or IL-5, for example a bispecific antigen binding protein which is capable of binding to IL-13 and IL-4, or IL-13 and IL-5, or a trispecific antigen binding protein which is capable of binding to IL-13, IL-4 and IL-5.

It will be understood that any of the antigen-binding proteins described herein may be capable of binding two or more antigens simultaneously, for example, as determined by stoichiometry analysis by using a suitable assay such as that described in Example 8.

The present invention provides an antigen-binding protein comprising the IL-13 antibody of the present invention which is linked to one or more epitope-binding domains, for example an antigen-binding protein comprising the IL-13 antibody of the present

invention linked to an epitope-binding domain which is capable of binding to IL-4, or an antigen-binding protein comprising the IL-13 antibody of the present invention linked to an epitope-binding domain which is capable of binding to IL-5, or an antigen-binding protein comprising the IL-13 antibody of the present invention linked to a first epitope-binding domain which is capable of binding to IL-4 and a second epitope-binding domain which is capable of binding to IL-5.

The epitope-binding domain may be attached to the c-terminus or the n-terminus of the heavy chain of the IL-13 antibody or the c-terminus or n-terminus of the light chain of the IL-13 antibody.

Antibodies of the present invention may be linked to epitope binding domains by the use of linkers. Examples of suitable linkers include amino acid sequences which may be from 1 amino acid to 150 amino acids in length, or from 1 amino acid to 140 amino acids, for example, from 1 amino acid to 130 amino acids, or from 1 to 120 amino acids, or from 1 to 80 amino acids, or from 1 to 50 amino acids, or from 1 to 20 amino acids, or from 1 to 10 amino acids, or from 5 to 18 amino acids. Such sequences may have their own tertiary structure, for example, a linker of the present invention may comprise a single variable domain. The size of a linker in one embodiment is equivalent to a single variable domain. Suitable linkers may be of a size from 1 to 20 angstroms, for example less than 15 angstroms, or less than 10 angstroms, or less than 5 angstroms.

In one embodiment of the present invention at least one of the epitope binding domains is directly attached to the IL-13 antibody with a linker comprising from 1 to 150 amino acids, for example 1 to 20 amino acids, for example 1 to 10 amino acids.

Such linkers may be selected from any one of those set out in SEQ ID NO:82-87, 92 to 93. or multiples of such linkers.

Linkers of use in the antigen-binding proteins of the present invention may comprise alone or in addition to other linkers, one or more sets of GS residues, for example 'GSTVAAPS' (SEQ ID NO: 92) or 'TVAAPSGS' (SEQ ID NO: 87) or 'GSTVAAPSGS' (SEQ ID NO: 93). In one embodiment the linker comprises SEQ ID NO: 83.

In one embodiment the epitope binding domain is linked to the IL-13 antibody by the linker '(PAS)_n(GS)_m'. In another embodiment the epitope binding domain is linked to the IL-13 antibody by the linker '(GGGGS)_n(GS)_m'. In another embodiment the epitope binding domain is linked to the IL-13 antibody by the linker '(TVAAPS)_n(GS)_m'. In another embodiment the epitope binding domain is linked to the IL-13 antibody by the linker '(GS)_m(TVAAPSGS)_n'. In another embodiment the epitope binding domain is linked to the IL-13 antibody by the linker '(PAVPPP)_n(GS)_m'. In another embodiment the epitope binding domain is linked to the IL-13 antibody by the linker '(TVSDVP)_n(GS)_m'. In another embodiment the epitope binding domain is linked to the IL-13 antibody by the linker '(TGLDSP)_n(GS)_m'. In all such embodiments, n = 1-10, and m = 0-4.

Examples of such linkers include $(PAS)_n(GS)_m$ wherein $n=1$ and $m=1$, $(PAS)_n(GS)_m$ wherein $n=2$ and $m=1$, $(PAS)_n(GS)_m$ wherein $n=3$ and $m=1$, $(PAS)_n(GS)_m$ wherein $n=4$ and $m=1$, $(PAS)_n(GS)_m$ wherein $n=2$ and $m=0$, $(PAS)_n(GS)_m$ wherein $n=3$ and $m=0$, $(PAS)_n(GS)_m$ wherein $n=4$ and $m=0$.

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Examples of such linkers include $(GGGGS)_n(GS)_m$ wherein $n=1$ and $m=1$, $(GGGGS)_n(GS)_m$ wherein $n=2$ and $m=1$, $(GGGGS)_n(GS)_m$ wherein $n=3$ and $m=1$, $(GGGGS)_n(GS)_m$ wherein $n=4$ and $m=1$, $(GGGGS)_n(GS)_m$ wherein $n=2$ and $m=0$, $(GGGGS)_n(GS)_m$ wherein $n=3$ and $m=0$, $(GGGGS)_n(GS)_m$ wherein $n=4$ and $m=0$.

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Examples of such linkers include $(TVAAPS)_n(GS)_m$ wherein $n=1$ and $m=1$ (SEQ ID NO:87), $(TVAAPS)_n(GS)_m$ wherein $n=2$ and $m=1$ (SEQ ID NO:145), $(TVAAPS)_n(GS)_m$ wherein $n=3$ and $m=1$ (SEQ ID NO:146), $(TVAAPS)_n(GS)_m$ wherein $n=4$ and $m=1$, $(TVAAPS)_n(GS)_m$ wherein $n=2$ and $m=0$, $(TVAAPS)_n(GS)_m$ wherein $n=3$ and $m=0$, $(TVAAPS)_n(GS)_m$ wherein $n=4$ and $m=0$.

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Examples of such linkers include $(GS)_m(TVAAPSGS)_n$ wherein $n=1$ and $m=1$ (SEQ ID NO:139), $(GS)_m(TVAAPSGS)_n$ wherein $n=2$ and $m=1$ (SEQ ID NO:140), $(GS)_m(TVAAPSGS)_n$ wherein $n=3$ and $m=1$ (SEQ ID NO:141), or $(GS)_m(TVAAPSGS)_n$ wherein $n=4$ and $m=1$ (SEQ ID NO:142), $(GS)_m(TVAAPSGS)_n$ wherein $n=5$ and $m=1$ (SEQ ID NO:143), $(GS)_m(TVAAPSGS)_n$ wherein $n=6$ and $m=1$ (SEQ ID NO:144), $(GS)_m(TVAAPSGS)_n$ wherein $n=1$ and $m=0$ (SEQ ID NO:87), $(GS)_m(TVAAPSGS)_n$ wherein $n=2$ and $m=10$, $(GS)_m(TVAAPSGS)_n$ wherein $n=3$ and $m=0$, or $(GS)_m(TVAAPSGS)_n$ wherein $n=0$.

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Examples of such linkers include $(PAVPPP)_n(GS)_m$ wherein $n=1$ and $m=1$, $(PAVPPP)_n(GS)_m$ wherein $n=2$ and $m=1$ (SEQ ID NO: 65), $(PAVPPP)_n(GS)_m$ wherein $n=3$ and $m=1$, $(PAVPPP)_n(GS)_m$ wherein $n=4$ and $m=1$, $(PAVPPP)_n(GS)_m$ wherein $n=2$ and $m=0$, $(PAVPPP)_n(GS)_m$ wherein $n=3$ and $m=0$, $(PAVPPP)_n(GS)_m$ wherein $n=4$ and $m=0$.

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Examples of such linkers include $(TVSDVP)_n(GS)_m$ wherein $n=1$ and $m=1$ (SEQ ID NO: 67), $(TVSDVP)_n(GS)_m$ wherein $n=2$ and $m=1$, $(TVSDVP)_n(GS)_m$ wherein $n=3$ and $m=1$, $(TVSDVP)_n(GS)_m$ wherein $n=4$ and $m=1$, $(TVSDVP)_n(GS)_m$ wherein $n=2$ and $m=0$, $(TVSDVP)_n(GS)_m$ wherein $n=3$ and $m=0$, $(TVSDVP)_n(GS)_m$ wherein $n=4$ and $m=0$.

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Examples of such linkers include $(TGLDSP)_n(GS)_m$ wherein $n=1$ and $m=1$, $(TGLDSP)_n(GS)_m$ wherein $n=2$ and $m=1$, $(TGLDSP)_n(GS)_m$ wherein $n=3$ and $m=1$, $(TGLDSP)_n(GS)_m$ wherein $n=4$ and $m=1$, $(TGLDSP)_n(GS)_m$ wherein $n=2$ and $m=0$, $(TGLDSP)_n(GS)_m$ wherein $n=3$ and $m=0$, $(TGLDSP)_n(GS)_m$ wherein $n=4$ and $m=0$.

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In another embodiment there is no linker between the epitope binding domain and the IL-13 antibody. In another embodiment the epitope binding domain is linked to the IL-13 antibody by the linker 'TVAAPS' (SEQ ID NO: 83). In another embodiment the epitope binding domain, is linked to the IL-13 antibody by the linker 'TVAAPSGS' (SEQ ID NO: 87). In another embodiment the epitope binding domain is linked to the IL-13 antibody by

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the linker 'GS'. In another embodiment the epitope binding domain is linked to the IL-13 antibody by the linker 'ASTKGPT' (SEQ ID NO: 84).

Epitope-binding domains of use in the present invention are domains that specifically bind an antigen or epitope independently of a different V region or domain, this may be a domain antibody or may be a non-Immunoglobulin domain, for example a domain which is a derivative of a scaffold selected from the group consisting of CTLA-4 (Evibody); lipocalin; Protein A derived molecules such as Z-domain of Protein A (Affibody, SpA), A-domain (Avimer/Maxibody); Heat shock proteins such as GroEl and GroES; transferrin (trans-body); ankyrin repeat protein (DARPin); peptide aptamer; C-type lectin domain (Tetranectin); human γ -crystallin and human ubiquitin (affilins); PDZ domains; scorpion toxin; kunitz type domains of human protease inhibitors; and fibronectin (adnectin); which has been subjected to protein engineering in order to obtain binding to a ligand other than the natural ligand. In one embodiment this may be an domain antibody or other suitable domains such as a domain selected from the group consisting of CTLA-4, lipocalin, SpA, an Affibody, an avimer, GroEl, transferrin, GroES and fibronectin. In one embodiment this may be selected from an immunoglobulin single variable domain, an Affibody, an ankyrin repeat protein (DARPin) and an adnectin. In another embodiment this may be selected from an Affibody, an ankyrin repeat protein (DARPin) and an adnectin. In another embodiment this may be a domain antibody, for example a domain antibody selected from a human, camelid (nanobody), or shark (NARV) domain antibody.

Examples of such antigen-binding proteins include the IL-13 antibodies of the present invention which have an epitope binding domain which is an IL-4 antagonist attached to the c-terminus or the n-terminus of the heavy chain or the c-terminus. Examples include an antigen binding protein comprising the heavy chain sequence set out in SEQ ID NO: 26, SEQ ID NO: 28, SEQ ID NO: 30, SEQ ID NO: 32, SEQ ID NO: 34, SEQ ID NO: 36, SEQ ID NO: 38, SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 50, SEQ ID NO: 52, SEQ ID NO: 54, SEQ ID NO: 98, SEQ ID NO: 100, SEQ ID NO: 102, SEQ ID NO: 104, SEQ ID NO: 106 or SEQ ID NO: 117-138, and the light chain sequence set out in SEQ ID NO: 24, SEQ ID NO: 108, SEQ ID NO: 110, SEQ ID NO: 112 or SEQ ID NO: 114, wherein one or both of the Heavy and Light chain further comprise one or more epitope-binding domains which is capable of antagonising IL-4, for example single variable domains which are capable of binding to IL-4. Such epitope-binding domains can be selected from those set out in SEQ ID NO: 78-81 and 94.

In one embodiment the antigen binding constructs of the present invention comprise the heavy chain sequence of SEQ ID NO: 62 and the light chain sequence of SEQ ID NO: 24, or the heavy chain sequence of SEQ ID NO: 64 and the light chain sequence of SEQ ID NO: 24, or the heavy chain sequence of SEQ ID NO: 66 and the light chain sequence of SEQ ID NO: 24, or the heavy chain sequence of SEQ ID NO: 68 and the light chain sequence of SEQ ID NO: 24, or the heavy chain sequence of SEQ ID NO: 70 and the light chain sequence of SEQ ID NO: 24, or the heavy chain sequence of SEQ ID NO: 72

and the light chain sequence of SEQ ID NO: 24, or the heavy chain sequence of SEQ ID NO:74 and the light chain sequence of SEQ ID NO: 24, or the heavy chain sequence of SEQ ID NO: 76 and the light chain sequence of SEQ ID NO: 24.

5 In one embodiment the antigen binding constructs of the present invention comprise the heavy chain sequence of SEQ ID NO: 94 and the light chain sequence of SEQ ID NO: 24, or the heavy chain sequence of SEQ ID NO: 96 and the light chain sequence of SEQ ID NO: 24, or the heavy chain sequence of SEQ ID NO: 98 and the light chain sequence of SEQ ID NO: 24, or the heavy chain sequence of SEQ ID NO: 100 and the light chain sequence of SEQ ID NO: 24, or the heavy chain sequence of SEQ ID NO: 102 and the light chain sequence of SEQ ID NO: 24, or the heavy chain sequence of SEQ ID NO: 104 and the light chain sequence of SEQ ID NO: 24, or the heavy chain sequence of SEQ ID NO:106 and the light chain sequence of SEQ ID NO: 24.

15 In one embodiment the antigen binding constructs of the present invention comprise the heavy chain sequence of SEQ ID NO: 62 and the light chain sequence of SEQ ID NO: 108, or the heavy chain sequence of SEQ ID NO: 64 and the light chain sequence of SEQ ID NO: 108, or the heavy chain sequence of SEQ ID NO: 66 and the light chain sequence of SEQ ID NO: 108, or the heavy chain sequence of SEQ ID NO: 68 and the light chain sequence of SEQ ID NO: 108, or the heavy chain sequence of SEQ ID NO: 70 and the light chain sequence of SEQ ID NO: 108, or the heavy chain sequence of SEQ ID NO: 72 and the light chain sequence of SEQ ID NO: 108, or the heavy chain sequence of SEQ ID NO:74 and the light chain sequence of SEQ ID NO: 108, or the heavy chain sequence of SEQ ID NO: 76 and the light chain sequence of SEQ ID NO: 108, or the heavy chain sequence of SEQ ID NO: 62 and the light chain sequence of SEQ ID NO: 110, or the heavy chain sequence of SEQ ID NO: 64 and the light chain sequence of SEQ ID NO: 110, or the heavy chain sequence of SEQ ID NO: 66 and the light chain sequence of SEQ ID NO: 110, or the heavy chain sequence of SEQ ID NO: 68 and the light chain sequence of SEQ ID NO: 110, or the heavy chain sequence of SEQ ID NO: 70 and the light chain sequence of SEQ ID NO: 110, or the heavy chain sequence of SEQ ID NO: 72 and the light chain sequence of SEQ ID NO: 110, or the heavy chain sequence of SEQ ID NO:74 and the light chain sequence of SEQ ID NO: 110, or the heavy chain sequence of SEQ ID NO: 76 and the light chain sequence of SEQ ID NO: 110.

In one embodiment the antigen binding constructs of the present invention comprise the heavy chain sequence of SEQ ID NO: 96 and the light chain sequence of SEQ ID NO: 108, or the heavy chain sequence of SEQ ID NO: 98 and the light chain sequence of SEQ ID NO: 108, or the heavy chain sequence of SEQ ID NO: 100 and the light chain sequence of SEQ ID NO: 108, or the heavy chain sequence of SEQ ID NO: 102 and the light chain sequence of SEQ ID NO: 108, or the heavy chain sequence of SEQ ID NO: 104 and the light chain sequence of SEQ ID NO: 108, or the heavy chain sequence of SEQ ID NO: 106 and the light chain sequence of SEQ ID NO: 108, or the heavy chain sequence of SEQ ID NO: 96 and the light chain sequence of SEQ ID NO: 110, or the

heavy chain sequence of SEQ ID NO: 98 and the light chain sequence of SEQ ID NO: 110, or the heavy chain sequence of SEQ ID NO: 100 and the light chain sequence of SEQ ID NO: 110, or the heavy chain sequence of SEQ ID NO: 102 and the light chain sequence of SEQ ID NO: 110, or the heavy chain sequence of SEQ ID NO: 104 and the light chain sequence of SEQ ID NO: 110, or the heavy chain sequence of SEQ ID NO: 106 and the light chain sequence of SEQ ID NO: 110.

In one embodiment the IL-13 antibody heavy chain is selected from those set out in SEQ ID NO: 48, SEQ ID NO: 50, SEQ ID NO: 52 and SEQ ID NO: 54. In another embodiment the heavy chain is selected from those set out in SEQ ID NO: 88-91, SEQ ID NO: 96-106, and SEQ ID NO: 117-138. In one such embodiment the heavy chain is selected from SEQ ID NO: 96, SEQ ID NO: 98, SEQ ID NO: 100, SEQ ID NO: 102, SEQ ID NO: 104 and SEQ ID NO: 106.

In one embodiment the antigen-binding protein will comprise an anti-IL-13 antibody linked to an epitope binding domain which is a IL-5 antagonist, wherein the anti-IL-13 antibody comprises the CDRH3 selected from those set out in SEQ ID NO: 3-18, for example SEQ ID NO: 15-18 and the light chain sequence of SEQ ID NO: 24.

Examples include an antigen binding protein comprising the heavy chain sequence set out in SEQ ID NO: 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52 or 54 and the light chain sequence set out in SEQ ID NO: 24 wherein one or both of the Heavy and Light chain further comprise one or more epitope-binding domains which is capable of antagonising IL-5, for example immunoglobulin single variable domains which are capable of binding to IL-5.

In a further embodiment, the antigen binding protein will comprise the heavy chain sequence set out in SEQ ID NO: 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52 or 54 and the light chain sequence set out in SEQ ID NO: 24 wherein one or both of the Heavy and Light chain further comprise one or more epitope-binding domains which are capable of antagonising IL-4 for example immunoglobulin single variable domains which are capable of binding to IL-4, and one or more epitope-binding domains which are capable of antagonising IL-5, for example immunoglobulin single variable domains which are capable of binding to IL-5.

In one embodiment, the antigen-binding protein of the present invention comprises at least one epitope binding domain, which is capable of binding human serum albumin.

In one embodiment, there are at least 3 antigen-binding sites, for example there are 4, or 5 or 6 or 8 or 10 antigen-binding sites and the antigen-binding protein is capable of binding at least 3 or 4 or 5 or 6 or 8 or 10 antigens, for example it is capable of binding 3 or 4 or 5 or 6 or 8 or 10 antigens simultaneously.

In one embodiment, a first epitope binding domain is linked to the protein scaffold and a second epitope binding domain is linked to the first epitope binding domain, for example

where the protein scaffold is an IgG scaffold, a first epitope binding domain may be linked to the c-terminus of the heavy chain of the IgG scaffold, and that epitope binding domain can be linked at its c-terminus to a second epitope binding domain, or for example a first epitope binding domain may be linked to the c-terminus of the light chain of the IgG scaffold, and that first epitope binding domain may be further linked at its c-terminus to a second epitope binding domain, or for example a first epitope binding domain may be linked to the n-terminus of the light chain of the IgG scaffold, and that first epitope binding domain may be further linked at its n-terminus to a second epitope binding domain, or for example a first epitope binding domain may be linked to the n-terminus of the heavy chain of the IgG scaffold, and that first epitope binding domain may be further linked at its n-terminus to a second epitope binding domain.

When the epitope-binding domain is a domain antibody, some domain antibodies may be suited to particular positions within the scaffold.

Immunoglobulin single variable domains of use in the present invention can be linked at the C-terminal end of the heavy chain and/or the light chain of the IL-13 mAb. In addition some immunoglobulin single variable domains can be linked to the C-terminal ends of both the heavy chain and the light chain of conventional antibodies.

In constructs where the N-terminus of immunoglobulin single variable domains are fused to an antibody constant domain (either C_H3 or CL), a peptide linker may help the immunoglobulin single variable domain to bind to antigen. Indeed, the N-terminal end of a dAb is located closely to the CDRs involved in antigen-binding activity. Thus a short peptide linker acts as a spacer between the epitope-binding domain, and the constant domain of the antibody, which may allow the dAb CDRs to more easily reach the antigen, which may therefore bind with high affinity.

The surroundings in which immunoglobulin single variable domains are linked to the IgG will differ depending on which antibody chain they are fused to:

When fused at the C-terminal end of the antibody light chain, each immunoglobulin single variable domain is expected to be located in the vicinity of the antibody hinge and the Fc portion. It is likely that such immunoglobulin single variable domains will be located far apart from each other. In conventional antibodies, the angle between Fab fragments and the angle between each Fab fragment and the Fc portion can vary quite significantly. It is likely that – with mAbdAbs – the angle between the Fab fragments will not be widely different, whilst some angular restrictions may be observed with the angle between each Fab fragment and the Fc portion.

When fused at the C-terminal end of the antibody heavy chain, each immunoglobulin single variable domain is expected to be located in the vicinity of the C_H3 domains of the Fc portion. This is not expected to impact on the Fc binding properties to Fc receptors (e.g. FcγRI, II, III and FcRn) as these receptors engage with the C_H2 domains (for the FcγRI, II and III class of receptors) or with the hinge between the C_H2 and C_H3 domains (e.g. FcRn receptor). Another feature of such antigen-binding proteins is that both immunoglobulin single variable domains are expected to be spatially close to each other

and provided that flexibility is provided by provision of appropriate linkers, these immunoglobulin single variable domains may even form homodimeric species, hence propagating the 'zipped' quaternary structure of the Fc portion, which may enhance stability of the construct.

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Such structural considerations can aid in the choice of the most suitable position to link an epitope-binding domain, for example an immunoglobulin single variable domain, on to an antibody.

- 10 The size of the antigen, its localization (in blood or on cell surface), its quaternary structure (monomeric or multimeric) can vary. Conventional antibodies are naturally designed to function as adaptor constructs due to the presence of the hinge region, wherein the orientation of the two antigen-binding sites at the tip of the Fab fragments can vary widely and hence adapt to the molecular feature of the antigen and its
- 15 surroundings. In contrast immunoglobulin single variable domains linked to an antibody with no hinge region, may have less structural flexibility either directly or indirectly.

- Understanding the solution state and mode of binding at the immunoglobulin single variable domain is also helpful. Evidence has accumulated that *in vitro* human dAbs can
- 20 predominantly exist in monomeric, homo-dimeric or multimeric forms in solution (Reiter et al. (1999) J Mol Biol 290 p685-698; Ewert et al (2003) J Mol Biol 325, p531-553, Jespers et al (2004) J Mol Biol 337 p893-903; Jespers et al (2004) Nat Biotechnol 22 p1161-1165; Martin et al (1997) Protein Eng. 10 p607-614; Sepulveda et al (2003) J Mol Biol 333 p355-365). This is fairly reminiscent to multimerisation events observed *in vivo*
- 25 with Ig domains such as Bence-Jones proteins (which are dimers of immunoglobulin light chains (Epp et al (1975) Biochemistry 14 p4943-4952; Huan et al (1994) Biochemistry 33 p14848-14857; Huang et al (1997) Mol immunol 34 p1291-1301) and amyloid fibers (James et al. (2007) J Mol Biol. **367**:603-8).

- 30 For example, it may be desirable to link dAbs that tend to dimerise in solution to the C-terminal end of the Fc portion in preference to the C-terminal end of the light chain as linking to the C-terminal end of the Fc will allow those dAbs to dimerise in the context of the antigen-binding protein of the invention.

- 35 The antigen-binding proteins of the present invention may comprise antigen-binding sites specific for a single antigen, or may have antigen-binding sites specific for two or more antigens, or for two or more epitopes on a single antigen, or there may be antigen-binding sites each of which is specific for a different epitope on the same or different antigens.

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The antigen binding proteins of the invention may comprise heavy chain variable regions and light chain variable regions of the invention which may be formatted into the structure of a natural antibody or functional fragment or equivalent thereof. An antigen binding protein of the invention may therefore comprise the VH regions of the invention

45 formatted into a full length antibody, a (Fab')₂ fragment, a Fab fragment, or equivalent

thereof (such as scFV, bi- tri- or tetra-bodies, Tandabs etc.), when paired with an appropriate light chain. The antibody may be an IgG1, IgG2, IgG3, or IgG4; or IgM; IgA, IgE or IgD or a modified variant thereof. The constant domain of the antibody heavy chain may be selected accordingly. The light chain constant domain may be a kappa or
 5 lambda constant domain. Furthermore, the antigen binding protein may comprise modifications of all classes e.g. IgG dimers, Fc mutants that no longer bind Fc receptors or mediate C1q binding. The antigen binding protein may also be a chimeric antibody of the type described in WO86/01533 which comprises an antigen binding region and a non-immunoglobulin region.

10

The constant region is selected according to any functionality required. An IgG1 may demonstrate lytic ability through binding to complement and/or will mediate ADCC (antibody dependent cell cytotoxicity). An IgG4 can be used if a non-cytotoxic blocking antibody is required. However, IgG4 antibodies can demonstrate instability in production
 15 and therefore an alternative is to modify the generally more stable IgG1. Suggested modifications are described in EP0307434, for example mutations at positions 235 and 237. The invention therefore provides a lytic or a non-lytic form of an antigen binding protein, for example an antibody according to the invention.

20

In certain forms the antibody of the invention is a full length (e.g. H2L2 tetramer) lytic or non-lytic IgG1 antibody having any of the heavy chain variable regions described herein. In a further aspect, the invention provides polynucleotides encoding the light and heavy chain variable regions as described herein.

25

In one embodiment of the invention the antigen-binding site binds to antigen with a K_d of at least about 1mM, for example a K_d of at least about 10nM, at least about 1nM, at least about 500pM, at least about 200pM, at least about 100pM, or at least about 50pM to each antigen as measured by BiacoreTM.

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In one embodiment of the invention the antigen-binding site binds to antigen with a K_d of at least about 1mM, for example a K_d of at least about 10nM, at least about 1nM, at least about 500pM, at least about 200pM, at least about 100pM, or at least about 50pM to each antigen as measured by BiacoreTM.

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In one embodiment the invention provides antigen binding proteins which have at least a 2 fold higher affinity, or at least 4 fold higher affinity, or at least 6 fold higher affinity, or at least 8 fold higher affinity, or at least 10 fold higher affinity for human IL-13 as measured by Biacore than the anti-IL-13 antibody comprising the heavy chain sequence set out in SEQ ID NO:22 and the light chain sequence set out in SEQ ID NO:24.

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The term "neutralises" and grammatical variations thereof as used throughout the present specification in relation to antigen binding proteins of the invention means that a biological activity of IL-13 is reduced, either totally or partially, in the presence of the antigen binding proteins of the present invention in comparison to the activity of IL-13 in
 45 the absence of such antigen binding proteins. Neutralisation may be due to but not

limited to one or more of blocking ligand binding, preventing the ligand activating the receptor, down regulating the IL-13 receptor or affecting effector functionality. Levels of neutralisation can be measured in several ways, for example by use of the assays as set out in the examples below, for example in a TF1 assay which may be carried out for example as described in Example 4. The neutralisation of IL-13, IL-4 or both of these cytokines in this assay is measured by assessing the inhibition of TF1 cell proliferation in the presence of neutralising antigen binding protein.

Other methods of assessing neutralisation, for example, by assessing the decreased binding between the IL-13 and its receptor in the presence of neutralising antigen binding protein are known in the art, and include, for example, Biacore assays.

In an alternative aspect of the present invention there is provided antigen binding proteins which have at least substantially equivalent neutralising activity to the antibodies exemplified herein, for example antigen binding proteins which retain the neutralising activity of A1Y100BAIaL1, A1Y100BIleL1, A1 Y100BTrpL1 or A1Y100BValL1 in a TF1 cell proliferation assay which can be carried out as set out in Example 4.

The antigen binding proteins, for example antibodies of the present invention may be produced by transfection of a host cell with an expression vector comprising the coding sequence for the antigen binding protein of the invention. An expression vector or recombinant plasmid is produced by placing these coding sequences for the antigen binding protein in operative association with conventional regulatory control sequences capable of controlling the replication and expression in, and/or secretion from, a host cell. Regulatory sequences include promoter sequences, e.g., CMV promoter, and signal sequences which can be derived from other known antibodies. Similarly, a second expression vector can be produced having a DNA sequence which encodes a complementary antigen binding protein light or heavy chain. In certain embodiments this second expression vector is identical to the first except insofar as the coding sequences and selectable markers are concerned, so to ensure as far as possible that each polypeptide chain is functionally expressed. Alternatively, the heavy and light chain coding sequences for the antigen binding protein may reside on a single vector. A selected host cell is co-transfected by conventional techniques with both the first and second vectors (or simply transfected by a single vector) to create the transfected host cell of the invention comprising both the recombinant or synthetic light and heavy chains. The transfected cell is then cultured by conventional techniques to produce the engineered antigen binding protein of the invention. The antigen binding protein which includes the association of both the recombinant heavy chain and/or light chain is screened from culture by appropriate assay, such as ELISA or RIA. Similar conventional techniques may be employed to construct other antigen binding proteins.

Suitable vectors for the cloning and subcloning steps employed in the methods and construction of the compositions of this invention may be selected by one of skill in the art. For example, the conventional pUC series of cloning vectors may be used. One vector, pUC19, is commercially available from supply houses, such as Amersham

(Buckinghamshire, United Kingdom) or Pharmacia (Uppsala, Sweden). Additionally, any vector which is capable of replicating readily, has an abundance of cloning sites and selectable genes (e.g., antibiotic resistance), and is easily manipulated may be used for cloning. Thus, the selection of the cloning vector is not a limiting factor in this invention.

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The expression vectors may also be characterized by genes suitable for amplifying expression of the heterologous DNA sequences, e.g., the mammalian dihydrofolate reductase gene (DHFR). Other vector sequences include a poly A signal sequence, such as from bovine growth hormone (BGH) and the betaglobin promoter sequence (betaglopro). The expression vectors useful herein may be synthesized by techniques well known to those skilled in this art.

10

The components of such vectors, e.g. replicons, selection genes, enhancers, promoters, signal sequences and the like, may be obtained from commercial or natural sources or synthesized by known procedures for use in directing the expression and/or secretion of the product of the recombinant DNA in a selected host. Other appropriate expression vectors of which numerous types are known in the art for mammalian, bacterial, insect, yeast, and fungal expression may also be selected for this purpose.

15

The present invention also encompasses a cell line transfected with a recombinant plasmid containing the coding sequences of the antigen binding proteins of the present invention. Host cells useful for the cloning and other manipulations of these cloning vectors are also conventional. However, cells from various strains of E. coli may be used for replication of the cloning vectors and other steps in the construction of antigen binding proteins of this invention.

20

Suitable host cells or cell lines for the expression of the antigen binding proteins of the invention include mammalian cells such as NS0, Sp2/0, CHO (e.g. DG44), COS, HEK, a fibroblast cell (e.g., 3T3), and myeloma cells, for example it may be expressed in a CHO or a myeloma cell. Human cells may be used, thus enabling the molecule to be modified with human glycosylation patterns. Alternatively, other eukaryotic cell lines may be employed. The selection of suitable mammalian host cells and methods for transformation, culture, amplification, screening and product production and purification are known in the art. See, e.g., Sambrook et al., cited above.

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Bacterial cells may prove useful as host cells suitable for the expression of the recombinant Fabs or other embodiments of the present invention (see, e.g., Plückthun, A., Immunol. Rev., 130:151-188 (1992)). However, due to the tendency of proteins expressed in bacterial cells to be in an unfolded or improperly folded form or in a non-glycosylated form, any recombinant Fab produced in a bacterial cell would have to be screened for retention of antigen binding ability. If the molecule expressed by the bacterial cell was produced in a properly folded form, that bacterial cell would be a desirable host, or in alternative embodiments the molecule may express in the bacterial host and then be subsequently re-folded. For example, various strains of E. coli used for

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expression are well-known as host cells in the field of biotechnology. Various strains of *B. subtilis*, *Streptomyces*, other bacilli and the like may also be employed in this method.

5 Where desired, strains of yeast cells known to those skilled in the art are also available as host cells, as well as insect cells, e.g. *Drosophila* and *Lepidoptera* and viral expression systems. See, e.g. Miller et al., *Genetic Engineering*, 8:277-298, Plenum Press (1986) and references cited therein.

10 The general methods by which the vectors may be constructed, the transfection methods required to produce the host cells of the invention, and culture methods necessary to produce the antigen binding protein of the invention from such host cell may all be conventional techniques. Typically, the culture method of the present invention is a serum-free culture method, usually by culturing cells serum-free in suspension. Likewise, once produced, the antigen binding proteins of the invention may be purified
15 from the cell culture contents according to standard procedures of the art, including ammonium sulfate precipitation, affinity columns, column chromatography, gel electrophoresis and the like. Such techniques are within the skill of the art and do not limit this invention. For example, preparation of altered antibodies are described in WO 99/58679 and WO 96/16990.

20 Yet another method of expression of the antigen binding proteins may utilize expression in a transgenic animal, such as described in U. S. Patent No. 4,873,316. This relates to an expression system using the animal's casein promoter which when transgenically incorporated into a mammal permits the female to produce the desired recombinant
25 protein in its milk.

In a further aspect of the invention there is provided a method of producing an antibody of the invention which method comprises the step of culturing a host cell transformed or transfected with a vector encoding the light and/or heavy chain of the antibody of the
30 invention and recovering the antibody thereby produced.

In accordance with the present invention there is provided a method of producing an anti-IL-13 antibody of the present invention which binds to and neutralises the activity of human IL-13 which method comprises the steps of;
35 (a) providing a first vector encoding a heavy chain of the antibody;
(b) providing a second vector encoding a light chain of the antibody;
(c) transforming a mammalian host cell (e.g. CHO) with said first and second vectors;
(d) culturing the host cell of step (c) under conditions conducive to the secretion of the antibody from said host cell into said culture media;
40 (e) recovering the secreted antibody of step (d).

Once expressed by the desired method, the antibody is then examined for in vitro activity by use of an appropriate assay. Presently conventional ELISA assay formats are employed to assess qualitative and quantitative binding of the antibody to IL-13.
45 Additionally, other in vitro assays may also be used to verify neutralizing efficacy prior to

subsequent human clinical studies performed to evaluate the persistence of the antibody in the body despite the usual clearance mechanisms.

The dose and duration of treatment relates to the relative duration of the molecules of the present invention in the human circulation, and can be adjusted by one of skill in the art depending upon the condition being treated and the general health of the patient. It is envisaged that repeated dosing (e.g. once a week or once every two weeks) over an extended time period (e.g. four to six months) maybe required to achieve maximal therapeutic efficacy.

The mode of administration of the therapeutic agent of the invention may be any suitable route which delivers the agent to the host. The antigen binding proteins, and pharmaceutical compositions of the invention are particularly useful for parenteral administration, i.e., subcutaneously (s.c.), intrathecally, intraperitoneally, intramuscularly (i.m.), intravenously (i.v.), or intranasally.

Therapeutic agents of the invention may be prepared as pharmaceutical compositions containing an effective amount of the antigen binding protein of the invention as an active ingredient in a pharmaceutically acceptable carrier. In one embodiment the prophylactic agent of the invention is an aqueous suspension or solution containing the antigen binding protein in a form ready for injection. In one embodiment the suspension or solution is buffered at physiological pH, In one embodiment the compositions for parenteral administration will comprise a solution of the antigen binding protein of the invention or a cocktail thereof dissolved in a pharmaceutically acceptable carrier. In one embodiment the carrier is an aqueous carrier. A variety of aqueous carriers may be employed, e.g., 0.9% saline, 0.3% glycine, and the like. These solutions may be made sterile and generally free of particulate matter. These solutions may be sterilized by conventional, well known sterilization techniques (e.g., filtration). The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions such as pH adjusting and buffering agents, etc. The concentration of the antigen binding protein of the invention in such pharmaceutical formulation can vary widely, i.e., from less than about 0.5%, usually at or at least about 1% to as much as about 15 or 20% by weight and will be selected primarily based on fluid volumes, viscosities, etc., according to the particular mode of administration selected.

Thus, a pharmaceutical composition of the invention for intramuscular injection could be prepared to contain about 1 mL sterile buffered water, and between about 1 ng to about 100 mg, e.g. about 50 ng to about 30 mg or about 5 mg to about 25 mg, of an antigen binding protein, for example an antibody of the invention. Similarly, a pharmaceutical composition of the invention for intravenous infusion could be made up to contain about 250 ml of sterile Ringer's solution, and about 1 to about 30 or 5 mg to about 25 mg of an antigen binding protein of the invention per ml of Ringer's solution. Actual methods for preparing parenterally administrable compositions are well known or will be apparent to those skilled in the art and are described in more detail in, for example, Remington's Pharmaceutical Science, 15th ed., Mack Publishing Company, Easton, Pennsylvania.

For the preparation of intravenously administrable antigen binding protein formulations of the invention see Lasmar U and Parkins D "The formulation of Biopharmaceutical products", Pharma. Sci.Tech.today, page 129-137, Vol.3 (3rd April 2000); Wang, W "Instability, stabilisation and formulation of liquid protein pharmaceuticals", Int. J. Pharm 5 185 (1999) 129-188; Stability of Protein Pharmaceuticals Part A and B ed Ahern T.J., Manning M.C., New York, NY: Plenum Press (1992); Akers,M.J. "Excipient-Drug interactions in Parenteral Formulations", J.Pharm Sci 91 (2002) 2283-2300; Imamura, K et al "Effects of types of sugar on stabilization of Protein in the dried state", J Pharm Sci 92 (2003) 266-274; Izutsu, Kkojima, S. "Excipient crystallinity and its protein-structure-stabilizing effect during freeze-drying", J Pharm. Pharmacol, 54 (2002) 1033-1039; 10 Johnson, R, "Mannitol-sucrose mixtures-versatile formulations for protein lyophilization", J. Pharm. Sci, 91 (2002) 914-922; and Ha,E Wang W, Wang Y.j. "Peroxide formation in polysorbate 80 and protein stability", J. Pharm Sci, 91, 2252-2264,(2002) the entire contents of which are incorporated herein by reference and to which the reader is 15 specifically referred.

In one embodiment the therapeutic agent of the invention, when in a pharmaceutical preparation, is present in unit dose forms. The appropriate therapeutically effective dose will be determined readily by those of skill in the art. Suitable doses may be calculated 20 for patients according to their weight, for example suitable doses may be in the range of about 0.1 to about 20mg/kg, for example about 1 to about 20mg/kg, for example about 10 to about 20mg/kg or for example about 1 to about 15mg/kg, for example about 10 to about 15mg/kg. To effectively treat conditions such as asthma or IPF in a human, suitable doses may be within the range of about 0.1 to about 1000 mg, for example 25 about 0.1 to about 500mg, for example about 500mg, for example about 0.1 to about 100mg, or about 0.1 to about 80mg, or about 0.1 to about 60mg, or about 0.1 to about 40mg, or for example about 1 to about 100mg, or about 1 to about 50mg, of an antigen binding protein of this invention, which may be administered parenterally, for example subcutaneously, intravenously or intramuscularly. Such dose may, if necessary, be 30 repeated at appropriate time intervals selected as appropriate by a physician.

The antigen binding proteins described herein can be lyophilized for storage and reconstituted in a suitable carrier prior to use. This technique has been shown to be effective with conventional immunoglobulins and art-known lyophilization and 35 reconstitution techniques can be employed.

In another aspect, the invention provides a pharmaceutical composition comprising an antigen binding protein of the present invention or a functional fragment thereof and a pharmaceutically acceptable carrier for treatment or prophylaxis of atopic diseases/ 40 disorders and chronic inflammatory diseases/disorders, for example, asthma, such as allergic asthma, particularly severe asthma (that is asthma that is unresponsive to current treatment, including systemically administered corticosteroids; see Busse WW et al, J Allergy Clin. Immunol 2000, 106: 1033-1042), "difficult" asthma (defined as the asthmatic phenotype characterised by failure to achieve control despite maximally 45 recommended doses of prescribed inhaled steroids, see Barnes PJ (1998), Eur Respir J

12:1208-1218), "brittle" asthma (defines a subgroup of patients with severe, unstable asthma who maintain a wide peak expiratory flow (PEF) variability despite high doses of inhaled steroids, see Ayres JG et al (1998) Thorax 58:315-321), nocturnal asthma, premenstrual asthma, steroid resistant asthma (see Woodcock AJ (1993) Eur Respir J 6:743-747), steroid dependent asthma (defined as asthma that can be controlled only with high doses of oral steroids), aspirin induced asthma, adult-onset asthma, paediatric asthma. Antibodies of the invention maybe used to prevent, reduce the frequency of, or mitigate the effects of acute, asthmatic episodes (*status asthmaticus*). Antibodies of the invention may also be used to reduce the dosing required (either in terms of amount administered or frequency of dosing) of other medicaments used in the treatment of asthma. For example, antibodies of the invention may be used to reduce the dosing required for steroid treatment of asthma such as corticosteroid treatment ("steroid sparing"). Other diseases or disorders that may be treated with antibodies of the invention include atopic dermatitis, allergic rhinitis, Crohn's disease, chronic obstructive pulmonary disease (COPD), eosinophilic esophagitis, fibrotic diseases or disorders such as idiopathic pulmonary fibrosis, progressive systemic sclerosis (scleroderma), hepatic fibrosis, hepatic granulomas, schistosomiasis, leishmaniasis, and diseases of cell cycle regulation, e.g. Hodgkins disease, B cell chronic lymphocytic leukaemia. In one embodiment the disorder is severe asthma. In a further embodiment the disorder is a fibrotic disorder such as IPF.

In a yet further aspect, the invention provides a pharmaceutical composition comprising an antigen binding protein of the present invention and a pharmaceutically acceptable carrier for treating atopic diseases/ disorders and chronic inflammatory diseases/disorders, for example, asthma, such as allergic asthma, particularly severe asthma (that is asthma that is unresponsive to current treatment, including systemically administered corticosteroids; see Busse WW et al, J Allergy Clin. Immunol 2000, 106: 1033-1042), "difficult" asthma (defined as the asthmatic phenotype characterised by failure to achieve control despite maximally recommended doses of prescribed inhaled steroids, see Barnes PJ (1998), Eur Respir J 12:1208-1218), "brittle" asthma (defines a subgroup of patients with severe, unstable asthma who maintain a wide peak expiratory flow (PEF) variability despite high doses of inhaled steroids, see Ayres JG et al (1998) Thorax 58:315-321), nocturnal asthma, premenstrual asthma, steroid resistant asthma (see Woodcock AJ (1993) Eur Respir J 6:743-747), steroid dependent asthma (defined as asthma that can be controlled only with high doses of oral steroids), aspirin induced asthma, adult-onset asthma, paediatric asthma. Antibodies of the invention maybe used to prevent, reduce the frequency of, or mitigate the effects of acute, asthmatic episodes (*status asthmaticus*). Antibodies of the invention may also be used to reduce the dosing required (either in terms of amount administered or frequency of dosing) of other medicaments used in the treatment of asthma. For example, antibodies of the invention may be used to reduce the dosing required for steroid treatment of asthma such as corticosteroid treatment ("steroid sparing"). Other diseases or disorders that may be treated with antibodies of the invention include atopic dermatitis, allergic rhinitis, Crohn's disease, chronic obstructive pulmonary disease (COPD), eosinophilic esophagitis, fibrotic diseases or disorders such as idiopathic pulmonary fibrosis, progressive systemic

sclerosis (scleroderma), hepatic fibrosis, hepatic granulomas, schistosomiasis, leishmaniasis, and diseases of cell cycle regulation, e.g. Hodgkins disease, B cell chronic lymphocytic leukaemia. In one embodiment the disorder is severe asthma. In a further embodiment the disorder is a fibrotic disorder such as IPF.

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It will be understood that the sequences described herein (SEQ ID NO: 26 to SEQ ID NO: 55 and SEQ NO:62 to SEQ ID NO: 146) include sequences which are substantially identical, for example sequences which are at least 90% identical, for example which are at least 91%, or at least 92%, or at least 93%, or at least 94% or at least 95%, or at least

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96%, or at least 97% or at least 98%, or at least 99% identical to the sequences described herein.

For nucleic acids, the term "substantial identity" indicates that two nucleic acids, or designated sequences thereof, when optimally aligned and compared, are identical, with appropriate nucleotide insertions or deletions, in at least about 80% of the nucleotides, at least about 90% to about 95%, or at least about 98% to about 99.5% of the nucleotides. Alternatively, substantial identity exists when the segments will hybridize under selective hybridization conditions, to the complement of the strand.

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For nucleotide and amino acid sequences, the term "identical" indicates the degree of identity between two nucleic acid or amino acid sequences when optimally aligned and compared with appropriate insertions or deletions. Alternatively, substantial identity exists when the DNA segments will hybridize under selective hybridization conditions, to the complement of the strand.

25

The percent identity between two sequences is a function of the number of identical positions shared by the sequences (i.e., % identity = # of identical positions/total # of positions times 100), taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences. The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm, as described in the non-limiting examples below.

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The percent identity between two nucleotide sequences can be determined using the GAP program in the GCG software package, using a NWSgapdna.CMP matrix and a gap weight of 40, 50, 60, 70, or 80 and a length weight of 1, 2, 3, 4, 5, or 6. The percent identity between two nucleotide or amino acid sequences can also be determined using the algorithm of E. Meyers and W. Miller (Comput. Appl. Biosci., 4:11-17 (1988)) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. In addition, the percent identity between two amino acid sequences can be determined using the Needleman and Wunsch (J. Mol. Biol. 48:444-453 (1970)) algorithm which has been incorporated into the GAP program in the GCG software package, using either a Blossum 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1,

40

45

2, 3, 4, 5, or 6.

By way of example, a polynucleotide sequence of the present invention may be identical to the reference sequence of SEQ ID NO: 25, that is be 100% identical, or it may include up to a certain integer number of nucleotide alterations as compared to the reference sequence. Such alterations are selected from the group consisting of at least one nucleotide deletion, substitution, including transition and transversion, or insertion, and wherein said alterations may occur at the 5' or 3' terminal positions of the reference nucleotide sequence or anywhere between those terminal positions, interspersed either individually among the nucleotides in the reference sequence or in one or more contiguous groups within the reference sequence. The number of nucleotide alterations is determined by multiplying the total number of nucleotides in SEQ ID NO: 25 by the numerical percent of the respective percent identity (divided by 100) and subtracting that product from said total number of nucleotides in SEQ ID NO: 25, or:

$$nn \leq xn - (xn \cdot y),$$

wherein nn is the number of nucleotide alterations, xn is the total number of nucleotides in SEQ ID NO: 25, and y is 0.50 for 50%, 0.60 for 60%, 0.70 for 70%, 0.80 for 80%, 0.85 for 85%, 0.90 for 90%, 0.95 for 95%, 0.97 for 97% or 1.00 for 100%, and wherein any non-integer product of xn and y is rounded down to the nearest integer prior to subtracting it from xn . Alterations of the polynucleotide sequence of SEQ ID NO: 25 may create nonsense, missense or frameshift mutations in this coding sequence and thereby alter the polypeptide encoded by the polynucleotide following such alterations.

Similarly, in another example, a polypeptide sequence of the present invention may be identical to the reference sequence encoded by SEQ ID NO: 24, that is be 100% identical, or it may include up to a certain integer number of amino acid alterations as compared to the reference sequence such that the % identity is less than 100%. Such alterations are selected from the group consisting of at least one amino acid deletion, substitution, including conservative and non-conservative substitution, or insertion, and wherein said alterations may occur at the amino- or carboxy-terminal positions of the reference polypeptide sequence or anywhere between those terminal positions, interspersed either individually among the amino acids in the reference sequence or in one or more contiguous groups within the reference sequence. The number of amino acid alterations for a given % identity is determined by multiplying the total number of amino acids in the polypeptide sequence encoded by SEQ ID NO: 24 by the numerical percent of the respective percent identity (divided by 100) and then subtracting that product from said total number of amino acids in the polypeptide sequence encoded by SEQ ID NO: 24, or:

$$na \leq xa - (xa \cdot y),$$

wherein na is the number of amino acid alterations, xa is the total number of amino acids in the polypeptide sequence encoded by SEQ ID NO: 24, and y is, for instance 0.70 for 70%, 0.80 for 80%, 0.85 for 85% etc., and wherein any non-integer product of xa and y is rounded down to the nearest integer prior to subtracting it from xa .

The following examples illustrate but do not limit the invention.

Examples**Example 1 - Construction of recombinant anti-IL-13 antibodies**

5 Original murine mAbs were produced by immunisation of mice with recombinant human IL-13. Spleens from responder animals were harvested and fused to myeloma cells to generate hybridomas. The hybridoma supernatant material was screened for binding. Hybridomas of interest were monocloned using standard techniques. The resulting murine antibody (6A1) comprises the variable regions shown in SEQ ID NO:58 and SEQ
 10 ID NO:59. Further details of this murine antibody and a humanised version of this antibody A1L1 (SEQ ID NO: 22 and 24) are described in WO2006/003407 which is herein incorporated by reference. The anti-IL-13 mAb antibody A1L1 was used in several of the following examples as a comparator antibody.

15 A number of variants of the humanised antibody comprising the heavy chain set out in SEQ ID NO: 22 were produced. These all differed in the CDRH3 region of the antibody (SEQ ID NO: 3).

20 The base DNA expression constructs for the antibodies of the present invention, SEQ ID NO: 23 (heavy chain) and SEQ ID NO:25 (light chain) were prepared de novo by build-up of overlapping oligonucleotides including restriction sites for cloning into Rld and Rln mammalian expression vectors as well as a human signal sequence. Hind III and Spe I restriction sites were introduced to frame the V_H domain containing the signal sequence (SEQ ID NO:56) for cloning into Rld containing the human γ 1 constant region. Hind III
 25 and BsiWI restriction sites were introduced to frame the V_L domain containing the signal sequence (SEQ ID NO: 56) for cloning into Rln containing the human kappa constant region. Alternative constructs were produced using pTT vectors which also included human constant regions. Where appropriate, site-directed mutagenesis (SDM) was used to generate different humanised constructs.

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Example 2 -Antibody expression in HEK 293 6E cells

pTT plasmids encoding the heavy and light chains respectively were transiently co-transfected into HEK 293 6E cells and expressed at small scale to produce antibody.
 35 Antibodies were assessed directly from the tissue culture supernatant. Other antibodies were purified using immobilised Protein A columns and quantified by reading absorbance at 280nm and where indicated, the purified antibody material was assessed in the assays described in the examples set out below.

40 Where we refer to the antibodies by code (i.e. A1Y100BTrpL1) we are referring to the mAb generated by co-transfection and expression of the noted first and second plasmid, for example 'A1Y100BTrpL1' relates to a mAb generated by co-transfection of a plasmid containing the A1Y100BTrp sequence and a plasmid containing the L1 sequence in a suitable cell line.

45

Example 3 - Biacore Analysis of Anti IL-13 humanised mAbs**Kinetic Analysis**

5 The initial screen of CDRH3 mutants was carried out on the ProteOn XPR36 (Biorad).
The method was as follows, antihuman IgG (Biacore BR-1008-39) was immobilised on a
GLM chip by primary amine coupling, CDRH3 mutant antibodies were then captured on
this surface and IL13 passed over at 256, 64, 16, 4, 1nM with a 0nM injection (i.e. buffer
alone) used to double reference. 3M MgCl₂ was used to regenerate the capture surface,
10 removing the bound CDRH3 mutant antibodies ready for another cycle of capture and
analyte injection. The data was fitted to the 1:1 model using the software inherent to the
machine. All work was carried out using antibodies directly from tissue culture
supernatants except for the parental antibody which was purified material.

15 The screen identified several antibodies that appeared to have better kinetic
profile than the parental molecule, these same samples were then analysed on the
Biacore T100 to confirm the results, using a similar method, in that the same antihuman
IgG capture antibody was immobilised on a CM5 chip by primary amine coupling, IL13
was passed over the surface at 256, 64, 16, 4, 1 and 0.25nM with a 0nM used for double
referencing , regeneration was with 3M MgCl₂ and the data was fitted to the 1:1 model
20 inherent to the T100. Table 1 details the overall affinities (equilibrium dissociation
constant K_D) for the selected constructs from the ProteOn screen and the T100 run

Table 1.

Molecule	ProteOn KD (pM)	Biacore KD (pM)
A1S95TrpL1	Not Analysable	216
A1I96ValL1	395	696
A1Y97PheL1	683	618
A1D98GluL1	873	779
A1H100A AlaL1	Not Analysable	172
A1H100A GluL1	110	195
A1H100A GlnL1	195	278
A1H100A ArgL1	256	307
A1H100A SerL1	131	174
A1H100A ThrL1	158	211
A1H100A ValL1	112	152
A1Y100B AlaL1	75	83
A1Y100B IleL1	75	73
A1Y100B TrpL1	68	95
A1L1	~450-600*	366

*A1L1 ran several times during the ProteOn screen so range of values obtained

The data highlighted that several mutations at the Y100B residue appeared to improve the overall affinity. In light of this, mutations at this residue that were not present in the initial screen were tested using the ProteOn using the same method as described earlier and again using antibodies direct from tissue culture supernatants. Of the mutations tested A1Y100B ValL1, appeared to improve the overall affinity (equilibrium dissociation constant K_D) with a value of 0.166nM obtained compared to a parental value of 0.390-0.460nM. When Y100B Val was tested on the Biacore T100 using the same methodology as described earlier, the equilibrium dissociation constant K_D was measured at 0.025nM compared to a parental value of 0.346nM.

In light of the work so far being carried out using antibody mutants direct from tissue culture supernatants, purified antibody was produced for A1Y100BL1 mutants Ala, Ile and Trp. These were run on the Biacore T100, using the same method as before and including the A1Y100B ValL1 mutant which was not purified at this stage. Table 2 shows the data obtained from this experiment.

Table 2

Molecule	k_a ($M^{-1}s^{-1}$)	k_d (s^{-1})	K_D (nM)
A1Y100B ValL1 (supernatant)	1.018E+6	3.455E-5	0.034
A1Y100B AlaL1	9.599E+5	3.004E-5	0.031
A1Y100B IleL1	1.149E+6	5.584E-5	0.049
A1Y100B TrpL1	2.572E+6	1.627E-4	0.063
A1L1	1.267E+6	4.560E-4	0.360

The experiment confirmed that the mutants did improve the binding affinity to IL13 compared to the parental molecule.

Given that the purified A1Y100BL1 mutants gave better binding affinities than those obtained from tissue culture supernatants, A1Y100B ValL1 was purified and run along side the other purified A1Y100BL1 mutants that also improved affinity using the Biacore T100 machine using the method described earlier. Table 3, shows the data obtained from this experiment. This experiment was in good agreement with the data in Table 2 and confirmed the improvement of affinity for the Y100B mutations.

Table 3

Molecule	$k_a(M^{-1}s^{-1})$	$k_d(s^{-1})$	KD(nM)
A1Y100B IleL1 (pur)	9.886E+5	4.214E-5	0.043
A1Y100B ValL1 (pur)	7.757E+5	2.123E-5	0.027
A1Y100B AlaL1 (pur)	8.096E+5	2.583E-5	0.032
A1Y100B TrpL1 (pur)	2.385E+6	1.253E-4	0.053
A1L1(pur)	1.128E+6	3.677E-4	0.326

Example 4 - Neutralisation of E.Coli-expressed recombinant human IL-13 in a TF-1 cell proliferation bioassay

5 TF-1 cells proliferate in response to a number of different cytokines including human IL-13. The proliferative response of these cells for IL-13 can therefore be used to measure the bioactivity of IL-13 and subsequently an assay has been developed to determine the IL-13 neutralisation potency (inhibition of IL-13 bioactivity) of mAbs.

10 The assay was performed in sterile 96-well tissue culture plates under sterile conditions and all test wells were performed in triplicate. 14ng/ml recombinant E.Coli-expressed human IL-13 was pre-incubated with various dilutions of mAbs (usually from 93.4nM titrated in 3-fold dilutions to 0.014nM) for 1 hour at 37C. An antibody of irrelevant specificity was similarly titrated as a negative control. These samples were then added to 50µl of TF-1 cells (at a concentration of 2×10^5 cells per ml) in a sterile 96-well tissue

15 culture plate. Thus the final 100µl assay volume contained various dilutions of mAbs (at a final concentration of 46.7nM titrated in 3-fold dilutions to 0.007nM), recombinant E.Coli-expressed human IL-13 (at a final concentration of 7ng/ml) and TF-1 cells (at a final concentration of 1×10^5 cells per ml). The assay plate was incubated at 37C for approximately 3 days in a humidified CO₂ incubator. The amount of cell proliferation was

20 then determined using the 'CellTitre 96® Non-Radioactive Cell Proliferation Assay' from Promega (catalogue number G4100), as described in the manufacturers instructions. The absorbance of the samples in the 96-well plate was read in a plate reader at 570nm.

25 The capacity of the mAbs to neutralise recombinant E.Coli-expressed human IL-13 bioactivity was expressed as that concentration of the mAb required to neutralise the bioactivity of the defined amount of human IL-13 (7ng/ml) by 50% (= ND₅₀). The lower the concentration of the mAb required, the more potent the neutralisation capacity. The ND₅₀ data provided herein (Table 4) were calculated using Robosage in Microsoft Excel. Graphical representation of the data can be seen in Figure 1.

30 Table 4

Molecule	ND ₅₀ (nM)	Standard Error (nM)
A1L1	9.77	34.82
A1Y100BAIa L1	0.92	0.08
A1Y100BIle L1	1.10	0.21
A1Y100BTrpL1	1.25	0.34

Example 5 - Construction and expression of mAb-dAbs comprising the CDRH3 variant anti-IL-13 mAb

5 Using standard molecular biology techniques, genes encoding each of the sequences for the variable heavy regions of the CDRH3 variants of the A1 antibodies were transferred from existing constructs to an expression vector containing the hlgG1 constant region fused to an anti-human IL-4 domain antibody (DOM9-112-210) via a TVAAPS or ASTKGPS linker at the c-terminus of the hlgG1 constant region. Details of the heavy chains constructed are listed in Table 5.

10

Table 5.

Molecule number	Name	Description	Protein Seq ID	DNA Seq ID
BPC1624	A1Y100BAIa H-TVAAPS-210 L1	H Chain = A1Y100B Ala H chain-TVAAPS linker-DOM9-112-210 dAb	62	63
		L chain =L1	24	25
BPC1625	A1Y100BIle H-TVAAPS-210 L1	H chain = A1Y100BIle H chain-TVAAPS linker-DOM9-112-210 dAb	64	65
		L chain = L1	24	25
BPC1626	A1Y100BTrp H-TVAAPS-210 L1	H chain = A1Y100BTrp H chain-TVAAPS linker-DOM9-112-210 dAb	66	67
		L chain = L1	24	25
BPC1627	A1Y100BVal H-TVAAPS-210 L1	H chain = A1Y100BVal H chain-TVAAPS linker-DOM9-112-210 dAb	68	69
		L chain = L1	24	25
BPC1628	A1Y100BAIa H-ASTKGPS-210 L1	H Chain = A1Y100B Ala H chain-ASTKGPS linker-DOM9-112-210 dAb	70	71
		L chain =L1	24	25
BPC1629	A1 Y100BIle H-ASTKGPS-210 L1	H chain = A1Y100BIle H chain-ASTKGPS linker-DOM9-112-210 dAb	72	73
		L chain = L1	24	25
BPC1630	A1Y100BTrp H-ASTKGPS-210 L1	H chain = A1Y100BTrp H chain-ASTKGPS linker-DOM9-112-210 dAb	74	75
		L chain = L1	24	25
BPC1631	A1Y100BVal H-ASTKGPS-210 L1	H chain = A1Y100BVal H chain-ASTKGPS linker-DOM9-112-210 dAb	76	77
		L chain = L1	24	25

BPC1624, BPC1625, BPC1626 and BPC1627 were expressed in HEK293 cells. Briefly, 250 ml of HEK293 cells at 1.5×10^6 cells/ml were co-transfected with heavy and light chain expression plasmids previously incubated with 293fectin reagent (Invitrogen # 51-0031). These were placed in a shaking incubator at 37°C, 5% CO₂, and 95% relative humidity. After 24 hours Tryptone feeding media was added and the cells grown for a further 5 days. Supernatant was harvested by centrifugation and filter sterilised. The expressed molecules were purified by affinity chromatography using immobilised Protein A columns and the concentration was determined by measuring the absorbance at 280nm. The level of aggregated protein in the purified samples was determined by size exclusion chromatography. The yield of purified protein and levels of aggregation are shown in Table 5b.

Table 5b

BPC	Name	Yield	% aggregate
BPC1624	586Y100BA H-TVAAPS-210	0.81mg	3.6%
BPC1625	586Y100BI H-TVAAPS-210	0.944mg	6.7%
BPC1626	586Y100BW H-TVAAPS-210	1.14mg	5.5%
BPC1627	586Y100BV H-TVAAPS-210	1.26mg	8.4%

Example 6 - Neutralisation activity data for mAb-dAbs comprising the CDRH3 variant anti-IL-13 mAb

mAb-dAbs comprising the CDRH3 variant anti-IL-13 mAb were tested for neutralisation of E.Coli-expressed recombinant human IL-13 in a TF-1 cell proliferation bioassay

The assay was performed in sterile 96-well tissue culture plates under sterile conditions and all test wells were performed in triplicate. Approximately 20ng/ml recombinant E.Coli-expressed human IL-13 was pre-incubated with various dilutions of mAbdAbs (usually from 50nM titrated in 3-fold dilutions to 0.02nM) (those mAbdAbs made in HEK cells and purified as described in example 5) in a total volume of 50µl for 1 hour at 37°C. An antibody of irrelevant specificity was similarly titrated as a negative control (data not shown). These samples were then added to 50µl of TF-1 cells (at a concentration of 2×10^5 cells per ml) in a sterile 96-well tissue culture plate. Thus the final 100µl assay volume contained various dilutions of mAbdAbs (at a final concentration of 25nM titrated in 3-fold dilutions to 0.01nM), recombinant E.Coli-expressed human IL-13 (at a final concentration of 10ng/ml) and TF-1 cells (at a final concentration of 1×10^5 cells per ml). The assay plate was incubated at 37°C for approximately 3 days in a humidified CO₂ incubator. The amount of cell proliferation was then determined using the 'CellTitre 96® Non-Radioactive Cell Proliferation Assay' from Promega (catalogue number G4100), as described in the manufacturer's instructions. The absorbance of the samples in the 96-well plate was read in a plate reader at 570nm.

The capacity of the mAbdAbs to neutralise human IL-13 bioactivity was expressed as that concentration of the mAb-dAb required to neutralise the bioactivity of the defined

amount of human IL-13 (10ng/ml) by 50% (= ND₅₀). The lower the concentration of the mAbdAb required, the more potent the neutralisation capacity. The ND₅₀ data provided herein (Table 6) were calculated using GraphPad Prism. These data are represented graphically in Figure 2.

5

Table 6

Antibody ID	Description	ND ₅₀ human IL-13
BPC1624	A1Y100BAIa H-TVAAPS-210L1	0.553nM
BPC1625	A1Y100BIle H-TVAAPS-210L1	0.542nM
BPC1626	A1Y100BTrp H-TVAAPS-210L1	0.681nM
BPC1627	A1Y100BVal H-TVAAPS-210L1	0.615nM
A1L1	Anti IL-13 antibody	2.524nM

Example 7 – Expression of mAb-dAbs comprising the CDRH3 variant anti-IL-13 mAb in the CHOE1a expression system

10

Molecules BPC 1624 to 1631 as shown in Table 5 were also expressed in CHOE1a cells. DNA vectors encoding the heavy and light chains were co-electroporated into suspension CHO cells. Cells were passaged in shake flasks in MR1 basal selective medium at 37°C, 5%CO₂, 130rpm until cell viability and cell counts improved. CHO cells were then inoculated into MR1 basal x2 selective medium and incubated for 8 to 12 days at 34°C, 5%CO₂, 130rpm. The cells were pelleted by centrifugation and the supernatant sterile filtered.

15

Expressed material was purified by affinity chromatography using immobilised protein A columns and the yield determined by measurement of absorbance at 280nm. The level of aggregates was determined by size exclusion chromatography. Aggregates were removed by preparative size exclusion chromatography and the yield re-assessed. Table 7 lists the yields and levels of aggregate obtained from this expression system.

20

Table 7

<u>Molecule</u>	<u>Expression Volume (ml)</u>	<u>Yield (mgs)</u> (post protein A pre clean-up)	<u>Aggregates (%)</u> (post protein A pre clean-up)	<u>Final Yield (mgs)</u>	<u>Final Aggregates (%)</u>
<u>BPC1628</u>	<u>850</u>	80.70	17.1%	39.50	2.6%
<u>BPC1629</u>	<u>850</u>	77.90	20.3%	35.25	2.8%
<u>BPC1630</u>	<u>850</u>	69.30	15.7%	38.00	3.3%
<u>BPC1631</u>	<u>850</u>	61.47	20.3%	30.00	2.3%
<u>BPC1624</u>	<u>850</u>	88.65	15.2%	45.00	2.6%
<u>BPC1625</u>	<u>850</u>	77.49	16.2%	37.49	2.3%
<u>BPC1626</u>	<u>850</u>	65.16	12.6%	30.80	3.1%
<u>BPC1627</u>	<u>850</u>	<u>73.26</u>	15.2%	34.44	1.9%

Example 8 - Stoichiometry assessment of antigen binding proteins (using Biacore™)

This example is prophetic. It provides guidance for carrying out an additional assay in which the antigen binding proteins of the invention can be tested,

5

Anti-human IgG is immobilised onto a CM5 biosensor chip by primary amine coupling. Antigen binding proteins are captured onto this surface after which a single concentration of IL-13 or IL-4 or IL-5 is passed over, this concentration is enough to saturate the binding surface and the binding signal observed reached full R-max.

10

Stoichiometries are then calculated using the given formula:

$$\text{Stoich} = R_{\text{max}} * M_w (\text{ligand}) / M_w (\text{analyte}) * R (\text{ligand immobilised or captured})$$

15

Where the stoichiometries are calculated for more than one analyte binding at the same time, the different antigens are passed over sequentially at the saturating antigen concentration and the stoichiometries calculated as above. The work can be carried out on the Biacore 3000, at 25°C using HBS-EP running buffer.

Example 9 - Dose prediction of improved humanised variant mAbs

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An antibody-ligand binding PK-PD model was developed in order to rank the different monoclonal antibody (mAb) candidates based on binding affinity and predicted potential therapeutic dose in human.

25

The predicted potential therapeutic dose in human was defined for this purpose as the dose providing 90% inhibition of the target IL-13 in the lung (site of action) at steady-state following monthly intravenous administration of the mAbs for 1 h. The molecular weight of each molecule was assumed to be the same and equal to the standard molecular weight of a mAb i.e. 150 kDa. In addition, in the absence of animal or human pharmacokinetics data for the different candidates, the human pharmacokinetics of the A1L1 antibody was inferred to all the candidates.

30

The same antibody-ligand binding PK-PD model is used for each mAb as well as the same assumptions regarding the target concentration, the target turnover, the target tissue:plasma ratio and the mAb tissue penetration. The ranking provided by the model is therefore solely based on the binding affinity of the molecules, the only parameter differing. In such conditions, the potential therapeutic dose in human for the 4 candidates A1Y100BIleL1, A1Y100BValL1, A1Y100BAIaL1 and A1Y100BTrpL1 is predicted to provide a substantial improvement above the predicted potential therapeutic dose in human for A1L1.

35

Example 10 - Anti-IL13/IL4 mAb dAbs with variant IL-4 dAbs

40

10.1 Construction and expression

The anti IL-4 dAb (DOM9-155-154, SEQ ID NO: 80), was investigated for aggregation-prone residues using an aggregation prediction algorithm. The leucine residue, at Kabat position 89 was identified as a key residue for promotion of aggregation.

45

In order to reduce the aggregation potential of mAbdAbs containing this dAb, this amino acid residue was substituted for other amino acids to generate a number of mAb-dAb variants. Expression constructs were generated by site directed mutagenesis using the DNA expression vector coding for the heavy chain of an existing mAbdAb construct. The protein sequences for the resulting new mAbdAb heavy chains comprising the mutated dAb sequences are given in SEQ ID NOs 117-134.

Other heavy chain sequences incorporating another mutation at position 89 are SEQ ID NOs: 96-106. These are described in detail in Example 11.

Table 8 provide a list of the molecules expressed.

Table 8

Identifier	Alternative names	Linker	Molecule description	Protein SEQ ID NO:
BPC1090	829H-(TVAAPS) ₂ GS-154 (89G)	(TVAAPS) ₂ GS	H chain: Anti-human IL-13 mAb heavy chain Y100B_V-(TVAAPS) ₂ GS-DOM9-155-154 (89G)	117
			L chain: Anti-human IL-13 mAb light chain	24
BPC1091	829H-(TVAAPS) ₂ GS-154 (89S)	(TVAAPS) ₂ GS	H chain: Anti-human IL-13 mAb heavy chain Y100B_V-(TVAAPS) ₂ GS-DOM9-155-154 (89S)	118
			L chain: Anti-human IL-13 mAb light chain	24
BPC1092	829H-(TVAAPS) ₂ GS-154 (89H)	(TVAAPS) ₂ GS	H chain: Anti-human IL-13 mAb heavy chain Y100B_V-(TVAAPS) ₂ GS-DOM9-155-154 (89H)	119
			L chain: Anti-human IL-13 mAb light chain	24
BPC1093	829H-(TVAAPS) ₂ GS-154 (89M)	(TVAAPS) ₂ GS	H chain: Anti-human IL-13 mAb heavy chain Y100B_V-(TVAAPS) ₂ GS-DOM9-155-154 (89M)	147
			L chain: Anti-human IL-13 mAb light chain	24
BPC1094	829H-(TVAAPS) ₂ GS-154 (89A)	(TVAAPS) ₂ GS	H chain: Anti-human IL-13 mAb heavy chain Y100B_V-(TVAAPS) ₂ GS-DOM9-155-154 (89A)	121
			L chain: Anti-human IL-13 mAb light chain	24
BPC1095	829H-(TVAAPS) ₂ GS-154 (89T)	(TVAAPS) ₂ GS	H chain: Anti-human IL-13 mAb heavy chain Y100B_V-(TVAAPS) ₂ GS-DOM9-155-154 (89T)	122
			L chain: Anti-human IL-13 mAb light chain	24
BPC1108	829H-(TVAAPS) ₂ GS-154 (89C)	(TVAAPS) ₂ GS	H chain: Anti-human IL-13 mAb heavy chain Y100B_V-(TVAAPS) ₂ GS-DOM9-155-154 (89C)	123

Identifier	Alternative names	Linker	Molecule description	Protein SEQ ID NO:
			L chain: Anti-human IL-13 mAb light chain	24
BPC1109	829H-(TVAAPS) ₂ GS-154 (89R)	(TVAAPS) ₂ GS	H chain: Anti-human IL-13 mAb heavy chain Y100B_V-(TVAAPS) ₂ GS-DOM9-155-154 (89R)	124
			L chain: Anti-human IL-13 mAb light chain	24
BPC1110	829H-(TVAAPS) ₂ GS-154 (89W)	(TVAAPS) ₂ GS	H chain: Anti-human IL-13 mAb heavy chain Y100B_V-(TVAAPS) ₂ GS-DOM9-155-154 (89W)	125
			L chain: Anti-human IL-13 mAb light chain	24
BPC1111	829H-(TVAAPS) ₂ GS-154 (89E)	(TVAAPS) ₂ GS	H chain: Anti-human IL-13 mAb heavy chain Y100B_V-(TVAAPS) ₂ GS-DOM9-155-154 (89E)	126
			L chain: Anti-human IL-13 mAb light chain	24
BPC1112	829H-(TVAAPS) ₂ GS-154 (89K)	(TVAAPS) ₂ GS	H chain: Anti-human IL-13 mAb heavy chain Y100B_V-(TVAAPS) ₂ GS-DOM9-155-154 (89K)	127
			L chain: Anti-human IL-13 mAb light chain	24
BPC1113	829H-(TVAAPS) ₂ GS-154 (89D)	(TVAAPS) ₂ GS	H chain: Anti-human IL-13 mAb heavy chain Y100B_V-(TVAAPS) ₂ GS-DOM9-155-154 (89D)	128
			L chain: Anti-human IL-13 mAb light chain	24
BPC1114	829H-(TVAAPS) ₂ GS-154 (89N)	(TVAAPS) ₂ GS	H chain: Anti-human IL-13 mAb heavy chain Y100B_V-(TVAAPS) ₂ GS-DOM9-155-154 (89N)	129
			L chain: Anti-human IL-13 mAb light chain	24
BPC1115	829H-(TVAAPS) ₂ GS-154 (89Y)	(TVAAPS) ₂ GS	H chain: Anti-human IL-13 mAb heavy chain Y100B_V-(TVAAPS) ₂ GS-DOM9-155-154 (89Y)	130
			L chain: Anti-human IL-13 mAb light chain	24
BPC1116	829H-(TVAAPS) ₂ GS-154 (89V)	(TVAAPS) ₂ GS	H chain: Anti-human IL-13 mAb heavy chain Y100B_V-(TVAAPS) ₂ GS-DOM9-155-154 (89V)	131
			L chain: Anti-human IL-13 mAb light chain	24
BPC1117	829H-(TVAAPS) ₂ GS-154 (89I)	(TVAAPS) ₂ GS	H chain: Anti-human IL-13 mAb heavy chain Y100B_V-(TVAAPS) ₂ GS-DOM9-155-154 (89I)	132

Identifier	Alternative names	Linker	Molecule description	Protein SEQ ID NO:
			L chain: Anti-human IL-13 mAb light chain	24
BPC1118	829H-(TVAAPS) ₂ GS-154 (89F)	(TVAAPS) ₂ GS	H chain: Anti-human IL-13 mAb heavy chain Y100B_V-(TVAAPS) ₂ GS-DOM9-155-154 (89F)	133
			L chain: Anti-human IL-13 mAb light chain	24
BPC1119	829H-(TVAAPS) ₂ GS-154 (89P)	(TVAAPS) ₂ GS	H chain: Anti-human IL-13 mAb heavy chain Y100B_V-(TVAAPS) ₂ GS-DOM9-155-154 (89P)	134
			L chain: Anti-human IL-13 mAb light chain	24

10.2 Molecule expression in HEK 293 6E cells

5 Plasmids encoding the heavy and light chains respectively were transiently co-transfected into HEK 293 6E cells and expressed at small scale to produce antibody molecules. A tryptone feed was added to each cell culture up to 24 hours after transfection and the cells were harvested after 3 days.

10 Antibody molecules were assessed directly from the tissue culture supernatant and quantified using the Gyrolab workstation.

Gyrolab workstation method for quantification of antibody molecules in cell supernatant

15 Antibodies produced from small scale transient HEK 2936E transfections (0.75-2.0ml) were quantified from tissue culture supernatants by a quantitative immunoassay using a Gyrolab Bioaffy Workstation (Gyros). Antibody was captured via the Fc region using a biotinylated anti-IgG Affibody molecule (Abcam) immobilised onto streptavidin-coated particles on a compact disc (CD) microlaboratory (Gyros). The Affibody reagent was vortexed briefly and diluted with PBS-Tween 20 (0.01% v/v) to a final working concentration of 0.1mg/ml. Antibody was then detected by an ALEXA 647 labelled Fab2

20 anti-human IgG kappa light chain molecule using laser-induced fluorescence. The ALEXA 647 labelled detection reagent was prepared by vortexing briefly and by centrifugation at 13000 rpm for 4 minutes. The labelled Fab2 detection reagent was added to unlabelled Fab2 which were diluted to final concentrations of 75nM and 1.5µM respectively using Rexcip F Detection reagent diluant (Gyros). The antibody

25 quantification range was between 0.244-250µg/ml relative to an anti-CD23 monoclonal antibody standard curve. The anti-CD23 (1mg/ml) standard curve was generated by serial dilution of the antibody with tissue culture media (Freestyle 293 Expression Media, Pluronic F68 and Geneticin, Invitrogen).

30

In some instances, the antibody molecules were purified using immobilised Protein A columns and quantified by reading absorbance at 280nm and where indicated, the purified antibody molecule was assessed in the assays described in the examples set out below.

5

10.3 IL-4 Binding ELISA

These mAbdAbs were tested for binding to IL-4 in a direct binding ELISA using the following method.

- 10 96-well high binding plates were coated with 5µg/ml human IL-4 (made at GSK) in NaHCO₃ and stored overnight at 4°C. The plates were washed twice with Tris-Buffered Saline with 0.05% of Tween-20 (TBST). 100µL of blocking solution (1% BSA in TBST buffer) was added in each well and the plates were incubated for at least one hour at room temperature. The mAbdAbs were successively diluted across the plates in blocking solution. After one hour incubation, the plates were washed three times. Goat anti-human kappa light chain specific peroxidase conjugated antibody (Sigma A7164) was diluted in blocking solution to 1µg/mL and 50µL was added to each well. The plates were incubated for one hour. After another three washing steps, 50µl of OPD (o-phenylenediamine dihydrochloride) SigmaFast substrate solution was added to each well and the reaction was stopped after about 5 minutes by addition of 25µL of 3M sulphuric acid. Absorbance was read at 490nm using the VersaMax Tunable Microplate Reader (Molecular Devices) using a basic endpoint protocol.
- 15
- 20

- The experiment was carried out using mAbdAbs directly from tissue culture supernatants which had been quantified using the gyrolab platform except for the positive control (anti-IL-4 mAb) and the anti-IL13 negative control mAb, which were purified material. These data are shown in Figure 17.
- 25

- The result of the ELISA shows that most of these transiently expressed anti-IL13 mAb-anti-IL4 dAbs bound IL-4, but some variation in IL-4 binding activity was observed.. The purified positive control anti-IL-4 mAb, also showed binding to IL-4, whereas the purified negative control mAb showed no binding to human IL-4.
- 30

10.4 Analysis of levels of aggregate in mAbdab expressions

- pTT plasmids encoding the heavy and light chains of BPC1090, BPC1091, BPC1092, BPC1093, BPC1094 and BPC1095 were transiently co-transfected into HEK 293 6E cells and expressed using 293fectin (Invitrogen, 12347019) at slightly larger scale (between 200 and 600ml) than the mAbdabs described above in Example 10.2. The BPC1111 and BPC1085 were independently transiently expressed in HEK293 6E cells using the same methodology. The plasmids used for the above transfections were generated using the EndoFree Plasmid Maxi Kit (Qiagen, 12362).
- 35
- 40

A tryptone feed was added to each of the cell cultures after 24 hours and the cells were harvested after 72 hours. The antibodies were purified using a Protein A column,

quantified by reading absorbance at 280nm and analyzed by size exclusion chromatography (SEC).

These mAbdAbs were compared with BPC2223, anti-IL13 mAb (829) and anti-IL-13 mAb (586) which had been independently expressed.

5

Both antibodies (586 with the original CDRH3 and 829 with the mutated CDRH3) showed low levels of aggregation, as did the mAbdAbs comprising the mutated dAb (BPC1090, BPC 1091, BPC 1093, BPC1094 and BPC1095). BPC2223 which comprised the original dAb i.e. where position 89 was not mutated had higher levels of aggregation, as did BPC1092 which had an L89H mutation. Representative aggregation data is shown in Table 8b.

10

Table 8b

Molecule number	Molecule description	% aggregates (SEC)
BPC1085	829H-GS(TVAAPSGS) ₂ -154 (89Q)	~1.6
BPC 1090	829H-(TVAAPS) ₂ GS -154 (89G)	~0.7
BPC 1091	829H-(TVAAPS) ₂ GS -154 (89S)	~1.5
BPC 1092	829H-(TVAAPS) ₂ GS -154 (89H)	~20
BPC 1093	829H-(TVAAPS) ₂ GS -154 (89M)	~4.3
BPC 1094	829H-(TVAAPS) ₂ GS -154 (89A)	~0.8
BPC 1095	829H-(TVAAPS) ₂ GS -154 (89T)	~2
BPC 1111	829H-(TVAAPS) ₂ GS -154 (89E)	<5%
BPC 2223	586H-GS(TVAAPSGS) ₂ -154	~25%
-	829 (mAb)	~2.1
-	586 (mAb)	<1

15

10.5 BIAcore analysis

Purified mAbs and mAbdAb constructs were tested in a BIAcore assay to determine whether the mutation of position 89 had any effect on the binding of the dAb to IL-4.

20

Protein A was immobilised on a CM5 chip by primary amine coupling; this surface was used as a capture surface for the antibody molecules to be tested. Recombinant E.coli-expressed Human IL4 was used as analyte at 256, 64, 16, 4 and 1, 0.25 and 0.0625 with

0nM (i.e. buffer alone) used to double reference the binding curves. Regeneration of the anti-Protein A surface was achieved using 50mM NaOH. The assay was run at 25°C using HBS-EP as running buffer. The data was fitted to 1:1 model inherent to the Biacore T100 analysis software.

5

Table 8c

Molecule Number	Molecule Description	ka (1/Ms)	kd (1/s)	KD (nM)
BPC1085	829H-GS(TVAAPSGS) ₂ -256	2.38E+07	1.23E-03	0.052
BPC2223	586H- GS(TVAAPSGS) ₂ -154	9.71E+06	9.34E-05	0.010
BPC1090	829H-(TVAAPS) ₂ GS-154 (89G)	3.00E+06	4.55E-04	0.152
BPC1091	829H-(TVAAPS) ₂ GS-154 (89S)	3.96E+06	9.66E-04	0.244
BPC1092	829H-(TVAAPS) ₂ GS-154 (89H)	2.98E+06	5.34E-03	1.794
BPC1093	829H-(TVAAPS) ₂ GS-154 (89M)	4.19E+06	2.16E-04	0.051
BPC1094	829H-(TVAAPS) ₂ GS-154 (89A)	1.91E+06	3.73E-03	1.948
BPC1095	829H-(TVAAPS) ₂ GS-154 (89T)	2.50E+06	1.44E-02	5.760
BPC1111	829H-(TVAAPS) ₂ GS-154 (89E)	3.37E+06	1.04E-04	0.031

Example 11 –Construction and testing of antigen binding proteins comprising the CDRH3 variant anti-IL-13 mAb and a mutated dAb (BPC1085, BPC1086 & BPC1087)

10

11.1 Construction and expression

Plasmids encoding heavy chains consisting of an anti-IL-13 mAb and an anti-IL-4 dAb were used as base constructs to generate alternative plasmid constructs. A two step cloning strategy was required. In step 1, the DNA sequence encoding the VH of the anti-IL13 mAb component of the H chain was replaced with the DNA sequence encoding the VH of another humanized anti-IL13 antibody (SEQ ID NO:54) by restriction cloning using HindIII and SpeI. In step 2, the codon encoding the leucine at Kabat position 89 in the anti-IL4 dAb (DOM9-155-154, SEQ ID NO: 80) component of the mAbdAb was mutated by site directed mutagenesis to glutamine. All of the resulting heavy chain DNA sequences generated are given in SEQ ID NOs: 96, 98 and 100. Table 9 provides a list of the molecules constructed and expressed.

15

20

25

Table 9 – Summary of the antibodies constructed and expressed

Identifier	Alternative names	Linker	Molecule description	Protein SEQ ID NO:
BPC1085	829H-GS(TVAAPSGS) ₂ -154 (89Q) <u>or</u> 829H-GS(TVAAPSGS) ₂ -256	GS(TVAAPSGS) ₂	H chain: Anti-human IL-13 mAb heavy chain Y100B_V – GS(TVAAPSGS) ₂ -DOM9-155-256	96
			L chain: Anti-human IL-13 mAb light chain	24
BPC1086	829H-GS(TVAAPSGS) ₃ -154 (89Q) <u>or</u> 829H-GS(TVAAPSGS) ₃ -256	GS(TVAAPSGS) ₃	H chain: Anti-human IL-13 mAb heavy chain Y100B_V – GS(TVAAPSGS) ₃ -DOM9-155-256	98
			L chain: Anti-human IL-13 mAb light chain	24
BPC1087	829H-GS(TVAAPSGS) ₄ -154 (89Q) <u>or</u> 829H-GS(TVAAPSGS) ₄ -256	GS(TVAAPSGS) ₄	H chain: Anti-human IL-13 mAb heavy chain Y100B_V – GS(TVAAPSGS) ₄ -DOM9-155-256	100
			L chain: Anti-human IL-13 mAb light chain	24

Heavy and light chain expression plasmids encoding BPC1085, BPC1086 and BPC1087 mAbdAbs were co-transfected into HEK 2936E cells using 293fectin (Invitrogen, 12347019). A tryptone feed was added to each of the cell cultures after 24 hours and the cells were harvested after 72 hours. The antibodies were purified using a Protein A column before being tested in binding assays.

BPC1085, BPC1086 and BPC1087 mAbdAbs were purified using Protein A affinity. 1ml Protein A columns were used (GE Healthcare) on the AKTA Xpress system, columns were equilibrated in PBS (Gibco/Invitrogen) and the antibodies eluted using Pierce IgG elute. Eluted fractions were neutralised using 1M Tris (Hydroxymethyl) Aminomethane buffer (in general 5-10% v/v). Eluted antibody fractions were pooled and analysed for aggregation by size exclusion chromatography and quantified by reading at OD_{280nm} using a spectrophotometer.

These were compared to equivalent mAbdAbs (2222, 2223, 2230 and 2231) which are described in Table 10. These comprise:

- i) a dAb which is identical to that used in BPC1085, BPC1086 and BPC1087 except for position 89 which is 'L' in BPC2222, BPC2223, BPC2230 & BPC2231 and 'Q' in BPC1085, BPC1086 & BPC1087).
- ii) same linkers

- iii) an IL-13 mAb sequence which is identical to that used BPC1085, BPC1086 and BPC1087 except for position 100B which is 'Y' in BPC2222, BPC2223, BPC2230 & BPC2231 and 'V' in BPC1085, BPC1086 & BPC1087).

5 Table 10:

Identifier	mAb	Linker	dAb	Heavy chain	Light chain
BPC2222	A1L1	GS(TVAAPSGS) ₁	DOM9-155-154	135	24
BPC2223	A1L1	GS(TVAAPSGS) ₂	DOM9-155-154	136	24
BPC2230	A1L1	GS(TVAAPSGS) ₃	DOM9-155-154	137	24
BPC2231	A1L1	GS(TVAAPSGS) ₄	DOM9-155-154	138	24

10 BPC2222, 2223, 2230 and 2231 mAbdAbs were purified using Protein A affinity. 1ml Protein A columns were used (GE Healthcare) on the AKTA Xpress system, columns were equilibrated in PBS (Gibco/Invitrogen) and the antibodies eluted using Pierce IgG elute. Eluted fractions were neutralised using 1M Tris (Hydroxymethyl) Aminomethane buffer (in general 5-10% v/v). Eluted antibody fractions were pooled and analysed for aggregation by size exclusion chromatography and quantified by reading at OD_{280nm} using a spectrophotometer.

15 BPC2222, 2223, 2230 and 2231 showed aggregation of between 30-40%, with the aggregated material eluting before 10 minutes. Compared to BPC2222, 2223, 2230 and 2231 the constructs BPC1085, 1086 and 1087 showed lower levels of aggregation as assessed by size exclusion chromatography. The SEC profiles for these molecules are shown in Figures 3-9

20 11.2 IL-4 Binding ELISA

Purified BPC1085, BPC1086 and BPC1087 mAbdAbs were tested for binding to IL-4 in a direct binding ELISA according to the method described in Example 10.3.

25 These data are shown in Figure 10. The results of the ELISA confirmed that these purified mAbdAbs bound to IL-4. The positive controls anti-IL-4 mAb and BPC2231 also showed binding to IL-4 whereas the negative control mAb (anti IL-13 mAb) showed no binding to IL-4. This indicated in this ELISA the dAb potency increased when the linker length was increased from GS(TVAAPSGS) to GS(TVAAPSGS)₂₋₄.

30

11.3 Neutralization of IL-4 in a TF-1 cell proliferation bioassay

35 Purified BPC1085, BPC1086 and BPC1087 mAbdAbs were tested for neutralization of human IL-4 in a TF-1 cell bioassay.

TF-1 cells proliferate in response to a number of different cytokines including human IL-4. The proliferative response of these cells for IL-4 can therefore be used to measure the bioactivity of IL-4 and subsequently an assay has been developed to determine the IL-4 neutralisation potency (inhibition of IL-4 bioactivity) of mAbdAbs.

The assay was performed in sterile 96-well tissue culture plates under sterile conditions and all test wells were performed in duplicate. Approximately 2.2ng/ml recombinant E.Coli-expressed human IL-4 was pre-incubated with various dilutions of mAbdAbs (usually from 560nM titrated in 3-fold dilutions to 0.009nM) in a total volume of 120µl for 1 hour at 37°C. An antibody of irrelevant specificity was similarly titrated as a negative control (anti-IL13 mAb). 50µl of these samples were then added to 50µl of TF-1 cells (at a concentration of 2×10^5 cells per ml) in a sterile 96-well tissue culture plate. Thus the final 100µl assay volume contained various dilutions of mAbdAbs (at a final concentration of 270nM titrated in 3-fold dilutions to 0.005nM), recombinant E.Coli-expressed human IL-4 (at a final concentration of 1.1ng/ml) and TF-1 cells (at a final concentration of 1×10^5 cells per ml). The assay plate was incubated at 37°C for approximately 4 days in a humidified CO₂ incubator. The amount of cell proliferation was then determined using the 'CellTitre 96® Non-Radioactive Cell Proliferation Assay' from Promega (catalogue number G4100), as described in the manufacturers instructions. The absorbance of the samples in the 96-well plate was read in a plate reader at 570nm. These data were entered on an Excel spreadsheet, values for duplicate test wells were averaged and the average background value (no mAb-dAb and no IL-4 test wells) was subtracted.

The capacity of the mAbdAbs to neutralise recombinant E.Coli-expressed human IL-4 bioactivity was expressed as that concentration of the mAb-dAb required to neutralise the bioactivity of the defined amount of human IL-4 (1.1ng/ml) by 50% (= ND₅₀). The lower the concentration of the mAbdAb required, the more potent the neutralisation capacity. The ND₅₀ data provided herein (Table 11) were calculated using the Robosage function in Excel. These data are represented graphically in Figure 11.

An anti-IL-4 mAb and DOM9-155-154 (SEQ ID NO: 80) were included as positive controls for neutralization of human and cynomolgus IL-4 in the TF-1 cell bioassays. Additionally, a dAb with specificity for an irrelevant antigen (dummy dAb) was also included as a negative control for neutralization of human or cynomolgus IL-4 in the TF-1 cell bioassays.

These were repeated several times and Figure 11 shows the results for one of these experiments. ND₅₀ values were calculated from the dataset. The ND₅₀ value is the concentration of the mAbdAb or mAb or dAb, which is able to neutralise the bioactivity of IL-4 by 50%. The mean ND₅₀ value and the number of times tested (n) are shown in Table 11.

Table 11

Molecule	Mean ND₅₀ value & standard deviation (nM)	Number of repeats
BPC1085	9.21	3
BPC1086	4.32	3
BPC1087	3.59	3
anti-IL-4 mAb	1.95	2
DOM9-155-154	0.98	2
Negative control dAb	did not neutralise	2

These data confirm that purified BPC1085, BPC1086 and BPC1087 mAbdAbs, neutralized the bioactivity of human and cyno IL-4. Anti-IL-4 mAb and DOM9-155-154 also neutralised the bioactivity of human and cynomolgus IL-4, whereas the negative dAb (dummy dAb) showed no neutralization in the same bioassay.

All three mAbdAbs show good potency, and there is a clear trend of increasing dAb potency with increasing linker length was apparent from the neutralisation assays, despite the more crude ELISA not picking up this difference in potency. A negative control anti-IL-4 mAb) showed no neutralization in the same bioassay.

11.4 Neutralization of human IL-13 in a TF-1 cell proliferation bioassay

Purified BPC1085, BPC1086 and BPC1087 mAbdAbs were tested for neutralization of human IL-13 in a TF-1 cell bioassay as described below.

TF-1 cells proliferate in response to a number of different cytokines including human IL-13. The proliferative response of these cells for IL-13 can therefore be used to measure the bioactivity of IL-13 and subsequently an assay has been developed to determine the IL-13 neutralisation potency (inhibition of IL-13 bioactivity) of mAbdAbs.

The assay was performed in sterile 96-well tissue culture plates under sterile conditions and all test wells were performed in duplicate. Approximately 14ng/ml recombinant E.Coli-expressed human IL-13 was pre-incubated with various dilutions of mAbdAbs (usually from 560nM titrated in 3-fold dilutions to 0.009nM) in a total volume of 120µl for 1 hour at 37°C. An antibody and dAb of irrelevant specificity was similarly titrated as negative controls (anti-IL-4 mAb and DOM9-155-154 respectively). 50µl of these samples were then added to 50µl of TF-1 cells (at a concentration of 2×10^5 cells per ml) in a sterile 96-well tissue culture plate. Thus the final 100µl assay volume contained various dilutions of mAbdAbs (at a final concentration of 270nM titrated in 3-fold dilutions to 0.005nM), recombinant E.Coli-expressed human IL-13 (at a final concentration of 7ng/ml) and TF-1 cells (at a final concentration of 1×10^5 cells per ml). The assay plate was incubated at 37°C for approximately 4 days in a humidified CO₂ incubator. The amount of cell proliferation was then determined using the 'CellTitre 96® Non-Radioactive Cell Proliferation Assay' from Promega (catalogue number G4100), as

described in the manufacturer's instructions. The absorbance of the samples in the 96-well plate was read in a plate reader at 570nm. These data were entered on an Excel spreadsheet, values for duplicate test wells were averaged and the average background value (no mAb-dAb and no IL-13 test wells) was subtracted.

5 The capacity of the mAbdAbs to neutralise recombinant E.Coli-expressed human IL-13 bioactivity was expressed as that concentration of the mAb-dAb required to neutralise the bioactivity of the defined amount of human IL-13 (7ng/ml) by 50% (= ND₅₀). The lower the concentration of the mAbdAb required, the more potent the neutralisation capacity. The ND₅₀ data provided herein (Table 12) were calculated using the Robosage
10 function in Excel. These data are represented graphically in Figure 12.

An anti IL-13 mAb (SEQ ID NO:22 & 24) was included as a positive control for neutralization of human IL-13 in the TF-1 cell bioassays. Additionally, an anti-IL-4 mAb was also included as a negative control.

15 Figure 12 shows the result of the TF-1 cell neutralization assay. ND₅₀ values were calculated from the dataset. The ND₅₀ value is the concentration of the mAbdAb or mAb or dAb, which is able to neutralise the bioactivity of IL-13 by 50%.
The mean ND₅₀ value and the number of times tested are shown in Table 12.

20

Table 12

Molecule	Mean ND₅₀ value & standard deviation (nM)	Number of repeats
BPC1085	0.88	1
BPC1086	1.01	1
BPC1087	1.14	1
Anti-IL-13 mAb	5.01	1
anti-IL-4 mAb	did not neutralise	1

These data confirm that purified BPC1085, BPC1086 and BPC1087 mAbdAbs, neutralized the bioactivity of recombinant human and cyno IL-13. A negative control anti-
25 IL-4 mAb showed no neutralization in the same bioassay.

Example 12 Re-humanisation of anti-IL-13 mAb light chain

12.1 Re-humanisation

30

The light chain CDRs of the murine antibody 6A1 (The light chain of which is set out in SEQ ID NO:59) were re-grafted onto new frameworks in order to improve the expression of some anti-IL-13 mAb-anti-IL-4 dAb molecules (BPC1085). Codon optimised light chain variable region sequences (summarised in Table 13) were constructed de novo
35 using a PCR-based strategy and overlapping oligonucleotides. PCR primers were

designed to incorporate the signal sequence (SEQ ID NO: 56) and to include HindIII and BsiWI restriction sites designed to frame the V_L domain and allow cloning into pTT and Rln mammalian expression vectors containing the human kappa C region. Table 13 summarises the re-humanised light chains that have been constructed.

5

Table 13

Light chain name	Description	Backbone	Back Mutations	SEQ ID NO: Nucleotide sequence	SEQ ID NO: Amino acid sequence
<u>P0</u>	<u>Anti-IL-13 808VL kappa light chain</u>	<u>IGKV1 39 + JK2</u>	<u>N/A</u>	<u>108</u>	<u>109</u>
<u>P1</u>	<u>Anti-IL-13 809VL kappa light chain</u>	<u>IGKV1 39 + JK2</u>	<u>I2V + Q3L</u>	<u>110</u>	<u>111</u>
<u>Q0</u>		<u>IGKV3 20 + JK2</u>	<u>N/A</u>	<u>112</u>	<u>113</u>
<u>Q1</u>		<u>IGKV3 20 + JK2</u>	<u>I2V, V3L, L4M, E1D, R45K, I58V</u>	<u>114</u>	<u>115</u>

12.2 Molecule expression in HEK 293 6E cells

- 10 Expression properties of the re-humanised light chains were initially examined in mAb format. Plasmids encoding the A1Y100BVAL1 (SEQ ID NO: 54) heavy chain, the existing light chain (SEQ ID NO: 24) and the re-humanised light chains were transiently co-transfected into HEK 293 6E cells using 293fectin (Invitrogen, 12347019). Plasmids were expressed at small scale (2x 0.75ml culture volumes) to produce antibody. A
- 15 tryptone feed was added to the cell culture after 24 hours and the cells were harvested after a further 72 hours. Table 14 summarises all of the mAbs which were constructed and expressed.

Table 14

Antibody ID	Molecule description	Protein SEQ ID NO:
<u>A1Y100BVAL1</u>	<u>H chain: Anti human IL-13 Y100b V mAb</u>	<u>54</u>
	<u>L chain: 586 anti-human IL-13 mAb</u>	<u>24</u>
<u>BPC3208</u>	<u>H chain: Anti human IL-13 Y100b V mAb</u>	<u>54</u>
	<u>L chain: P0 re-humanised anti-human IL-13 mAb</u>	<u>108</u>

<u>BPC3211</u>	H chain: Anti human IL-13 Y100b V mAb	<u>54</u>
	L chain: P1 re-humanised anti-human IL-13 mAb	<u>110</u>
<u>BPC3219</u>	H chain: Anti human IL-13 Y100b V mAb	<u>54</u>
	L chain: Q0 re-humanised anti-human IL-13 mAb	<u>112</u>
<u>BPC3220</u>	H chain: Anti human IL-13 Y100b V mAb	<u>54</u>
	L chain: Q1 re-humanised anti-human IL-13 mAb	<u>114</u>

Antibody expression was assessed directly from the tissue culture supernatant, by a quantitative immunoassay using a Gyrolab workstation. Antibodies BPC3208 and BPC3211 containing re-humanised light chains (denoted P0 and P1 respectively), exhibited improved expression yields in comparison to the A1Y100BVAL1 mAb. Q0 and Q1 light chains (BPC3219 and BPC3220) did not improve expression of the anti-IL-13 mAb. Expression data is presented in Table 15.

Table 15

Antibody ID	Total yield in cell supernatant (µg)
<u>A1Y100BVAL1</u>	<u>19.9</u>
<u>BPC3208</u>	<u>111.0</u>
<u>BPC3211</u>	<u>115.0</u>
<u>BPC3219</u>	<u>16.0</u>
<u>BPC3220</u>	<u>18.3</u>

12.3 mAb-dAb expression in HEK 293 6E cells

As the re-humanised light chains of BPC3208 and BPC3211 exhibited improved expression of the anti-IL-13 mAb, they were examined in the context of an anti-IL-13mAb-anti IL-4dAb. Re-humanised light chains P0 and P1 and the 586 (L1) light chain were co-transfected with the 829H-GS(TVAAPSGS)₂-256 heavy chain (SEQ ID NO: 96, details summarised in Table 16) into HEK 293 6E cells using 293fectin (Invitrogen, 12347019). Plasmids were expressed at the 50 to 500ml scale to produce antibody molecules. A tryptone feed was added to the cell culture after 24 hours and the cells were harvested after a further 48 hours. Antibodies were purified using immobilised Protein A columns and quantified by reading absorbance at 280nm and where indicated, the purified antibody molecule was assessed in the assays described in the examples

set out below. BPC3214 and BPC3215 were analysed by size exclusion chromatography (SEC) as illustrated in Figure 13 and 14.

Table 16

<u>Antibody ID</u>	<u>Alternative names</u>	<u>Linker</u>	<u>Molecule description</u>	<u>Protein SEQ ID NO:</u>	<u>DNA SEQ ID NO:</u>
<u>BPC1085</u>	<u>829H-GS(TVAAPSGS)₂-256</u>	<u>GS(TVAAPSGS)₂</u>	<u>H chain: Anti-human IL-13 mAb heavy chain Y100B V – GS(TVAAPSGS)₂-DOM9-155-256</u>	<u>96</u>	<u>97</u>
			<u>L chain: 586 anti-human IL-13 mAb light chain</u>	<u>24</u>	<u>25</u>
<u>BPC3214</u>	<u>808H-GS(TVAAPSGS)₂-256</u>	<u>GS(TVAAPSGS)₂</u>	<u>H chain: Anti-human IL-13 mAb heavy chain Y100B V – GS(TVAAPSGS)₂-DOM9-155-256</u>	<u>96</u>	<u>97</u>
			<u>L chain: P0 re-humanised anti-human IL-13 mAb</u>	<u>108</u>	<u>109</u>
<u>BPC3215</u>	<u>809H-GS(TVAAPSGS)₂-256</u>	<u>GS(TVAAPSGS)₂</u>	<u>H chain: Anti-human IL-13 mAb heavy chain Y100B V – GS(TVAAPSGS)₂-DOM9-155-256</u>	<u>96</u>	<u>97</u>
			<u>L chain: P1 re-humanised anti-human IL-13 mAb</u>	<u>110</u>	<u>111</u>

5

Consistent with observations in the mAb format, the mAbdAbs containing the re-humanised light chains (BPC3214 and BPC3215) exhibited improved expression in comparison to BPC1085. Representative expression data is summarised in table 17 5.

10 Table 17

<u>Antibody ID</u>	<u>Yield of purified mAbdAb (µg/ml)</u>
BPC1085	5.6
BPC3214	9.8
BPC3215	7.2

12.4 Human IL-13 Binding ELISA

15 Purified BPC3214 and BPC3215 were tested for binding to human IL-13 in comparison to BPC1085 (described in Example 10) via a direct binding ELISA. Anti-IL-13 mAb A1Y100BVAL1 and anti-IL-4 mAb were also examined as positive and negative controls

respectively. 96-well high binding plates were coated with 50µl/well of recombinant E.coli-expressed human IL-13 (Batch number: GRITS31061) at 5µg/ml and incubated at +4°C overnight. All subsequent steps were carried out at room temperature. The plates were washed 3 times with phosphate-buffered saline with 0.05% of Tween-20. 100µL of blocking solution (1% BSA in phosphate-buffered saline with 0.05% of Tween-20) was added to each well and the plates were incubated for at least 1 hour at room temperature. Another wash step was then performed. The purified antibodies were successively diluted across the plates in blocking solution. After 1 hour incubation, the plate was washed. Goat anti-human kappa light chain specific peroxidase conjugated antibody was diluted in blocking solution to 0.75µg/ml and 50µl was added to each well. The plates were incubated for one hour. After another two wash steps, 50µl of OPD (o-phenylenediamine dihydrochloride) SigmaFast substrate solution was added to each well and the reaction was stopped by addition of 50µL of 3M sulphuric acid. Absorbance was read at 490nm using the VersaMax Microplate Reader (Molecular Devices) using a basic endpoint protocol. These data are shown in Figure 15. Direct binding ELISA confirmed that BPC3214 and BPC3215 bind to human IL-13. BPC3214 and BPC3215 exhibit similar IL-13 binding potency to BPC1085. Positive control anti-IL-13 mAb A1Y100BVAL1 also showed binding to recombinant IL-13 whereas negative control anti-IL-4 mAb demonstrated no binding to human IL-13.

20 **12.5 Human IL-4 Binding ELISA**

Purified BPC3214 and BPC3215 were also tested for binding to recombinant E.coli-expressed human IL-4 in a direct binding ELISA. An ELISA was performed as described in example 4, coating 96-well high binding plates with 50µl/well of recombinant E.coli-expressed human IL-4 at 5µg/ml and incubated at +4°C overnight. These data are shown in Figure 16. Direct binding ELISA confirms that BPC3214 and BPC3215 bind to human IL-4. BPC1085 was also examined. BPC3214 exhibits similar IL-4 binding potency to BPC1085. Positive control anti-IL-4 mAb also showed binding to recombinant IL-4 whereas negative control anti-IL-13 mAb A1Y100BVAL1 demonstrated no binding to human IL-4.

Example 13 –Binding Affinity of mAbdAbs comprising the original IL-13 mAb CDRH3 (BPC2222, BPC2223 & BPC2230-2231) for IL-13 and IL-4 as assessed by BIAcore™ analysis

Method

Protein A was immobilised on a C1 chip by primary amine coupling; this surface was used as a capture surface for the antibody molecules to be tested. Recombinant E.coli-expressed human IL13 was used at 256, 64, 16, 4, and 1nM, recombinant E.coli-expressed human IL4 was used at 64, 16, 4, 1 and 0.25nM, with 0nM (i.e. buffer alone) used to double reference the binding curves of both IL4 and IL13 binding. Regeneration the Protein A surface was with 100mM Phosphoric acid. The assay was run at 25°C

using HBS-EP as running buffer. The data was fitted to 1:1 model inherent to the Biacore T100 analysis software.

5 The results of binding to human IL13 are shown in Table 18 and the result of binding to human IL4 are shown in Table 19.

Table 18

Molecule name	ka(M/s)	kd(1/s)	KD (nM)
BPC2222	1.31E+06	4.93E-04	0.376
BPC2223	1.32E+06	4.90E-04	0.372
BPC2230	1.31E+06	4.88E-04	0.373
BPC2231	1.30E+06	5.13E-04	0.394

10

Table 19

Molecule name	ka(M/s)	kd(1/s)	KD (nM)
BPC2222	1.06E+05	1.09E-04	1.027
BPC2223	8.59E+06	1.56E-04	0.018
BPC2230*	2.48E+07	2.48E-04	0.010
BPC2231*	4.03E+07	2.31E-04	0.006

15

*The on-rate for BPC2230 and 2231 are beyond the sensitivity of Biacore, but the fact that we cannot accurately analyse this data does indicate that the interaction with IL4 is likely to be of high affinity with a fast on-rate.

Example 14 – Binding Affinity of mAbdAbs comprising the original IL-13 mAb CDRH3 (BPC2222, BPC2231) & variant anti-IL-13 mAb CDRH3 (BPC1085-1087) for IL-13 and IL-4 as assessed by BIAcore™ analysis

20

Method

25

Protein A was immobilised on a CM5 chip by primary amine coupling; this surface was used as a capture surface for the antibody molecules to be tested. Recombinant E.coli-expressed human IL13 was used at 256nM only, Recombinant E.coli-expressed human IL4 was used at 64, 16, 4 and 1nM, with 0nM (i.e. buffer alone) used to double reference the binding curves for both IL4 and IL13 binding. Regeneration the Protein A surface was with 50mM NaOH. The assay was run at 25°C using HBS-EP as running buffer. The data was fitted to 1:1 model inherent to the Biacore T100 analysis software.

The results of binding to human IL13 are shown in Table 20, and the results of binding to human IL4 are shown in Table 21.

Table 20

Molecule name	ka(M/s)	kd(1/s)	KD (nM)
BPC2222	1.64E+05	5.15E-05	0.314
BPC2231	5.36E+08	1.16E-03	0.002
BPC1085	1.87E+07	8.97E-04	0.048
BPC1086	7.99E+07	1.64E-03	0.021
BPC1087	9.86E+07	1.79E-03	0.018

- 5 On-rate for BPC1086 and BPC1087 are beyond the sensitivity of Biacore, but the fact that we cannot accurately analyse this data does indicate that the interaction with IL4 is likely to be of high affinity with a fast on-rate.

10

Table 21

Molecule name	ka(M/s)	kd(1/s)	KD (nM)
BPC2222	1.44E+06	4.44E-04	0.308
BPC2231	1.56E+06	4.95E-04	0.316
BPC1085	1.20E+06	6.39E-05	0.053
BPC1086	1.28E+06	6.57E-05	0.051
BPC1087	1.13E+06	6.42E-05	0.057

15

Example 15 – Binding Affinity of mAbdAbs comprising a number of variant anti-IL-13 mAb CDRH3 (BPC1085, BPC1090-BPC1095, & BPC1108-BPC1119) for IL-4 as assessed by BIAcore™ analysis

Method (human IL-4 binding affinity)

20

Protein A was immobilised on a CM5 chip by primary amine coupling; this surface was used as a capture surface for the antibody molecules to be tested.

Recombinant E.coli-expressed human IL4 was used at 64, 16, 4, 1 and 0.25nM. All binding curves were double referenced with a 0nM injection (i.e. buffer alone).

25

Regeneration of the Protein A surface was with 50mM NaOH. The assay was run at 25°C using HBS-EP as running buffer. The data was fitted to 1:1 model inherent to the Biacore T100 analysis software.

The results of binding to human IL4 are shown in Table 22.

5

Table 22

Molecule name	ka(M/s)	kd(1/s)	KD (nM)
BPC1085	1.07E+07	8.34E-04	0.078
BPC1090	4.34E+06	4.16E-04	0.096
BPC1091	6.05E+06	1.02E-03	0.168
BPC1092	2.27E+06	3.89E-03	1.713
BPC1093	3.84E+06	2.11E-04	0.055
BPC1094	1.46E+06	3.04E-03	2.078
BPC1095	6.78E+06	3.18E-02	4.687
BPC1108	4.38E+06	1.23E-03	0.281
BPC1109	1.20E+06	1.77E-01	147.300
BPC1110	1.07E+06	1.73E-03	1.626
BPC1111	2.98E+06	1.11E-04	0.037
BPC1112*	1.14E+08	3.31E+00	28.980
BPC1113	no	binding	seen
BPC1114	3.89E+06	2.55E-03	0.656
BPC1115**	1.44E+08	3.29E-01	2.292
BPC1116	6.82E+06	2.74E-03	0.402
BPC1117	3.95E+06	9.13E-04	0.231
BPC1118	6.39E+06	2.58E-03	0.405
BPC1119	no	binding	seen

10

*BPC1112 data has a positive off-rate as a result of the machine being unable to calculate real off-rate, possibly due to the fact it is so rapid, in addition the on-rate for this

construct is beyond what is measurable by Biacore, but construct is a very poor binder to IL4.

*BPC1115 also has an impossible on-rate, it is outside scope of BIAcore to calculate affinity.

5

10

Example 16 – IL-13 Binding Affinity of mAbdAbs comprising the re-humanised light chain (BPC3214 & BPC3215) compared to the original light chain (BPC1085) as assessed by BIAcore™ analysis

15 Method (human and cyno IL-13 binding affinity)

Protein A was immobilised on a CM5 chip by primary amine coupling; this surface was used as a capture surface for the antibody molecules to be tested.

Recombinant E.coli-expressed human IL13 and cyno IL13 were used 64, 16, 4, 1 and 0.25nM. All binding curves were double referenced with a 0nM injection (i.e. buffer alone).

20

Regeneration of the Protein A surface was with 50mM NaOH. The assay was run at 25°C using HBS-EP as running buffer. The data was fitted to 1:1 model inherent to the Biacore T100 analysis software.

25 The results of binding to human and cyno IL13 are shown in Table 23.

Table 23

Molecule name	ka(M/s)	kd(1/s)	KD (nM)	Comment
Binding to human IL13				
BPC3214	7.749E+05	7.18E-05	0.093	
BPC3215	8.220E+05	5.23E-05	0.064	
BPC1085	8.652E+05	6.34E-05	0.073	
Binding to cyno IL13				
BPC3214*	3.214E+05	5.07E-06	0.015770	Impossible off-rates
BPC3215*	3.283E+05	3.13E-06	0.009546	Impossible off-rates
BPC1085*	3.552E+05	5.19E-10	0.000001	Impossible off-rates

*The off-rates (k_a) for cyno IL13 binding to BPC3214, BPC3215 and BPC1085 are beyond the sensitivity of the Biacore T100, this indicates the dissociation rate is very slow and that the interaction is likely to be of very high affinity.

5

Example 17 - Stressor Studies of mAbdAbs with and without the mutated dAb

10 A number of mAbdAbs were placed in PBS or 50mM acetate buffer and incubated at 37°C for up to 14 days. They were then analysed for presence of a visual precipitate, soluble aggregate and adherence to concentration stability.

15 The results indicate that the mAbdAbs comprising the mutated dAb (BPC2222, 2223, 2230, 2231) behaved similarly to the non-mutated dAb (BPC1085, 1086, 1087) both categories of mAbdAb appeared to be stable in both PBS and acetate buffers over the two week incubation period at 37°C, as indicated by no change in the protein concentration in the solutions. In addition no or very little change was noted for the levels of aggregates in the solutions and no precipitation was observed.

20 **Example 18 - PK assessment**

The pharmacokinetics of BPC1085, BPC1086, and BPC1087 were investigated in separate studies following IV administration to rats. The PK of BPC1085 was also investigated in cynomolgus monkeys following IV administration.

25

The PK of all three molecules in rat and BPC1085 in monkey were found to be consistent with that of a standard mAb.

Brief Description of Figures

Figure 1: A graph showing the capacity of the mAbdAbs comprising the Y100B variants to neutralise human IL-13 in a TF-1 cell proliferation assay

- 5 Figure 2: A graph showing the capacity of the mAbdAbs comprising the Y100B variants to neutralise human IL-13 in a TF-1 cell proliferation assay

Figure 3: SEC trace of BPC2222

Figure 4: SEC trace of BPC2223

Figure 5: SEC trace of BPC2230

- 10 Figure 6: SEC trace of BPC2231

Figure 7: SEC trace of BPC1085

Figure 8: SEC trace of BPC1086

Figure 9: SEC trace of BPC1087

- 15 Figure 10: A graph showing binding of purified mAbdAbs (BPC1085, BPC1086 and BPC1087) to human IL-4 as determined by ELISA. The IL-4 control mAb is labelled as 'pascolizumab'.

- 20 Figure 11: A graph showing neutralization of human IL-4 by purified mAbdAbs (BPC1085, BPC1086 and BPC1087) to human IL-4 in the TF-1 cell bioassay. The IL-4 control mAb is labelled as 'pascolizumab'.

- 25 Figure 12: A graph showing neutralization of human IL-13 by purified mAbdAbs (BPC1085, BPC1086 and BPC1087) to human IL-13 in the TF-1 cell bioassay. The IL-4 control mAb is labelled as 'pascolizumab'.

Figure 13: SEC profile for BPC3214.

Figure 14: SEC profile for BPC3215.

- 30 Figure 15: A graph showing binding of purified mAbdAbs BPC3214, BPC3215, BPC1085 and control mAbs A1Y100BVAL1 and anti-IL-4 mAb to human IL-13 as determined by ELISA. The IL-4 control mAb is labelled as 'pascolizumab'.

- 35 Figure 16: A graph showing binding of purified mAbdAbs BPC3214, BPC3215, BPC1085 and control mAbs A1Y100BVAL1 and anti-IL-4 mAb to human IL-4 as determined by ELISA. The IL-4 control mAb is labelled as 'pascolizumab'.

Figure 17: A graph showing binding of transiently expressed mAbdAbs to recombinant E.coli-expressed human IL-4 as determined by ELISA. The IL-4 control mAb is labelled as 'pascolizumab'.

5

Sequence Summary (Table 24)

Description	Sequence identifier (SEQ ID NO)	
	amino acid sequence	Polynucleotide sequence
Anti IL13 A1, CDRH1	1	-
Anti IL13 A1, CDRH2	2	-
Anti IL13 A1, CDRH3	3	-
CDRH3 alternative	4	-
CDRH3 alternative	5	-
CDRH3 alternative	6	-
CDRH3 alternative	7	-
CDRH3 alternative	8	-
CDRH3 alternative	9	-
CDRH3 alternative	10	-
CDRH3 alternative	11	-
CDRH3 alternative	12	-
CDRH3 alternative	13	-
CDRH3 alternative	14	-
CDRH3 alternative	15	-
CDRH3 alternative	16	-
CDRH3 alternative	17	-
CDRH3 alternative	18	-
Anti IL13 L1, CDRL1	19	-
Anti IL13 L1, CDRL2	20	-
Anti IL13 L1, CDRL3	21	-
Anti IL13 A1 (Heavy Chain)	22	23
Anti IL13 L1 (Light Chain)	24	25
Anti IL13 humanised variant A1 S95 Trp (Heavy Chain)	26	27
Anti IL13 humanised variant A1 I96 Val (Heavy Chain)	28	29
Anti IL13 humanised variant A1 Y97 Phe (Heavy Chain)	30	31
Anti IL13 humanised variant A1 D98 Glu (Heavy Chain)	32	33
Anti IL13 humanised variant A1 H100A Ala (Heavy Chain)	34	35
Anti IL13 humanised variant A1 H100A Glu (Heavy Chain)	36	37
Anti IL13 humanised variant A1 H100A Gln (Heavy Chain)	38	39
Anti IL13 humanised variant A1 H100A Arg (Heavy	40	41

Chain)		
Anti IL13 humanised variant A1 H100A Ser (Heavy Chain)	42	43
Anti IL13 humanised variant A1 H100A Thr (Heavy Chain)	44	45
Anti IL13 humanised variant A1 H100A Val (Heavy Chain)	46	47
Anti IL13 humanised variant A1 Y100B Ala (Heavy Chain)	48	49
Anti IL13 humanised variant A1 Y100B Ile (Heavy Chain)	50	51
Anti IL13 humanised variant A1 Y100B Trp (Heavy Chain)	52	53
Anti IL13 humanised variant A1 Y100B Val (Heavy Chain)	54	55
Signal sequence	56	-
Human IL13	57	-
Murine 6A1 VH	58	-
Murine 6A1 VL	59	-
Alternative CDRH1 (Chothia and Kabat numbering)	60	-
Alternative CDRH1 (Chothia and Kabat numbering)	61	-
A1Y100BAIa H-TVAAPS-210 (Heavy chain)	62	63
A1 Y100BIle H-TVAAPS-210 (Heavy chain)	64	65
A1Y100BTrp H-TVAAPS -210 (Heavy chain)	66	67
A1Y100BVal H-TVAAPS-210 (Heavy chain)	68	69
A1Y100BAIa H-ASTKGPS-210 (Heavy chain)	70	71
A1 Y100BIle H-ASTKGPS-210 (Heavy chain)	72	73
A1Y100BTrp H-ASTKGPS-210 (Heavy chain)	74	75
A1Y100BVal H-ASTKGPS-210 (Heavy chain)	76	77
DOM9-155-25	78	
DOM9-155-147	79	
DOM9-155-154	80	
DOM9-112-210	81	
Linker	82	
Linker	83	
Linker	84	
Linker	85	
Linker	86	
Linker	87	
147-TVAAPS-586 Y100B V Heavy chain	88	
147-ASTKG-586 Y100B V Heavy chain	89	
154-TVAAPS-586 Y100B V Heavy chain	90	
154- ASTKG -586 Y100B V Heavy chain	91	

Linker	92	
Linker	93	
DOM9-155-154 L89Q (aka DOM9-155-256)	94	95
829H-GS(TVAAPSGS) ₂ -154 L89Q	96	97
829H-GS(TVAAPSGS) ₃ -154 L89Q	98	99
829H-GS(TVAAPSGS) ₄ -154 L89Q	100	101
829H-(TVAAPS) ₂ GS-154 L89Q	102	103
829H-(TVAAPS) ₃ GS-154 L89Q	104	105
829H-(TVAAPS) ₄ GS-154 L89Q	106	107
P0	108	109
P1	110	111
Q0	112	113
Q1	114	115
586H-TVAAPS-154 (H chain)	116	
Anti-human IL-13 mAb heavy chain Y100B_V-(TVAAPS) ₂ GS-DOM9-155-154 (89G)	117	
Anti-human IL-13 mAb heavy chain Y100B_V-(TVAAPS) ₂ GS-DOM9-155-154 (89S)	118	
Anti-human IL-13 mAb heavy chain Y100B_V-(TVAAPS) ₂ GS-DOM9-155-154 (89H)	119	
Anti-human IL-13 mAb heavy chain Y100B_V-(TVAAPS) ₂ GS-DOM9-155-154 (89M)	120	
Anti-human IL-13 mAb heavy chain Y100B_V-(TVAAPS) ₂ GS-DOM9-155-154 (89A)	121	
Anti-human IL-13 mAb heavy chain Y100B_V-(TVAAPS) ₂ GS-DOM9-155-154 (89T)	122	
Anti-human IL-13 mAb heavy chain Y100B_V-(TVAAPS) ₂ GS-DOM9-155-154 (89C)	123	
Anti-human IL-13 mAb heavy chain Y100B_V-(TVAAPS) ₂ GS-DOM9-155-154 (89R)	124	
Anti-human IL-13 mAb heavy chain Y100B_V-(TVAAPS) ₂ GS-DOM9-155-154 (89W)	125	
Anti-human IL-13 mAb heavy chain Y100B_V-(TVAAPS) ₂ GS-DOM9-155-154 (89E)	126	
Anti-human IL-13 mAb heavy chain Y100B_V-(TVAAPS) ₂ GS-DOM9-155-154 (89K)	127	
Anti-human IL-13 mAb heavy chain Y100B_V-(TVAAPS) ₂ GS-DOM9-155-154 (89D)	128	
Anti-human IL-13 mAb heavy chain Y100B_V-(TVAAPS) ₂ GS-DOM9-155-154 (89N)	129	
Anti-human IL-13 mAb heavy chain Y100B_V-(TVAAPS) ₂ GS-DOM9-155-154 (89Y)	130	
Anti-human IL-13 mAb heavy chain Y100B_V-(TVAAPS) ₂ GS-DOM9-155-154 (89V)	131	

Anti-human IL-13 mAb heavy chain Y100B_V-(TVAAPS) ₂ GS-DOM9-155-154 (89I)	132	
Anti-human IL-13 mAb heavy chain Y100B_V-(TVAAPS) ₂ GS-DOM9-155-154 (89F)	133	
Anti-human IL-13 mAb heavy chain Y100B_V-(TVAAPS) ₂ GS-DOM9-155-154 (89P)	134	
Anti-IL-13 mAb heavy chain-GS(TVAAPSGS) ₁ -DOM9-155-154	135	-
Anti-IL-13 mAb heavy chain-GS(TVAAPSGS) ₂ -DOM9-155-154	136	-
Anti-IL-13 mAb heavy chain-GS(TVAAPSGS) ₃ -DOM9-155-154	137	-
Anti-IL-13 mAb heavy chain-GS(TVAAPSGS) ₄ -DOM9-155-154	138	
GS(TVAAPSGS) ₁	139	
GS(TVAAPSGS) ₂	140	
GS(TVAAPSGS) ₃	141	
GS(TVAAPSGS) ₄	142	
GS(TVAAPSGS) ₅	143	
GS(TVAAPSGS) ₆	144	
(TVAAPS) ₂ (GS) ₁	145	
(TVAAPS) ₃ (GS) ₁	146	
Anti-human IL-13 mAb heavy chain Y100B_V-(TVAAPS) ₂ GS-DOM9-155-154 (89M)	147	

SEQUENCES

SEQ ID NO: 1

DTYMH

5

SEQ ID NO: 2

TIDPANGNTKYVPKFQG

SEQ ID NO: 3

10 SIYDDYHYDDYYAMDY

SEQ ID NO: 4

WIYDDYHYDDYYAMDY

15

SEQ ID NO: 5

SVYDDYHYDDYYAMDY

SEQ ID NO: 6

20

SIFDDYHYDDYYAMDY

SEQ ID NO: 7

SIYEDYHYDDYYAMDY

SEQ ID NO: 8

25 SIYDDYAYDDYYAMDY

SEQ ID NO: 9

SIYDDYEYDDYYAMDY

30

SEQ ID NO: 10

SIYDDYQYDDYYAMDY

SEQ ID NO: 11

35

SIYDDYRYDDYYAMDY

SEQ ID NO: 12

SIYDDYSYDDYYAMDY

SEQ ID NO: 13

40 SIYDDYTYDDYYAMDY

SEQ ID NO: 14

SIYDDYVYDDYYAMDY

45

SEQ ID NO: 15

45

GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATCGAGAAAACCATCAGCAAGGC
 CAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA
 ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAG
 AGCAACGGCCAGCCCAGAGAACAACACTACAAGACCACCCCCCTGTGCTGGACAGCGATGGCAGCTT
 5 CTTCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTTCAGCTGCT
 CCGTGATGCACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAG

SEQ ID NO: 24

10 DIVMTQSPLSLPVTGPGEPAISCRSSQNIVHINGNTYLEWYLQKPGQSPRLLIYKISDRFSGVPD
 RFSGSGSGTDFTLKISRVEADDVGIYYCFQGSHVPWTFGQGTKLEIKRTVAAPSVFIFPPSDEQL
 KSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHK
 VYACEVTHQGLSSPVTKSFNRGEC

15 SEQ ID NO: 25

GACATCGTGATGACCCAGTCTCCTCTGAGCCTCCCCGTGACCCCCGGCGAACCAGCCAGCATCTC
 CTGCAGAAGCAGCCAGAACATCGTGACATCAACGGCAACACCTACCTGGAGTGGTACCTGCAAA
 AGCCCGGCCAGAGCCCCAGGCTGCTGATCTACAAGATCAGCGACAGGTTTCAGCGGCGTGCCCGAT
 AGGTTTCAGCGGCAGCGGCAGCGGCACCGACTTCACCCTGAAGATCAGCAGGGTGGAGGCCGACGA
 20 CGTGGGCATCTACTACTGCTTCCAGGGCAGCCACGTCCCCTGGACTTTCGGACAGGGCACCAAGC
 TGGAGATTAAGCGTACGGTGGCCGCCCCAGCGTGTTTCATCTTCCCCCCCAGCGATGAGCAGCTG
 AAGAGCGGCACCGCCAGCGTGGTGTGTCTGCTGAACAACCTTCTACCCCCGGGAGGCCAAGGTGCA
 GTGGAAGGTGGACAATGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGCAGGACAGCA
 AGGACTCCACCTACAGCCTGAGCAGCACCCCTGACCCTGAGCAAGGCCGACTACGAGAAGCACAAG
 25 GTGTACGCCTGTGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGACCAAGAGCTTCAACCGGGG
 CGAGTGC

SEQ ID NO: 26

30 QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWRQAPGQGLEWMGTIDPANGNTKYVPKFQ
 GRVTITADESTSTAYMELSSLRSED TAVYYCARWIYDDYHYDDYYAMDYWGQGTLVTVSSASTKG
 PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
 VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
 ISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
 35 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
 SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 27

CAGGTGCAGCTCGTGACAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTGAGCTG
 40 CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTCAGGCAGGCTCCTGGCCAGG
 GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCAAGTTCCAG
 GGCAGGGTGACCATCACCGCCGATGAGAGCACCGAGCACCGCCTACATGGAAGTGGAGCAGCCTGAG
 GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGTGGATCTACGACGACTACCACTACGACGACT
 ACTACGCCATGGACTACTGGGGACAGGGCACACTAGTGACCGTGTCCAGCGCCAGCACCAAGGGC
 45 CCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCGCGGCGGCACAGCCGCCCTGGGCTG
 CCTGGTGAAGGACTACTTCCCCGAACCGGTGACCGTGTCTTGGAACAGCGGAGCCCTGACCAGCG

GCGTGCACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACC
 GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACAC
 CAAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCTGCCCTG
 CCCCCGAGCTGCTGGGAGGCCCCAGCGTGTTCCCTGTTCCCCCCCCAAGCCTAAGGACACCCTGATG
 5 ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA
 GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGT
 ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAG
 GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATCGAGAAAACCATCAGCAAGGC
 CAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA
 10 ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAG
 AGCAACGGCCAGCCCGAGAACAACACTACAAGACCACCCCCCCTGTGCTGGACAGCGATGGCAGCTT
 CTTCCCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTTCAGCTGCT
 CCGTGATGCACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAG

15 SEQ ID NO: 28

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWRQAPGQGLEWMGTIDPANGNTKYVPKFQ
 GRVTITADESTSTAYMELSSLRSEDYAVYYCARSVYDDYHYDDYYAMDYWGQGTILTVTVSSASTKG
 PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
 VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKHTCTPPCPAPELLGGPSVFLFPPKPKDTLM
 20 ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
 SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQSVMEALHNHYTQKSLSLSPGK

SEQ ID NO: 29

25 CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTGAGCTG
 CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTCAGGCAGGCTCCTGGCCAGG
 GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCAAGTTCCAG
 GGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACCGCCTACATGGAAGTGAAGCAGCCTGAG
 GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCGTCTACGACGACTACCACTACGACGACT
 30 ACTACGCCATGGACTACTGGGGACAGGGCACACTAGTGACCGTGTCCAGCGCCAGCACCAAGGGC
 CCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTG
 CCTGGTGAAGGACTACTTCCCCGAACCGGTGACCGTGTCTGGAACAGCGGAGCCCTGACCAGCG
 GCGTGCACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACC
 GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACAC
 35 CAAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCTGCCCTG
 CCCCCGAGCTGCTGGGAGGCCCCAGCGTGTTCCCTGTTCCCCCCCCAAGCCTAAGGACACCCTGATG
 ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA
 GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGT
 ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAG
 40 GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATCGAGAAAACCATCAGCAAGGC
 CAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA
 ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAG
 AGCAACGGCCAGCCCGAGAACAACACTACAAGACCACCCCCCCTGTGCTGGACAGCGATGGCAGCTT
 CTTCCCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTTCAGCTGCT
 45 CCGTGATGCACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAG

SEQ ID NO: 30

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
 GRVTITADESTSTAYMELSSLRSED TAVYYCARSIFDDYHYDDYYAMDYWGQGT LVT VSSASTKG
 PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
 5 VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
 ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
 SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK

10 SEQ ID NO: 31

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTGAGCTG
 CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTCAGGCAGGCTCCTGGCCAGG
 GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCAAGTTCCAG
 GGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACCGCCTACATGGAACTGAGCAGCCTGAG
 15 GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATCTTTGACGACTACCACTACGACGACT
 ACTACGCCATGGACTACTGGGGACAGGGCACACTAGTGACCGTGTCCAGCGCCAGCACCAAGGGC
 CCCAGCGTGTTCCTCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTG
 CCTGGTGAAGGACTACTTCCCCGAACCGGTGACCGTGTCTTGGAAACAGCGGAGCCCTGACCAGCG
 GCGTGCACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACC
 20 GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACAC
 CAAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCCCTGCCCTG
 CCCCCGAGCTGCTGGGAGGCCCCAGCGTGTTCCTGTTCCCCCCCCAAGCCTAAGGACACCCTGATG
 ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA
 GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGT
 25 ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAG
 GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATCGAGAAAACCATCAGCAAGGC
 CAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA
 ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAG
 AGCAACGGCCAGCCCAGAGAACAATAAGACCACCCCCCTGTGCTGGACAGCGATGGCAGCTT
 30 CTTCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTTCAGCTGCT
 CCGTGATGCACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAG

SEQ ID NO: 32

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
 GRVTITADESTSTAYMELSSLRSED TAVYYCARSIIYEDYHYDDYYAMDYWGQGT LVT VSSASTKG
 PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
 VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
 ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
 40 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
 SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 33

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTGAGCTG
 45 CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTCAGGCAGGCTCCTGGCCAGG
 GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCAAGTTCCAG

GGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACCGCCTACATGGAACTGAGCAGCCTGAG
 GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATCTACGAGGACTACCACTACGACGACT
 ACTACGCCATGGACTACTGGGGACAGGGCACACTAGTGACCGTGTCCAGCGCCAGCACCAAGGGC
 CCCAGCGTGTTCCTTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTG
 5 CCTGGTGAAGGACTACTTCCCCGAACCGGTGACCGTGTCTTGGAACAGCGGAGCCCTGACCAGCG
 GCGTGCACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACC
 GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACAC
 CAAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCCCTGCCCTG
 CCCCCGAGCTGCTGGGAGGCCCCAGCGTGTTCCTGTTCCCCCCCCAAGCCTAAGGACACCCTGATG
 10 ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA
 GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGT
 ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGTGTCACCAGGATTGGCTGAACGGCAAG
 GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATCGAGAAAACCATCAGCAAGGC
 CAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA
 15 ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAG
 AGCAACGGCCAGCCCAGAGAACAATAAGACCACCCCCCTGTGCTGGACAGCGATGGCAGCTT
 CTTCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTTCAGCTGCT
 CCGTGATGCACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAG

 20 **SEQ ID NO: 34**
 QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWRQAPGQGLEWMGTIDPANGNTKYVPKFQ
 GRVTITADESTSTAYMELSSLRSEDYAVYYCARSYDDYAYDDYAMDYWGQGLTVTVSSASTKG
 PSVFPLAPSSKSTSGGTAALGLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
 VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
 25 ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
 SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSVMSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 35
 30 CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTGAGCTG
 CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTGAGGCAGGCTCCTGGCCAGG
 GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCAAGTTCCAG
 GGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACCGCCTACATGGAACTGAGCAGCCTGAG
 GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATCTACGACGACTACGCGTACGACGACT
 35 ACTACGCCATGGACTACTGGGGACAGGGCACACTAGTGACCGTGTCCAGCGCCAGCACCAAGGGC
 CCCAGCGTGTTCCTTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTG
 CCTGGTGAAGGACTACTTCCCCGAACCGGTGACCGTGTCTTGGAACAGCGGAGCCCTGACCAGCG
 GCGTGCACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACC
 GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACAC
 40 CAAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCCCTGCCCTG
 CCCCCGAGCTGCTGGGAGGCCCCAGCGTGTTCCTGTTCCCCCCCCAAGCCTAAGGACACCCTGATG
 ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA
 GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGT
 ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGTGTCACCAGGATTGGCTGAACGGCAAG
 45 GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATCGAGAAAACCATCAGCAAGGC
 CAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA

ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAG
 AGCAACGGCCAGCCCGAGAACAACACTACAAGACCACCCCCCTGTGCTGGACAGCGATGGCAGCTT
 CTTCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTTCAGCTGCT
 CCGTGATGCACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAG

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SEQ ID NO: 36

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
 GRVTITADESTSTAYMELSSLRSEDVAVYYCARSYDDYDYDDYYAMDYWGQGLTVTVSSASTKG
 PSVFPLAPSSKSTSGGTAAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
 VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
 ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
 SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSVCSVMHEALHNHYTQKSLSLSPGK

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15 **SEQ ID NO: 37**

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTGAGCTG
 CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTCAGGCAGGCTCCTGGCCAGG
 GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCAAGTTCCAG
 GGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACCGCCTACATGGAAGTGAAGCAGCCTGAG
 GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATCTACGACGACTACGAGTACGACGACT
 ACTACGCCATGGACTACTGGGGACAGGGCACACTAGTGACCGTGTCCAGCGCCAGCACCAAGGGC
 CCCAGCGTGTTCCTCCCTGGCCCCCAGCAGCAAGAGCACAGCGGCGGCACAGCCGCCCTGGGCTG
 CCTGGTGAAGGACTACTTCCCCGAACCGGTGACCGTGTCTTGAACAGCGGAGCCCTGACCAGCG
 GCGTGACACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACC
 GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACAC
 CAAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCCCTGCCCTG
 CCCCCGAGCTGCTGGGAGGCCCCAGCGTGTTCCTGTTCCCCCCCCAAGCCTAAGGACACCCTGATG
 ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA
 GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGT
 ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGTGACCCAGGATTGGCTGAACGGCAAG
 GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATCGAGAAAACCATCAGCAAGGC
 CAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA
 ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAG
 AGCAACGGCCAGCCCGAGAACAACACTACAAGACCACCCCCCTGTGCTGGACAGCGATGGCAGCTT
 CTTCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTTCAGCTGCT
 CCGTGATGCACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAG

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SEQ ID NO: 38

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
 GRVTITADESTSTAYMELSSLRSEDVAVYYCARSYDDYQYDDYYAMDYWGQGLTVTVSSASTKG
 PSVFPLAPSSKSTSGGTAAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
 VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
 ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
 SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSVCSVMHEALHNHYTQKSLSLSPGK

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SEQ ID NO: 39

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTGAGCTG
 CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTCAGGCAGGCTCCTGGCCAGG
 GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCAAGTTCCAG
 5 GGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACCGCCTACATGGAACTGAGCAGCCTGAG
 GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATCTACGACGACTACCAGTACGACGACT
 ACTACGCCATGGACTACTGGGGACAGGGCACACTAGTGACCGTGTCCAGCGCCAGCACCAAGGGC
 CCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTG
 CCTGGTGAAGGACTACTTCCCCGAACCGGTGACCGTGTCTTGGAACAGCGGAGCCCTGACCAGCG
 10 GCGTGCACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACC
 GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACAC
 CAAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCCCTGCCCTG
 CCCCCGAGCTGCTGGGAGGCCCCAGCGTGTTCTTGTTCCCCCCAAGCCTAAGGACACCCTGATG
 ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA
 15 GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGT
 ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAG
 GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATCGAGAAAACCATCAGCAAGGC
 CAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA
 ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAG
 20 AGCAACGGCCAGCCCCGAGAACAATAAGACCACCCCCCTGTGCTGGACAGCGATGGCAGCTT
 CTTCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTTCAGCTGCT
 CCGTGATGCACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAG

SEQ ID NO: 40

25 QVQLVQSGAEVKKPGSSSVKVSCKASGFYIKDTYMHVVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
 GRVTITADESTSTAYMELSSLRSED TAVYYCARS IYDDYRYDDYYAMDYWGQGTLVTVSSASTKG
 PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
 VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPPKPKDTLM
 ISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
 30 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
 SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 41

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTGAGCTG
 35 CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTCAGGCAGGCTCCTGGCCAGG
 GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCAAGTTCCAG
 GGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACCGCCTACATGGAACTGAGCAGCCTGAG
 GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATCTACGACGACTACAGGTACGACGACT
 ACTACGCCATGGACTACTGGGGACAGGGCACACTAGTGACCGTGTCCAGCGCCAGCACCAAGGGC
 40 CCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTG
 CCTGGTGAAGGACTACTTCCCCGAACCGGTGACCGTGTCTTGGAACAGCGGAGCCCTGACCAGCG
 GCGTGCACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACC
 GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACAC
 CAAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCCCTGCCCTG
 45 CCCCCGAGCTGCTGGGAGGCCCCAGCGTGTTCTTGTTCCCCCCAAGCCTAAGGACACCCTGATG
 ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA

GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGT
 ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAG
 GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATCGAGAAAACCATCAGCAAGGC
 CAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA
 5 ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAG
 AGCAACGGCCAGCCCGAGAACAACACTACAAGACCACCCCCCTGTGCTGGACAGCGATGGCAGCTT
 CTTCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTTCAGCTGCT
 CCGTGATGCACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAG

10 SEQ ID NO: 42

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWRQAPGQGLEWMGTIDPANGNTKYVPKFQ
 GRVTITADESTSTAYMELSSLRSEDVAVYYCARSYDDYSYDDYYAMDYWGQGLTVTVSSASTKG
 PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
 VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
 15 ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
 SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 43

20 CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTGAGCTG
 CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTCAGGCAGGCTCCTGGCCAGG
 GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCAAGTTCCAG
 GGCAGGGTGACCATCACCGCCGATGAGAGCACCGAGCACCGCCTACATGGAAGTGAAGCAGCCTGAG
 GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATCTACGACGACTACTCCTACGACGACT
 25 ACTACGCCATGGACTACTGGGGACAGGGCACACTAGTGACCGTGTCCAGCGCCAGCACCAAGGGC
 CCCAGCGTGTTCCTCCCTGGCCCCCAGCAGCAAGAGCACCGAGCGGCGGCACAGCCGCCCTGGGCTG
 CCTGGTGAAGGACTACTTCCCCGAACCGGTGACCGTGTCTTGAACAGCGGAGCCCTGACCAGCG
 GCGTGCACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACC
 GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACAC
 30 CAAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCCCTGCCCTG
 CCCCCGAGCTGCTGGGAGGCCCCAGCGTGTTCTCTGTTCCCCCCCCAAGCCTAAGGACACCCTGATG
 ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA
 GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGT
 ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAG
 35 GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATCGAGAAAACCATCAGCAAGGC
 CAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA
 ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAG
 AGCAACGGCCAGCCCGAGAACAACACTACAAGACCACCCCCCTGTGCTGGACAGCGATGGCAGCTT
 CTTCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTTCAGCTGCT
 40 CCGTGATGCACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAG

SEQ ID NO: 44

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWRQAPGQGLEWMGTIDPANGNTKYVPKFQ
 GRVTITADESTSTAYMELSSLRSEDVAVYYCARSYDDYTYDDYYAMDYWGQGLTVTVSSASTKG
 45 PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
 VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM

ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSVCSVMHEALHNHYTQKSLSLSPGK

5 SEQ ID NO: 45

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTGAGCTG
CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTCAGGCAGGCTCCTGGCCAGG
GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCAAGTTCCAG
GGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACCGCCTACATGGAACTGAGCAGCCTGAG
10 GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATCTACGACGACTACACGTACGACGACT
ACTACGCCATGGACTACTGGGGACAGGGCACACTAGTGACCGTGTCCAGCGCCAGCACCAAGGGC
CCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACAGCGGCGGCACAGCCGCCCTGGGCTG
CCTGGTGAAGGACTACTTCCCCGAACCGGTGACCGTGTCTTGGAACAGCGGAGCCCTGACCAGCG
GCGTGCACACCTTCCCCGCGGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACC
15 GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACAC
CAAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCTGCCCTG
CCCCCGAGCTGCTGGGAGGCCCCAGCGTGTTCTTCTGTTCCCCCCCCAAGCCTAAGGACACCCTGATG
ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA
GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGT
20 ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAG
GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATCGAGAAAACCATCAGCAAGGC
CAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA
ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAG
AGCAACGGCCAGCCCCGAGAACAATAAGACCACCCCCCTGTGCTGGACAGCGATGGCAGCTT
25 CTTCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTTCAGCTGCT
CCGTGATGCACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAG

SEQ ID NO: 46

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWRQAPGQGLEWMGTIDPANGNTKYVPKFQ
30 GRVTITADESTSTAYMELSSLRSED TAVYYCARS IYDDYVYDDY YAMDYWGQGTLVTVSSASTKG
PSVFPLAPSSKSTSGGTAA LGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
35 SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSVCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 47

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTGAGCTG
CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTCAGGCAGGCTCCTGGCCAGG
40 GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCAAGTTCCAG
GGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACCGCCTACATGGAACTGAGCAGCCTGAG
GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATCTACGACGACTACGTGTACGACGACT
ACTACGCCATGGACTACTGGGGACAGGGCACACTAGTGACCGTGTCCAGCGCCAGCACCAAGGGC
CCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACAGCGGCGGCACAGCCGCCCTGGGCTG
45 CCTGGTGAAGGACTACTTCCCCGAACCGGTGACCGTGTCTTGGAACAGCGGAGCCCTGACCAGCG
GCGTGCACACCTTCCCCGCGGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACC

GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACAC
 CAAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCCCTGCCCTG
 CCCCCGAGCTGCTGGGAGGCCCCAGCGTGTTCTGTTCACCCCAAGCCTAAGGACACCCTGATG
 ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA
 5 GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGT
 ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAG
 GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATCGAGAAAACCATCAGCAAGGC
 CAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA
 ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAG
 10 AGCAACGGCCAGCCCAGAGAACAACACTACAAGACCACCCCCCTGTGCTGGACAGCGATGGCAGCTT
 CTTCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTTCAGCTGCT
 CCGTGATGCACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAG

SEQ ID NO: 48

15 QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
 GRVTITADESTSTAYMELSSLRSEDYAVYYCARSIDDDYHADDYYAMDYWGQGTLVTVSSASTKG
 PSVFPLAPSSKSTSGGTAAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
 VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
 ISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
 20 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
 SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSVMSVHEALHNHYTQKSLSLSPGK

SEQ ID NO: 49

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTGAGCTG
 25 CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTCAGGCAGGCTCCTGGCCAGG
 GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCCAAGTTCCAG
 GGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACCGCCTACATGGAACTGAGCAGCCTGAG
 GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATCTACGACGACTACCACGCGGACGACT
 ACTACGCCATGGACTACTGGGGACAGGGCACACTAGTGACCGTGTCAGCGCCAGCACCAAGGGC
 30 CCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCGCGGCGGCACAGCCGCCCTGGGCTG
 CCTGGTGAAGGACTACTTCCCCGAACCGGTGACCGTGTCCTGGAACAGCGGAGCCCTGACCAGCG
 GCGTGACACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACC
 GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACAC
 CAAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCCCTGCCCTG
 35 CCCCCGAGCTGCTGGGAGGCCCCAGCGTGTTCTGTTCACCCCAAGCCTAAGGACACCCTGATG
 ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA
 GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGT
 ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAG
 GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATCGAGAAAACCATCAGCAAGGC
 40 CAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA
 ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAG
 AGCAACGGCCAGCCCAGAGAACAACACTACAAGACCACCCCCCTGTGCTGGACAGCGATGGCAGCTT
 CTTCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTTCAGCTGCT
 CCGTGATGCACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAG
 45

SEQ ID NO: 50

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
 GRVTITADESTSTAYMELSSLRSED TAVYYCARS IYDDYHIDDYAMDYWGQGLTVTVSSASTKG
 PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
 VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
 5 ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
 SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 51

10 CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTGAGCTG
 CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTCAGGCAGGCTCCTGGCCAGG
 GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCAAGTTCCAG
 GGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACCGCCTACATGGAAGTGAAGCAGCCTGAG
 GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATCTACGACGACTACCACATTGACGACT
 15 ACTACGCCATGGACTACTGGGGACAGGGCACACTAGTGACCGTGTCCAGCGCCAGCACCAAGGGC
 CCCAGCGTGTTCCTTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTG
 CCTGGTGAAGGACTACTTCCCCGAACCGGTGACCGTGTCTTGAACAGCGGAGCCCTGACCAGCG
 GCGTGCACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACC
 GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACAC
 20 CAAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCTGCCCTG
 CCCCCGAGCTGCTGGGAGGCCCCAGCGTGTTCCTGTTCCTTCAAGCCTAAGGACACCCTGATG
 ATCAGCAGAACCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA
 GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGT
 ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGTGACCCAGGATTGGCTGAACGGCAAG
 25 GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATCGAGAAAACCATCAGCAAGGC
 CAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA
 ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAG
 AGCAACGGCCAGCCCGAGAACAACACTACAAGACCACCCCCCTGTGCTGGACAGCGATGGCAGCTT
 CTTCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTTCAGCTGCT
 30 CCGTGATGCACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAG

SEQ ID NO: 52

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
 GRVTITADESTSTAYMELSSLRSED TAVYYCARS IYDDYHWDDYAMDYWGQGLTVTVSSASTKG
 35 PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
 VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
 ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
 SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK

40

SEQ ID NO: 53

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTGAGCTG
 CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTCAGGCAGGCTCCTGGCCAGG
 GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCAAGTTCCAG
 45 GGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACCGCCTACATGGAAGTGAAGCAGCCTGAG
 GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATCTACGACGACTACCACTGGGACGACT

ACTACGCCATGGACTACTGGGGACAGGGCACACTAGTGACCGTGTCCAGCGCCAGCACCAAGGGC
 CCCAGCGTGTTCCTCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTG
 CCTGGTGAAGGACTACTTCCCCGAACCGGTGACCGTGTCTTGGAACAGCGGAGCCCTGACCAGCG
 GCGTGCACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACC
 5 GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACAC
 CAAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCCCTGCCCTG
 CCCCCGAGCTGCTGGGAGGCCCCAGCGTGTTCCTGTTCCCCCCCCAAGCCTAAGGACACCCTGATG
 ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA
 GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGT
 10 ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAG
 GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATCGAGAAAACCATCAGCAAGGC
 CAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA
 ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAG
 AGCAACGGCCAGCCCCGAGAACAACACTACAAGACCACCCCCCCTGTGCTGGACAGCGATGGCAGCTT
 15 CTTCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTTCAGCTGCT
 CCGTGATGCACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAG

SEQ ID NO: 54

QVQLVQSGAEVKKPGSSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
 20 GRVTITADESTSTAYMELSSLRSEDVAVYYCARSYDDYHVDDYYAMDYWGQGLTVTVSSASTKG
 PSVFPLAPSSKSTSGGTAALGLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
 VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
 ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
 25 SNGQPENNYKTTTPVLDS DGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 55

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTGAGCTG
 CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTGAGGCAGGCTCCTGGCCAGG
 30 GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCAAGTTCCAG
 GGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACCGCCTACATGGAAGTGAAGCAGCCTGAG
 GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATCTACGACGACTACCACGTCGACGACT
 ACTACGCCATGGACTACTGGGGACAGGGCACACTAGTGACCGTGTCCAGCGCCAGCACCAAGGGC
 CCCAGCGTGTTCCTCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTG
 35 CCTGGTGAAGGACTACTTCCCCGAACCGGTGACCGTGTCTTGGAACAGCGGAGCCCTGACCAGCG
 GCGTGCACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACC
 GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACAC
 CAAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCCCTGCCCTG
 CCCCCGAGCTGCTGGGAGGCCCCAGCGTGTTCCTGTTCCCCCCCCAAGCCTAAGGACACCCTGATG
 40 ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA
 GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGT
 ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAG
 GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATCGAGAAAACCATCAGCAAGGC
 CAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA
 45 ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAG
 AGCAACGGCCAGCCCCGAGAACAACACTACAAGACCACCCCCCCTGTGCTGGACAGCGATGGCAGCTT

CTTCCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTTCAGCTGCT
CCGTGATGCACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAG

5 SEQ ID NO: 56

MGWSCIILFLVATATGVHS

SEQ ID NO: 57

GPVPPSTALRELIEELVNITQNQKAPLCNGSMVWSINLTAGMYCAALES LINVSGCSAIEKTQRM
10 LSGFCPHKVSAGQFSSLHVRDTKIEVAQFVKDLLLHLKKLFREGFEN

SEQ ID NO: 58

EIQLQQSVAELVRPGASVRLSCTASGFYIKDTYMHWVIQRPEQGLEWIGTIDPANGNTKYVPKFQ
15 GKATITADTSSNTAYLRLSSLTSEDTAIYYCARS IYDDYHYDDYYAMDYWGQGTSVTVSS

SEQ ID NO: 59

DVLMTQTPLSLPVSLGDQASISCRSSQNIVHINGNTYLEWYLQKPGQSPKLLIYKISDRFSGVPD
20 RFSGSGSGTDFTLKISRVEAEDLGVYYCFQGSHVPWTFGGGTKLEIK

SEQ ID NO: 60

FYIKDTYMH

SEQ ID NO: 61

25 GFYIKDTYMH

SEQ ID 62: A1Y100BAIa H-TVAAPS-210 (Protein sequence)

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
GRVTITADESTSTAYMELSSLRSED TAVYYCARS IYDDYHADDYYAMDYWGQGT LVTVSSASTKG
30 PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
ISRTPDEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK
35 TVAAPSEVQLLES GGGLVQPGGSLRLSCAASGFTFRNFGMGWVRQAPGKGLEWVSWIISSGTETY
YADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKSLGRFDYWGQGT LVTVSS

SEQ ID 63: A1Y100BAIa H-TVAAPS-210 (DNA sequence)

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTGAGCTG
40 CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTCAGGCAGGCTCCTGGCCAGG
GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCAAGTTCCAG
GGCAGGGTGACCATCACCGCCGATGAGAGCACCGAGCACCGCCTACATGGAAGTACGAGCAGCCTGAG
GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATCTACGACGACTACCACGCGGACGACT
ACTACGCCATGGACTACTGGGGACAGGGCACACTAGTGACCGTGTCTAGCGCCAGCACCAAGGGC
45 CCCAGCGTGTTCCCCTGGCCCCCAGCAGCAAGAGCACCGAGCGGCGGCACAGCCGCCCTGGGCTG

CCTGGTGAAGGACTACTTCCCCGAACCGGTGACCGTGTCCTGGAACAGCGGAGCCCTGACCAGCG
 GCGTGCACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACC
 GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACAC
 CAAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCCCTGCCCTG
 5 CCCCCGAGCTGCTGGGAGGCCCCAGCGTGTTCTCTGTTCCCCCCCCAAGCCTAAGGACACCCTGATG
 ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA
 GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGT
 ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAG
 GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATCGAGAAAACCATCAGCAAGGC
 10 CAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA
 ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAG
 AGCAACGGCCAGCCCCGAGAACAATAAGACCACCCCCCCTGTGCTGGACAGCGATGGCAGCTT
 CTTCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTTCAGCTGCT
 CCGTGATGCACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAG
 15 ACCGTGGCCGCCCCCTCGGAAGTGCAGCTCCTGGAGAGCGGCGGCGGCCTGGTGCAGCCCCGGCGG
 CAGCCTGAGGCTGAGCTGCGCCGCTAGCGGCTTCACCTTCAGGAACCTTCGGCATGGGCTGGGTCA
 GGCAGGCCCCCGGCAAGGGCCTGGAGTGGGTGAGCTGGATCATCAGCTCCGGCACCGAGACCTAC
 TACGCCGACAGCGTGAAGGGCAGGTTACCATCAGCCGCGACAACAGCAAGAACACCCTGTACCT
 GCAGATGAACAGCCTGAGGGCCGAGGACACCGCCGTCTACTACTGCGCCAAGAGCCTGGGCAGGT
 20 TCGACTACTGGGGACAGGGGACCCTGGTGACTGTGAGCAGC

SEQ ID 64: A1Y100B1le H-TVAAPS-210 (Protein sequence)

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHVVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
 GRVTITADESTSTAYMELSSLRSED TAVYYCARS IYDDYHIDDYAMDYWGQGTLVTVSSASTKG
 25 PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
 VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
 ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
 SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQSVMHEALHNHYTQKSLSLSPGK
 30 TVAAPSEVQLLES GGGLVQPGGSLRLSCAASGFTFRNFGMGWVRQAPGKGLEWVSWIISSGTETY
 YADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKSLGRFDYWGQGT LTVTVSS

SEQ ID 65: A1Y100B1le H-TVAAPS-210 (DNA sequence)

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTGAGCTG
 CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTCAGGCAGGCTCCTGGCCAGG
 GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCAAGTTCCAG
 GGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACCGCCTACATGGAACCTGAGCAGCCTGAG
 GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATCTACGACGACTACCACATTGACGACT
 40 ACTACGCCATGGACTACTGGGGACAGGGCACACTAGTGACCGTGTCTAGCGCCAGCACCAAGGGC
 CCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCGCGGCGGCACAGCCGCCCTGGGCTG
 CCTGGTGAAGGACTACTTCCCCGAACCGGTGACCGTGTCCTGGAACAGCGGAGCCCTGACCAGCG
 GCGTGCACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACC
 GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACAC
 45 CAAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCCCTGCCCTG
 CCCCCGAGCTGCTGGGAGGCCCCAGCGTGTTCTCTGTTCCCCCCCCAAGCCTAAGGACACCCTGATG

ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA
 GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGT
 ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAG
 GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATCGAGAAAACCATCAGCAAGGC
 5 CAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA
 ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAG
 AGCAACGGCCAGCCCCGAGAACAATAAAGACCACCCCCCTGTGCTGGACAGCGATGGCAGCTT
 CTTCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTTCAGCTGCT
 CCGTGATGCACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAG
 10 ACCGTGGCCGCCCCCTCGGAAGTGCAGCTCCTGGAGAGCGGCGGCGGCCTGGTGCAGCCCGGCGG
 CAGCCTGAGGCTGAGCTGCGCCGCTAGCGGCTTCACCTTCAGGAACCTTCGGCATGGGCTGGGTCA
 GGCAGGCCCCCGGCAAGGGCCTGGAGTGGGTGAGCTGGATCATCAGCTCCGGCACCGAGACCTAC
 TACGCCGACAGCGTGAAGGGCAGGTTCACCATCAGCCGCGACAACAGCAAGAACACCCTGTACCT
 GCAGATGAACAGCCTGAGGGCCGAGGACACCGCCGTCTACTACTGCGCCAAGAGCCTGGGCAGGT
 15 TCGACTACTGGGGACAGGGGACCCTGGTGACTGTGAGCAGC

SEQ ID 66: A1Y100BTrp H-TVAAPS-210 (Protein sequence)

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHVVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
 GRVTITADESTSTAYMELSSLRSED TAVYYCARS IYDDYHWDDYYAMDYWGQGT LVT VSSASTKG
 20 PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
 VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
 ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
 SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGK
 25 TVAAPSEVQLLES GGGGLVQPGGSLRLS CAASGFTFRNFGMGWVRQAPGKGLEWVSWI IISGTETY
 YADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKSLGRFDYWGQGT LVT VSS

SEQ ID 67: A1Y100BTrp H-TVAAPS-210 (DNA sequence)

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTGAGCTG
 30 CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTCAGGCAGGCTCCTGGCCAGG
 GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCAAGTTCCAG
 GGCAGGGTGACCATCACCGCCGATGAGAGCACCGACCGCCTACATGGAAGTGAAGCAGCCTGAG
 GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATCTACGACGACTACCACTGGGACGACT
 ACTACGCCATGGACTACTGGGGACAGGGCACACTAGTGACCGTGTCTAGCGCCAGCACCAAGGGC
 35 CCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCGCGGCGGCACAGCCGCCCTGGGCTG
 CCTGGTGAAGGACTACTTCCCCGAACCGGTGACCGTGTCTTGGAAACAGCGGAGCCCTGACCAGCG
 GCGTGCACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACC
 GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACAC
 CAAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCCCTGCCCTG
 40 CCCCCGAGCTGCTGGGAGGCCCCAGCGTGTTCTGTTCACCCCCCAAGCCTAAGGACACCCTGATG
 ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA
 GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGT
 ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAG
 GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATCGAGAAAACCATCAGCAAGGC
 45 CAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA
 ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAG

AGCAACGGCCAGCCCGAGAACAACACTACAAGACCACCCCCCTGTGCTGGACAGCGATGGCAGCTT
 CTTCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTTCAGCTGCT
 CCGTGATGCACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAG
 ACCGTGGCCGCCCCCTCGGAAGTGCAGCTCCTGGAGAGCGGCGGCGGCCTGGTGCAGCCCGGCGG
 5 CAGCCTGAGGCTGAGCTGCGCCGCTAGCGGCTTCACCTTCAGGAACCTTCGGCATGGGCTGGGTCA
 GGCAGGCCCCCGGCAAGGGCCTGGAGTGGGTCAGCTGGATCATCAGCTCCGGCACCGAGACCTAC
 TACGCCGACAGCGTGAAGGGCAGGTTACCATCAGCCGCGACAACAGCAAGAACACCCTGTACCT
 GCAGATGAACAGCCTGAGGGCCGAGGACACCGCCGTCTACTACTGCGCCAAGAGCCTGGGCAGGT
 TCGACTACTGGGGACAGGGGACCCTGGTGA CTGTGAGCAGC

10

SEQ ID 68: A1Y100BVal H-TVAAPS-210 (Protein sequence)

QVQLVQSGAEVKKPGSSVKVSCASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
 GRVTITADESTSTAYMELSSLRSEDTAVYYCARSIIYDDYHVDDYYAMDYWGQGLTVTVSSASTKG
 PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
 15 VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
 ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
 SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK
 TVAAPSEVQLLES GGGLVQPGGSLRLSCAASGFTFRNFGMGWVRQAPGKGLEWVSWIISSGTETY
 20 YADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKSLGRFDYWGQGLTVTVSS

SEQ ID 69: A1Y100BVal H-TVAAPS-210 (DNA sequence)

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTGAGCTG
 CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTCAGGCAGGCTCCTGGCCAGG
 25 GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCAAGTTCCAG
 GGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACCGCCTACATGGA ACTGAGCAGCCTGAG
 GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATCTACGACGACTACCACGTCGACGACT
 ACTACGCCATGGACTACTGGGGACAGGGCACACTAGTGACCGTGTCCAGCGCCAGCACCAAGGGC
 CCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAAGCGGCGGCACAGCCGCCCTGGGCTG
 30 CCTGGTGAAGGACTACTTCCCCGAACCGGTGACCGTGTCTTGGAAACAGCGGAGCCCTGACCAGCG
 GCGTGCACACCTTCCCCGCGGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACC
 GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACAC
 CAAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCCCTGCCCTG
 CCCCCGAGCTGCTGGGAGGCCCCAGCGTGTTCTTCCCCCCCCAAGCCTAAGGACACCCTGATG
 35 ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA
 GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGT
 ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAG
 GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATCGAGAAAACCATCAGCAAGGC
 CAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA
 40 ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAG
 AGCAACGGCCAGCCCCGAGAACAACACTACAAGACCACCCCCCTGTGCTGGACAGCGATGGCAGCTT
 CTTCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTTCAGCTGCT
 CCGTGATGCACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAG
 ACCGTGGCCGCCCCCTCGGAAGTGCAGCTCCTGGAGAGCGGCGGCGGCCTGGTGCAGCCCGGCGG
 45 CAGCCTGAGGCTGAGCTGCGCCGCTAGCGGCTTCACCTTCAGGAACCTTCGGCATGGGCTGGGTCA
 GGCAGGCCCCCGGCAAGGGCCTGGAGTGGGTCAGCTGGATCATCAGCTCCGGCACCGAGACCTAC

TACGCCGACAGCGTGAAGGGCAGGTTACCATCAGCCGCGACAACAGCAAGAACACCCTGTACCT
GCAGATGAACAGCCTGAGGGCCGAGGACACCGCCGTCTACTACTGCGCCAAGAGCCTGGGCAGGT
TCGACTACTGGGGACAGGGGACCCTGGTGACTGTGAGCAGC

5 SEQ ID 70: A1Y100BAIa H-ASTKGPS-210 (Protein sequence)

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHVVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
GRVTITADESTSTAYMELSSLRSED TAVYYCARS IYDDYHADDYYAMDYWGQGLTVTVSSASTKG
PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
10 ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK
ASTKGPSEVQLLES GGGGLVQPGGSLRLSCAASGFTFRNFGMGWVRQAPGKGLEWVSWI IISGTET
YYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKSLGRFDYWGQGLTVTVSS

15

SEQ ID 71: A1Y100BAIa H-ASTKGPS-210 (DNA sequence)

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTGAGCTG
CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTCAGGCAGGCTCCTGGCCAGG
GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCAAGTTCCAG
20 GGCAGGGTGACCATCACCGCCGATGAGAGCACCGACCGCCTACATGGAAGTGAAGCAGCCTGAG
GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATCTACGACGACTACCACGCGGACGACT
ACTACGCCATGGACTACTGGGGACAGGGCACACTAGTGACCGTGTCCAGCGCCAGCACCAAGGGC
CCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCGCGCGGCACAGCCGCCCTGGGCTG
CCTGGTGAAGGACTACTTCCCCGAACCGGTGACCGTGTCTTGAACAGCGGAGCCCTGACCAGCG
25 GCGTGCACACCTTCCCCGCGGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACC
GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACAC
CAAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCTGCCCTG
CCCCCGAGCTGCTGGGAGGCCCCAGCGTGTTCTTCTGTTCCCCCCCCAAGCCTAAGGACACCCTGATG
ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA
30 GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGT
ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGTGACCCAGGATTGGCTGAACGGCAAG
GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATCGAGAAAACCATCAGCAAGGC
CAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA
ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCCAGCGATATCGCCGTGGAGTGGGAG
35 AGCAACGGCCAGCCCGAGAACA ACTACAAGACCACCCCCCTGTGCTGGACAGCGATGGCAGCTT
CTTCCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTTCAGCTGCT
CCGTGATGCACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAG
GCCAGCACCAAGGGCCCCCTCGGAAGTGCAGCTCCTGGAGAGCGGCGGCGGCTGGTGCAGCCCGG
CGGCAGCCTGAGGCTGAGCTGCGCCGCTAGCGGCTTCACCTTCAGGAACCTTCGGCATGGGCTGGG
40 TCAGGCAGGCCCCCGGCAAGGGCCTGGAGTGGGTCAGCTGGATCATCAGCTCCGGCACCGAGACC
TACTACGCCGACAGCGTGAAGGGCAGGTTACCATCAGCCGCGACAACAGCAAGAACACCCTGTA
CCTGCAGATGAACAGCCTGAGGGCCGAGGACACCGCCGTCTACTACTGCGCCAAGAGCCTGGGCA
GGTTCGACTACTGGGGACAGGGGACCCTGGTGACTGTGAGCAGC

45 SEQ ID 72: A1Y100BIle H-ASTKGPS -210 (Protein sequence)

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
 GRVTITADESTSTAYMELSSLRSED TAVYYCARS IYDDYHIDDYAMDYWGQGTLVTVSSASTKG
 PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
 VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
 5 ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
 SNGQPENNYKTTTPVLDS DGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK
 ASTKGPSEVQLLES GGGGLVQPGGSLRLSCAASGFTFRNFGMGWVRQAPGKGLEWVSWI ISSGTET
 YYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKSLGRFDYWGQGTLVTVSS

10

SEQ ID 73: A1Y100BIle H- ASTKGPS -210 (DNA sequence)

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTGAGCTG
 CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTCAGGCAGGCTCCTGGCCAGG
 GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCAAGTTCCAG
 15 GGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACCGCCTACATGGAACTGAGCAGCCTGAG
 GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATCTACGACGACTACCACATTGACGACT
 ACTACGCCATGGACTACTGGGGACAGGGCACACTAGTGACCGTGTCCAGCGCCAGCACCAAGGGC
 CCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTG
 CCTGGTGAAGGACTACTTCCCCGAACCGGTGACCGTGTCTTGGAAACAGCGGAGCCCTGACCAGCG
 20 GCGTGCACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACC
 GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACTGAACCACAAGCCCAGCAACAC
 CAAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCCCTGCCCTG
 CCCCCGAGCTGCTGGGAGGCCCCAGCGTGTTCTTCTTCCCCCCCCAAGCCTAAGGACACCCTGATG
 ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA
 25 GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGT
 ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAG
 GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATCGAGAAAACCATCAGCAAGGC
 CAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA
 ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCCAGCGATATCGCCGTGGAGTGGGAG
 30 AGCAACGGCCAGCCCCGAGAACA ACTACAAGACCACCCCCCTGTGCTGGACAGCGATGGCAGCTT
 CTTCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTTACGCTGCT
 CCGTGATGCACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAG
 GCCAGCACCAAGGGCCCCCTCGGAAGTGCAGCTCCTGGAGAGCGGCGGCGGCTGGTGCAGCCCGG
 CGGCAGCCTGAGGCTGAGCTGCGCCGCTAGCGGCTTACCTTCAGGAACCTTCGGCATGGGCTGGG
 35 TCAGGCAGGCCCCCGGCAAGGGCCTGGAGTGGGTGAGCTGGATCATCAGCTCCGGCACCGAGACC
 TACTACGCCGACAGCGTGAAGGGCAGGTTTACCATCAGCCGCGACAACAGCAAGAACACCCTGTA
 CCTGCAGATGAACAGCCTGAGGGCCGAGGACACCGCCGTCTACTACTGCGCCAAGAGCCTGGGCA
 GGTTCGACTACTGGGGACAGGGGACCCTGGTGACTGTGAGCAGC

40

SEQ ID 74: A1Y100BTrp H- ASTKGPS -210 (Protein sequence)

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
 GRVTITADESTSTAYMELSSLRSED TAVYYCARS IYDDYHWDDYAMDYWGQGTLVTVSSASTKG
 PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
 VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
 45 ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE

SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
 ASTKGPSEVQLLESGGGLVQPGGSLRLSCAASGFTFRNFGMGWVRQAPGKGLEWVSWIISSGTET
 YYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKSLGRFDYWGQGLTVTVSS

5 SEQ ID 75: A1Y100BTrp H- ASTKGPS -210 (DNA sequence)

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTGAGCTG
 CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTCAGGCAGGCTCCTGGCCAGG
 GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCAAGTTCCAG
 10 GGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACC GCCTACATGGAACTGAGCAGCCTGAG
 GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATCTACGACGACTACCACTGGGACGACT
 ACTACGCCATGGACTACTGGGGACAGGGCACACTAGTGACCGTGTCCAGCGCCAGCACCAAGGGC
 CCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTG
 CCTGGTGAAGGACTACTTCCCCGAACCGGTGACCGTGTCTTGGAACAGCGGAGCCCTGACCAGCG
 15 GCGTGCACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACC
 GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACAC
 CAAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCCCTGCCCTG
 CCCCCGAGCTGCTGGGAGGCCCCAGCGTGTTCTGTTCCCCCCAAGCCTAAGGACACCCTGATG
 ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA
 20 GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGT
 ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAG
 GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATCGAGAAAACCATCAGCAAGGC
 CAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA
 ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCCAGCGATATCGCCGTGGAGTGGGAG
 25 AGCAACGGCCAGCCCCGAGAACA ACTACAAGACCACCCCCCTGTGCTGGACAGCGATGGCAGCTT
 CTTCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTTACGCTGCT
 CCGTGATGCACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAG
 GCCAGCACCAAGGGCCCCCTCGGAAGTGCAGCTCCTGGAGAGCGGCGGCGGCCTGGTGCAGCCCGG
 CGGCAGCCTGAGGCTGAGCTGCGCCGCTAGCGGCTTACCTTCAGGAACTTCGGCATGGGCTGGG
 30 TCAGGCAGGCCCCCGGCAAGGGCCTGGAGTGGGTCAGCTGGATCATCAGCTCCGGCACCGAGACC
 TACTACGCCGACAGCGTGAAGGGCAGGTTTACCATCAGCCGCGACAACAGCAAGAACACCCTGTA
 CCTGCAGATGAACAGCCTGAGGGCCGAGGACACCGCCGTCTACTACTGCGCCAAGAGCCTGGGCA
 GGTTCGACTACTGGGGACAGGGGACCCTGGTGACTGTGAGCAGC

35 SEQ ID 76: A1Y100BVal H- ASTKGPS -210 (Protein sequence)

QVQLVQSGAEVKKPGSSVKV SCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
 GRVTITADESTSTAYMELSSLRSED TAVYYCARS IYDDYHVDDYYAMDYWGQGLTVTVSSASTKG
 PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
 40 VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
 ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
 SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
 ASTKGPSEVQLLESGGGLVQPGGSLRLSCAASGFTFRNFGMGWVRQAPGKGLEWVSWIISSGTET
 45 YYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKSLGRFDYWGQGLTVTVSS

SEQ ID 77: A1Y100BVal H- ASTKGPS -210 (DNA sequence)

5 CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCCGGCAGCAGCGTGAAGGTGAGCTG
CAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTCAGGCAGGCTCCTGGCCAGG
GCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTACGTGCCCAAGTTCCAG
GGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACCGCCTACATGGAACTGAGCAGCCTGAG
GTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATCTACGACGACTACCACGTCGACGACT
10 ACTACGCCATGGACTACTGGGGACAGGGCACACTAGTGACCGTGTCCAGCGCCAGCACCAAGGGC
CCCAGCGTGTTCCTCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTG
CCTGGTGAAGGACTACTTCCCCGAACCGGTGACCGTGTCTTGGAACAGCGGAGCCCTGACCAGCG
GCGTGCACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACC
GTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACAC
15 CAAGGTGGACAAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCCCTGCCCTG
CCCCCGAGCTGCTGGGAGGCCCCAGCGTGTTCCTGTTCCCCCCCCAAGCCTAAGGACACCCTGATG
ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA
GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGT
ACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAG
GAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATCGAGAAAACCATCAGCAAGGC
20 CAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA
ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCCAGCGATATCGCCGTGGAGTGGGAG
AGCAACGGCCAGCCCAGAGAACAATAACAAGACACCCCCCTGTGCTGGACAGCGATGGCAGCTT
CTTCCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTTCAGCTGCT
CCGTGATGCACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAG
25 GCCAGCACCAAGGGCCCCCTCGGAAGTGCAGCTCCTGGAGAGCGGCGGCGGCCTGGTGCAGCCCGG
CGGCAGCCTGAGGCTGAGCTGCGCCGCTAGCGGCTTCACCTTCAGGAACTTCGGCATGGGCTGGG
TCAGGCAGGCCCCCGCAAGGGCCTGGAGTGGGTGAGCTGGATCATCAGCTCCGGCACCGAGACC
TACTACGCCGACAGCGTGAAGGGCAGGTTACCATCAGCCGCGACAACAGCAAGAACACCCTGTA
CCTGCAGATGAACAGCCTGAGGGCCGAGGACACCGCCGTCTACTACTGCGCCAAGAGCCTGGGCA
30 GGTTCGACTACTGGGGACAGGGGACCCTGGTGACTGTGAGCAGC

SEQ ID NO: 78 = DOM9-155- 25

DIQMTQSPSSLSASVGDRVITICRASRPISDWLHWYQQKPGKAPKLLIAWASTLD SGVPSRFS GS
35 GSGTDFTLTISSLQPEDFATYYCLQEGWGPPTFGQG TKVEIKR

SEQ ID NO: 79 = DOM9-155-147

DIQMTQSPSSLSASVGDRVITICRASRPISDWLHWYQQKPGKAPKLLIAWASSLYEGVPSRFS GS
40 GSGTDFTLTISSLQPEDFATYYCLQEGWGPPTFGQG TKVEIKR

SEQ ID NO: 80 = DOM9-155-154

DIQMTQSPSSLSASVGDRVITICRASRPISDWLHWYQQKPGKAPKLLIAWASSLQGGVPSRFS GS
45 GSGTDFTLTISSLQPEDFATYYCLQEGWGPPTFGQG TKVEIKR

SEQ ID NO: 81 = DOM9-112-210

EVQLLES G GGLVQ P G G S L R L S C A A S G F T F R N F G M G W V R Q A P G K G L E W V S W I I S S G T E T Y Y A D S V K
G R F T I S R D N S K N T L Y L Q M N S L R A E D T A V Y Y C A K S L G R F D Y W G Q G T L V T V S S

5 SEQ ID NO: 82 (G4S linker)

GGGGS

SEQ ID NO: 83 (linker)

TVAAPS

10

SEQ ID NO: 84 (linker)

ASTKGPT

SEQ ID NO: 85 (linker)

15

ASTKGPS

SEQ ID NO: 86 (linker)

GS

20

SEQ ID NO: 87 (linker)

TVAAPSGS

SEQ ID NO: 88 = 147-TVAAPS-586 Y100B V (Heavy chain)

25

DIQMTQSPSSLSASVGDRVITITCRASRPISDWLHWYQQKPGKAPKLLIAWASSLYEGVPSRFSGS
GSGTDFTLTISSSLQPEDFATYYCLQEGWGPPTFGQGTKVEIKRGSTVAAPSQVQLVQSGAEVKKP
GSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQGRVTITADESTSTA
YME LSSLRSED TAVYYCARS IYDDYHVDDYAMDYWGQGT LVT VSSASTKGPSVFPLAPSSKSTS
GGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICN
VNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDV
30 SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP
VLDS DGSFFLYSKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGK

SEQ ID NO: 89 = 147-ASTKG-586 Y100B V (Heavy chain)

35

40

DIQMTQSPSSLSASVGDRVITITCRASRPISDWLHWYQQKPGKAPKLLIAWASSLYEGVPSRFSGS
GSGTDFTLTISSSLQPEDFATYYCLQEGWGPPTFGQGTKVEIKRGSASTKGPSQVQLVQSGAEVKK
PGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQGRVTITADESTST
AYME LSSLRSED TAVYYCARS IYDDYHVDDYAMDYWGQGT LVT VSSASTKGPSVFPLAPSSKST
SGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC
NVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD
VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA
PIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTP
PVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGK

SEQ ID NO: 90 = 154-TVAAPS-586 Y100B V (Heavy chain)

DIQMTQSPSSLSASVGDRVTITCRASRPISDWLHWYQQKPGKAPKLLIAWASSLQGGVPSRFSGS
 GSGTDFTLTISSSLQPEDFATYYCLQEGWGPPTFGQGTKVEIKRGSTVAAPSQVQLVQSGAEVKKP
 GSSVKVSCKASGFYIKDTYMHWVRQAPGGGLEWMGTIDPANGNTKYVPKFQGRVTITADESTSTA
 5 YMELSSLRSEDTAVYYCARSIIYDDYHVDDYYAMDYWGQGTSLTVTVSSASTKGPSVFPLAPSSKSTS
 GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICN
 VNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDV
 SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
 IEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP
 10 VLDSGDGSFFLYSKLTVDKSRWQQGNVFSVCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 91 = 154-ASTKG-586 Y100B V (Heavy chain)

DIQMTQSPSSLSASVGDRVTITCRASRPISDWLHWYQQKPGKAPKLLIAWASSLQGGVPSRFSGS
 GSGTDFTLTISSSLQPEDFATYYCLQEGWGPPTFGQGTKVEIKRGSTVAAPSQVQLVQSGAEVKK
 PGSSVKVSCKASGFYIKDTYMHWVRQAPGGGLEWMGTIDPANGNTKYVPKFQGRVTITADESTST
 15 AYMELSSLRSEDTAVYYCARSIIYDDYHVDDYYAMDYWGQGTSLTVTVSSASTKGPSVFPLAPSSKST
 SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC
 NVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD
 VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA
 PIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTP
 20 PVLDSGDGSFFLYSKLTVDKSRWQQGNVFSVCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 92 (linker)

GSTVAAPS

SEQ ID NO: 93 (linker)

GSTVAAPSGS

25

SEQ ID NO: 94**DOM9-155-154 L89Q (aka DOM9-155-256)**

DIQMTQSPSSLSASVGDRVTITCRASRPISDWLHWYQQKPGKAPKLLIAWASSLQGGVPS
 RFSGSGSGTDFTLTISSSLQPEDFATYYCQQEGWGPPTFGQGTKVEIKR
 30

SEQ ID NO: 95**DOM9-155-154 L89Q (aka DOM9-155-256)**

GACATCCAGATGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACAGGGTGACC
 ATTACCTGCAGGGGCCAGCAGGCCCATCAGCGACTGGCTGCACTGGTACCAACAGAAGCCC
 35 GGCAAGGCTCCCAAGCTGCTGATCGCCTGGGCCAGCAGCCTGCAGGGAGGCGTGCCCAGC
 AGGTTTAGCGGCAGCGGCAGCGGCACCGACTTCACCCTCACCATCTCTTCCCTGCAGCCC
 GAGGACTTCGCCACCTACTACTGCCAGCAGGAGGGCTGGGGGGCCCCCTACTTTTCGGCCAG
 GGCACCAAGGTGGAGATCAAGAGG

40

SEQ ID NO: 96**829H-GS(TVAAPSGS)₂-154 L89Q**

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWRQAPGQGLEWMGTIDPANGNTKY
 VPKFQGRVTITADESTSTAYMELSSLRSEDVAVYYCARSIIYDDYHVDDYYAMDYWGQGT
 LTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA
 VLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP
 5 ELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR
 EEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL
 PPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV
 DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGSTVAAPSGSTVAAPSGSDIQMTQS
 PSSLSASVGDRVTITCRASRPISDWLHWYQQKPGKAPKLLIAWASSLQGGVPSRFSGSGS
 10 GTDFTLTISLQPEDFATYYCQQEGWGPPTFGQGTKVEIKR

SEQ ID NO: 97**829H-GS(TVAAPSGS)₂-154 L89Q**

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTG
 15 AGCTGCAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTCAGGCAGGCT
 CCTGGCCAGGGCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTAC
 GTGCCCAAGTTCCAGGGCAGGGTGACCATCACCGCCGATGAGAGCACCAGCACCGCCTAC
 ATGGAAGTGAAGCAGCCTGAGGTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATC
 TACGACGACTACCACGTCGACGACTACTACGCCATGGACTACTGGGGACAGGGCACACTA
 20 GTGACCGTGTCCAGCGCCAGCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGC
 AAGAGCACCCAGCGGCGGCACAGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAA
 CCGGTGACCGTGTCTGGAACAGCGGAGCCCTGACCAGCGGCGTGCACACCTTCCCCGCC
 GTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGAACCGTGCCAGCAGCAGC
 CTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACACCAAGGTGGAC
 25 AAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCTGCCCTGCCCC
 GAGCTGCTGGGAGGCCCCAGCGTGTTCCCTGTTCCCCCCCCAAGCCTAAGGACACCCTGATG
 ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAG
 GTGAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGG
 GAGGAGCAGTACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGAT
 30 TGGCTGAACGGCAAGGAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCTATC
 GAGAAAACCATCAGCAAGGCCAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCC
 CCTAGCAGAGATGAGCTGACCAAGAACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTC
 TACCCAGCGACATCGCCGTGGAGTGGGAGAGCAACGGCCAGCCCGAGAACAACACTACAAG
 ACCACCCCCCTGTGCTGGACAGCGATGGCAGCTTCTTCCCTGTACAGCAAGCTGACCGTG
 35 GACAAGAGCAGATGGCAGCAGGGCAACGTGTTCAGCTGCTCCGTGATGCACGAGGCCCTG
 CACAATCACTACACCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAGGGATCTACCGTGGCA
 GCACCATCCGGATCTACCGTAGCAGCACCATCCGGATCCGACATCCAGATGACCCAGAGC
 CCCAGCAGCCTGAGCGCCAGCGTGGGCGACAGGGTGACCATACCTGCAGGGCCAGCAGG
 CCCATCAGCGACTGGCTGCACTGGTACCAACAGAAGCCCGGCAAGGCTCCCAAGCTGCTG
 40 ATCGCCTGGGCCAGCAGCCTGCAGGGAGGCGTGCCAGCAGGTTTAGCGGCAGCGGCAGC
 GGCACCGACTTCACCCTCACCATCTCTTCCCTGCAGCCCGAGGACTTCGCCACCTACTAC

TGCCAGCAGGAGGGCTGGGGGCCCCCTACTTTCGGCCAGGGCACCAAGGTGGAGATCAAG
AGG

SEQ ID NO: 98**5 829H-GS(TVAAPSGS)₃-154 L89Q**

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKY
VPKFQGRVTITADESTSTAYMELSSLRSEDVAVYYCARSIIYDDYHVDDYYAMDYWGQGT
VTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA
VLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP
10 ELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR
EEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL
PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV
DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGSTVAAPSGSTVAAPSGSTVAAPSG
SDIQMTQSPSSLSASVGRVTITCRASRPISDWLHWYQQKPGKAPKLLIAWASSLQGGVP
15 SRFSGSGSGTDFTLTISSLQPEDFATYYCQQEGWGPPTFGQGTKVEIKR

SEQ ID NO: 99**829H-GS(TVAAPSGS)₃-154 L89Q**

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCCGGCAGCAGCGTGAAGGTG
20 AGCTGCAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTCAGGCAGGCT
CCTGGCCAGGGCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTAC
GTGCCCAAGTTCCAGGGCAGGGTGACCATCACCGCCGATGAGAGCACCAAGCAGCACC
ATGGAAGTGCAGCAGCCTGAGGTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATC
TACGACGACTACCACTCGACGACTACTACGCCATGGACTACTGGGGACAGGGCACACTA
25 GTGACCGTGTCCAGCGCCAGCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGC
AAGAGCACCAAGCGGCGGCACAGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAA
CCGGTGACCGTGTCTGGAACAGCGGAGCCCTGACCAGCGGCGTGACACCTTCCCCGCC
GTGCTGCAGAGCAGCGGCTGTACAGCCTGAGCAGCGTGGTGACCGTGCCCAGCAGCAGC
CTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACACCAAGGTGGAC
30 AAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCCCTGCCCTGCCCC
GAGCTGCTGGGAGGCCCCAGCGTGTTCCCTGTTCCCCCCCCAAGCCTAAGGACACCCTGATG
ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAG
GTGAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGG
GAGGAGCAGTACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGAT
35 TGGCTGAACGGCAAGGAGTACAAGTGTAAAGTGTCCAACAAGGCCCTGCCTGCCCCCTATC
GAGAAAACCATCAGCAAGGCCAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCC
CCTAGCAGAGATGAGCTGACCAAGAACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTC
TACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAACGGCCAGCCCCGAGAACAACACTACAAG
ACCACCCCCCTGTGCTGGACAGCGATGGCAGCTTCTTCCTGTACAGCAAGCTGACCGTG
40 GACAAGAGCAGATGGCAGCAGGGCAACGTGTTTCAGCTGCTCCGTGATGCACGAGGCCCTG
CACAATCACTACACCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAGGGATCTACCGTGGCA
GCACCATCAGGATCTACCGTGGCAGCACCATCAGGTTCAACAGTAGCTGCTCCTTCTGGA

TCCGACATCCAGATGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACAGGGTG
 ACCATTACCTGCAGGGCCAGCAGGCCCATCAGCGACTGGCTGCACTGGTACCAACAGAAG
 CCCGGCAAGGCTCCCAAGCTGCTGATCGCCTGGGCCAGCAGCCTGCAGGGAGGCGTGCCC
 AGCAGGTTTAGCGGCAGCGGCAGCGGCACCGACTTCACCCTCACCATCTCTTCCCTGCAG
 5 CCCGAGGACTTCGCCACCTACTACTGCCAGCAGGAGGGCTGGGGGCCCCCTACTTTCGGC
 CAGGGCACCAAGGTGGAGATCAAGAGG

SEQ ID NO: 100**10 829H-GS(TVAAPSGS)₄-154 L89Q**

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKY
 VPKFQGRVTITADESTSTAYMELSSLRSEDVAVYYCARSIIYDDYHVDDYYAMDYWGQGT
 VTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA
 VLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP
 15 ELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR
 EEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL
 PSRDELTKNQLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTV
 DKSRWQQGNVFSQSVMEALHNHYTQKSLSLSPGKGSTVAAPSGSTVAAPSGSTVAAPSG
 STVAAPSGSDIQMTQSPSSLSASVGDRVTITCRASRPISDWLHWYQQKPGKAPKLLIAWA
 20 SSLQGGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQEGWGPPTFGQGTKVEIKR

SEQ ID NO: 101**829H-GS(TVAAPSGS)₄-154 L89Q**

25 CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTG
 AGCTGCAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTCAGGCAGGCT
 CCTGGCCAGGGCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTAC
 GTGCCCAAGTTCCAGGGCAGGGTGACCATCACCGCCGATGAGAGCACCCAGCACCGCCTAC
 ATGGAACTGAGCAGCCTGAGGTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATC
 30 TACGACGACTACCACGTCGACGACTACTACGCCATGGACTACTGGGGACAGGGCACACTA
 GTGACCGTGTCCAGCGCCAGCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGC
 AAGAGCACCCAGCGGCGGCACAGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAA
 CCGGTGACCGTGTCTTGGAACAGCGGAGCCCTGACCAGCGGCGTGCACACCTTCCCCGCC
 GTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACCGTGCCCAGCAGCAGC
 35 CTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACACCAAGGTGGAC
 AAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCCCTGCCCTGCCCCC
 GAGCTGCTGGGAGGCCCCAGCGTGTTCTTGTTCCTGTTCCCCCCCCAAGCCTAAGGACACCCTGATG
 ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAG
 GTGAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGG
 40 GAGGAGCAGTACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGAT
 TGGCTGAACGGCAAGGAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCTATC
 GAGAAAACCATCAGCAAGGCCAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCC

CCTAGCAGAGATGAGCTGACCAAGAACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTC
 TACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAACGGCCAGCCCGAGAACAACACTACAAG
 ACCACCCCCCTGTGCTGGACAGCGATGGCAGCTTCTTCCTGTACAGCAAGCTGACCGTG
 GACAAGAGCAGATGGCAGCAGGGCAACGTGTTTCAGCTGCTCCGTGATGCACGAGGCCCTG
 5 CACAATCACTACACCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAGGGATCTACCGTGGCA
 GCACCATCAGGATCTACCGTGGCAGCACCATCAGGTTCAACAGTAGCTGCTCCTTCTGGT
 TCAACAGTAGCTGCTCCTTCTGGATCCGACATCCAGATGACCCAGAGCCCCAGCAGCCTG
 AGCGCCAGCGTGGGCGACAGGGTGACCATTACCTGCAGGGCCAGCAGGCCCCATCAGCGAC
 TGGCTGCACTGGTACCAACAGAAGCCCGGCAAGGCTCCCAAGCTGCTGATCGCCTGGGCC
 10 AGCAGCCTGCAGGGAGGCGTGCCCAGCAGGTTTAGCGGCAGCGGCAGCGGCACCGACTTC
 ACCCTCACCATCTCTTCCCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCAGCAGGAG
 GGCTGGGGGGCCCCCTACTTTCGGCCAGGGCACCAAGGTGGAGATCAAGAGG

SEQ ID NO: 102**15 829H-(TVAAPS)₂GS-154 L89Q**

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKY
 VPKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARSIIYDDYHVDDYYAMDYWGQGL
 VTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA
 VLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP
 20 ELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR
 EEQYNSTYRVVSVLTVHLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL
 PSRDELTKNQLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTV
 DKSRLVQGGNVFSCSVMHEALHNHYTQKSLSLSPGKTVAAPSTVAAPSGSDIQMTQSPSSL
 SASVGDRVTITCRASRPISDWLHWYQQKPGKAPKLLIAWASSLQGGVPSRFSGSGSGTDF
 25 TLTISSLQPEDFATYYCQQEGWGPPTFGQGTKVEIKR

SEQ ID NO: 103**829H-(TVAAPS)₂GS-154 L89Q**

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAAGGTG
 30 AGCTGCAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTCAGGCAGGCT
 CCTGGCCAGGGCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTAC
 GTGCCCAAGTTCCAGGGCAGGGTGACCATCACCGCCGATGAGAGCACCCAGCACCGCCTAC
 ATGGAACTGAGCAGCCTGAGGTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATC
 TACGACGACTACCACGTCGACGACTACTACGCCATGGACTACTGGGGACAGGGCACACTA
 35 GTGACCGTGTCCAGCGCCAGCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGC
 AAGAGCACCCAGCGGCGGCACAGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAA
 CCGGTGACCGTGTCTTGAACAGCGGAGCCCTGACCAGCGGCGTGCACACCTTCCCCGCC
 GTGCTGCAGAGCAGCGGCTGTACAGCCTGAGCAGCGTGGTGACCGTGCCCAGCAGCAGC
 CTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACACCAAGGTGGAC
 40 AAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCCCTGCCCTGCCCCC
 GAGCTGCTGGGAGGCCCCAGCGTGTTCTTCTGTTCCCCCCCCAAGCCTAAGGACACCCTGATG
 ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAG

GTGAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGG
 GAGGAGCAGTACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGAT
 TGGCTGAACGGCAAGGAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATC
 GAGAAAACCATCAGCAAGGCCAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCC
 5 CCTAGCAGAGATGAGCTGACCAAGAACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTC
 TACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAACGGGCCAGCCCCGAGAACAACACTACAAG
 ACCACCCCCCTGTGCTGGACAGCGATGGCAGCTTCTTCCTGTACAGCAAGCTGACCGTG
 GACAAGAGCAGATGGCAGCAGGGCAACGTGTTTCAGCTGCTCCGTGATGCACGAGGCCCTG
 CACAATCACTACACCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAGACCGTGGCAGCACCA
 10 TCCACCGTAGCAGCACCATCCGGATCCGACATCCAGATGACCCAGAGCCCCAGCAGCCTG
 AGCGCCAGCGTGGGCGACAGGGTGACCATTACCTGCAGGGGCCAGCAGGCCCATCAGCGAC
 TGGCTGCACTGGTACCAACAGAAGCCCGGCAAGGCTCCCAAGCTGCTGATCGCCTGGGCC
 AGCAGCCTGCAGGGAGGCGTGCCCAGCAGGTTTAGCGGCAGCGGCAGCGGCACCGACTTC
 ACCCTCACCATCTCTTCCCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCAGCAGGAG
 15 GGCTGGGGGGCCCCCTACTTTCGGCCAGGGCACCAAGGTGGAGATCAAGAGG

SEQ ID NO: 104**829H-(TVAAPS)₃GS-154 L89Q**

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKY
 20 VPKFQGRVTITADESTSTAYMELSSLRSEDVAVYYCARSIIYDDYHVDDYYAMDYWGQGTL
 VTVSSASTKGPSVFPLAPSSKSTSGGTAAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA
 VLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP
 ELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR
 EEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLF
 25 PSRDELTKNQLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTV
 DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKTVAAPSTVAAPSTVAAPSGSDIQMT
 QSPSSLSASVGDRVTITCRASRPISDWLHWYQQKPGKAPKLLIAWASSLQGGVPSRFSGS
 GSGTDFTLTISSLQPEDFATYYCQQEGWGPPTFGQGTKVEIKR

30 SEQ ID NO: 105**829H-(TVAAPS)₃GS-154 L89Q**

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTG
 AGCTGCAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTCAGGCAGGCT
 CCTGGCCAGGGCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTAC
 35 GTGCCCAAGTTCCAGGGCAGGGTGACCATCACCGCCGATGAGAGCACCAAGCAGCAGCCTAC
 ATGGAAGTGAAGCAGCCTGAGGTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATC
 TACGACGACTACCACGTCGACGACTACTACGCCATGGACTACTGGGGACAGGGCACACTA
 GTGACCGTGTCCAGCGCCAGCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGC
 AAGAGCACCAAGCGGCGGCACAGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAA
 40 CCGGTGACCGTGTCTGGAACAGCGGAGCCCTGACCAGCGGCGTGCACACCTTCCCCGCC
 GTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACCGTGCCCAGCAGCAGC
 CTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACACCAAGGTGGAC

AAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCTGCCCTGCCCCC
 GAGCTGCTGGGAGGCCCCAGCGTGTTCCCTGTTCCCCCCTAAGCCTAAGGACACCCTGATG
 ATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAG
 GTGAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGG
 5 GAGGAGCAGTACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGAT
 TGGCTGAACGGCAAGGAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATC
 GAGAAAACCATCAGCAAGGCCAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCTGCCC
 CCTAGCAGAGATGAGCTGACCAAGAACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTC
 TACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAACGGCCAGCCCCGAGAACAACACTACAAG
 10 ACCACCCCCCCTGTGCTGGACAGCGATGGCAGCTTCTTCCTGTACAGCAAGCTGACCGTG
 GACAAGAGCAGATGGCAGCAGGGCAACGTGTTACAGCTGCTCCGTGATGCACGAGGCCCTG
 CACAATCACTACACCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAGACCGTGGCAGCACCA
 TCAACCGTGGCAGCACCATCAACAGTAGCTGCTCCTTCTGGATCCGACATCCAGATGACC
 CAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACAGGGTGACCATTACCTGCAGGGCC
 15 AGCAGGCCCATCAGCGACTGGCTGCACTGGTACCAACAGAAGCCCGGCAAGGCTCCCAAG
 CTGCTGATCGCCTGGGCCAGCAGCCTGCAGGGAGGCGTGCCCAGCAGGTTTAGCGGCAGC
 GGCAGCGGCACCGACTTCACCCTCACCATCTCTTCCCTGCAGCCCGAGGACTTCGCCACC
 TACTACTGCCAGCAGGAGGGCTGGGGGCCCCCTACTTTTCGGCCAGGGCACCAAGGTGGAG
 ATCAAGAGG

20

SEQ ID NO: 106**829H-(TVAAPS)₄GS-154 L89Q**

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKY
 VPKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARSIIYDDYHVDDYYAMDYWGQGL
 25 VTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA
 VLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP
 ELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR
 EEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL
 PSRDELTKNQLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTV
 30 DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKTVAAPSTVAAPSTVAAPSTVAAPSG
 SDIQMTQSPSSLSASVGDRVTITCRASRPISDWLHWYQQKPGKAPKLLIAWASSLQGGVP
 SRFSGSGSGTDFTLTISLQPEDFATYYCQQEGWGPPTFGQGTKVEIKR

SEQ ID NO: 107**35 829H-(TVAAPS)₄GS-154 L89Q**

CAGGTGCAGCTCGTGCAGAGCGGCGCCGAAGTGAAAAAGCCCGGCAGCAGCGTGAAGGTG
 AGCTGCAAGGCCTCCGGCTTCTACATCAAGGACACCTACATGCACTGGGTCAGGCAGGCT
 CCTGGCCAGGGCCTGGAGTGGATGGGCACTATCGACCCCGCCAACGGCAACACCAAGTAC
 GTGCCCAAGTTCCAGGGCAGGGTGACCATCACCGCCGATGAGAGCACCAAGCAGCAGCCTAC
 40 ATGGAAGTGAAGCAGCCTGAGGTCTGAGGACACCGCCGTGTACTATTGCGCCAGGAGCATC
 TACGACGACTACCACGTCGACGACTACTACGCCATGGACTACTGGGGACAGGGCACACTA
 GTGACCGTGTCCAGCGCCAGCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGC

ATGGGCTGGTCCTGCATCATCCTGTTTCTGGTGGCCACCGCCACCGGCGTGACACAGCGACATCCA
GATGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACAGGGTGACTATCACCTGCAGGA
GCAGCCAGAACATCGTGCACATCAACGGCAACACCTACCTCGAGTGGTACCAGCAGAAACCCGGG
AAGGCCCCCAAGCTGCTGATCTACAAGATCAGCGACAGGTTTACGCGGCGTGCCCAGCAGGTTTAG
CGGCTCCGGCTCAGGCACCGATTTACCCCTGACCATTAGCAGCCTGCAGCCCGAGGACTTCGCCA
CCTACTACTGCTTCCAGGGCTCTCACGTCCCCTGGACCTTCGGCCAGGGCACCAAGCTGGAGATC
AAGCGTACGGTGGCCGCCCCCAGCGTGTTTCATCTTCCCCCCCAGCGATGAGCAGCTGAAGAGCGG
CACCGCCAGCGTGGTGTGTCTGCTGAACAACCTTCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGG
TGGACAATGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGCAGGACAGCAAGGACTCC
ACCTACAGCCTGAGCAGCACCCCTGACCCTGAGCAAGGCCGACTACGAGAAGCACAAAGGTGTACGC
CTGTGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGACCAAGAGCTTCAACCGGGGCGAGTGC

SEQ ID NO: 110

DVLMTQSPSSLSASVGDRVITITCRSSQNIVHINGNTYLEWYQQKPGKAPKLLIYKISDRFSGVPS
RFSGSGSGTDFTLTISLQPEDFATYYCFQGSHVPWTFGQGTKLEIKRTVAAPSVFIFPPSDEQL
5 KSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKADYEKHK
VYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 111

ATGGGCTGGTCCTGCATCATCCTGTTTCTGGTGGCCACCGCCACCGGCGTGACACAGCGACGTGCT
10 GATGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACAGGGTGACTATCACCTGCAGGA
GCAGCCAGAACATCGTGACATCAACGGCAACACCTACCTCGAGTGGTACCAGCAGAAACCCGGG
AAGGCCCCCAAGCTGCTGATCTACAAGATCAGCGACAGGTTTCAGCGGCGTGCCCAGCAGGTTTAG
CGGCTCCGGCTCAGGCACCGATTTACCCCTGACCATTAGCAGCCTGCAGCCCGAGGACTTCGCCA
CCTACTACTGCTTCCAGGGCTCTCACGTCCCCTGGACCTTCGGCCAGGGCACCAAGCTGGAGATC
15 AAGCGTACGGTGGCCGCCCCCAGCGTGTTTCATCTTCCCCCCCAGCGATGAGCAGCTGAAGAGCGG
CACCGCCAGCGTGGTGTGTCTGCTGAACAACCTTCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGG
TGGACAATGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGCAGGACAGCAAGGACTCC
ACCTACAGCCTGAGCAGCACCCCTGACCCTGAGCAAGGCCGACTACGAGAAGCACAAAGGTGTACGC
CTGTGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGACCAAGAGCTTCAACCGGGGCGAGTGC
20

SEQ ID NO: 112

EIVLTQSPGTLSLSPGERATLSCRSSQNIVHINGNTYLEWYQQKPGQAPRLLIYKISDRFSGIPD
RFSGSGSGTDFTLTISRLEPEDFAVYYCFQGSHVPWTFGQGTKLEIKRTVAAPSVFIFPPSDEQL
KSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKADYEKHK
25 VYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 113

ATGGGCTGGTCCTGCATCATCCTGTTTCTGGTGGCCACCGCCACCGGCGTGACACAGCGAGATCGT
30 GCTGACCCAGAGCCCTGGCACACTGAGCCTGAGCCCCGGAGAGAGGGCCACCCTGAGCTGCAGGT
CTAGCCAGAACATCGTGACATCAACGGCAACACCTACCTGGAGTGGTATCAGCAGAAGCCCGGC
CAGGCCCCCAGGCTGCTGATCTACAAGATCAGCGACAGGTTTCAGCGGCATCCCCGACAGGTTTAG
CGGCAGCGGCAGCGGCACCGACTTCACCCTGACCATTAGCAGGCTGGAGCCCGAGGACTTCGCCG
TGTACTACTGCTTCCAGGGGAGCCACGTGCCCTGGACCTTCGGCCAGGGCACCAAGCTCGAAATC
35 AAGCGTACGGTGGCCGCCCCCAGCGTGTTTCATCTTCCCCCCCAGCGATGAGCAGCTGAAGAGCGG
CACCGCCAGCGTGGTGTGTCTGCTGAACAACCTTCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGG
TGGACAATGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGCAGGACAGCAAGGACTCC
ACCTACAGCCTGAGCAGCACCCCTGACCCTGAGCAAGGCCGACTACGAGAAGCACAAAGGTGTACGC
CTGTGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGACCAAGAGCTTCAACCGGGGCGAGTGC
40

SEQ ID NO: 114

DVLMTQSPGTLSLSPGERATLSCRSSQNIVHINGNTYLEWYQQKPGQAPKLLIYKISDRFSGVPD
RFSGSGSGTDFTLTISRLEPEDFAVYYCFQGSHVPWTFGQGTKLEIKRTVAAPSVFIFPPSDEQL
KSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKADYEKHK
45 VYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 115

GACGTGCTGATGACCCAGAGCCCTGGCACACTGAGCCTGAGCCCCGGAGAGAGGGCCACCCTGAG
 CTGCAGGTCTAGCCAGAACATCGTGCACATCAACGGCAACACCTACCTGGAGTGGTATCAGCAGA
 5 AGCCCGGCCAGGCCCCCAAGCTGCTGATCTACAAGATCAGCGACAGGTTTCAGCGGCGTGCCCGAC
 AGGTTTAGCGGCAGCGGCAGCGGCACCGACTTCACCCTGACCATTAGCAGGCTGGAGCCCCGAGGA
 CTTCGCCGTGTACTACTGCTTCCAGGGGAGCCACGTGCCCTGGACCTTCGGCCAGGGCACCAGC
 TCGAAATCAAGCGTACGGTGGCCGCCCCCAGCGTGTTTCATCTTCCCCCCCAGCGATGAGCAGCTG
 AAGAGCGGCACCGCCAGCGTGGTGTGTCTGCTGAACAACCTTCTACCCCCGGGAGGCCAAGGTGCA
 10 GTGGAAGGTGGACAATGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGCAGGACAGCA
 AGGACTCCACCTACAGCCTGAGCAGCACCCCTGACCCTGAGCAAGGCCGACTACGAGAAGCACAAG
 GTGTACGCCTGTGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGACCAAGAGCTTCAACCGGGG
 CGAGTGC

15 SEQ ID NO:116 = 586H-TVAAPS-154 (H chain)

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
 GRVTITADESTSTAYMELSSLRSED TAVYYCARS IYDDYHYDDYYAMDYWGQGTLVTVSSASTKG
 PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
 VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
 20 ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
 SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK
TVAAPSGS DIQMTQSPSSLSASVGDRVTITCRASRPISDWLHWYQQKPGKAPKLLIAWASSLQGG
 VPSRFSGSGSGTDFTLTIS SLQPEDFATYYCLQEGWGPPTFGQGTKVEIKR

25

SEQ ID NO:117

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
 GRVTITADESTSTAYMELSSLRSED TAVYYCARS IYDDYHVDDYYAMDYWGQGTLVTVSSASTKG
 PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
 30 VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
 ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
 SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK
TVAAPSTVAAPSGSDI QMTQSPSSLSASVGDRVTITCRASRPISDWLHWYQQKPGKAPKLLIAWA
 35 SSLQGGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCSQEGWGPPTFGQGTKVEIKR

SEQ ID NO:118

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
 GRVTITADESTSTAYMELSSLRSED TAVYYCARS IYDDYHVDDYYAMDYWGQGTLVTVSSASTKG
 40 PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
 VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
 ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
 SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK
 45 **TVAAPSTVAAPSG**SDI QMTQSPSSLSASVGDRVTITCRASRPISDWLHWYQQKPGKAPKLLIAWA
 SSLQGGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCSQEGWGPPTFGQGTKVEIKR

SEQ ID NO:119

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
 GRVTITADESTSTAYMELSSLRSED TAVYYCARS IYDDYHVDDYYAMDYWGQGTLVTVSSASTKG
 5 PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
 VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
 ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
 SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK
 10 **TVAAPSTVAAPSG**SDIQMTQSPSSLSASVGDRVTITCRASRPISDWLHWYQQKPGKAPKLLIAWA
 SSLQGGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCHQEGWGPPTFGQGTKVEIKR

SEQ ID NO:120

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
 15 GRVTITADESTSTAYMELSSLRSED TAVYYCARS IYDDYHVDDYYAMDYWGQGTLVTVSSASTKG
 PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
 VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
 ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
 20 SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK
TVAAPSTVAAPSGSDIQMTQSPSSLSASVGDRVTITCRASRPISDWLHWYQQKPGKAPKLLIAWA
 SSLQGGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCMQEGWGPPTFGQGTKVEIKR

SEQ ID NO:121

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
 25 GRVTITADESTSTAYMELSSLRSED TAVYYCARS IYDDYHVDDYYAMDYWGQGTLVTVSSASTKG
 PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
 VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
 ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
 30 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
 SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK
TVAAPSTVAAPSGSDIQMTQSPSSLSASVGDRVTITCRASRPISDWLHWYQQKPGKAPKLLIAWA
 SSLQGGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCAQEGWGPPTFGQGTKVEIKR

SEQ ID NO:122

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
 35 GRVTITADESTSTAYMELSSLRSED TAVYYCARS IYDDYHVDDYYAMDYWGQGTLVTVSSASTKG
 PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
 VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
 40 ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
 SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK
TVAAPSTVAAPSGSDIQMTQSPSSLSASVGDRVTITCRASRPISDWLHWYQQKPGKAPKLLIAWA
 45 SSLQGGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCTQEGWGPPTFGQGTKVEIKR

SEQ ID NO:123

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
 GRVTITADESTSTAYMELSSLRSED TAVYYCARS IYDDYHVDDYYAMDYWGQGTLVTVSSASTKG
 PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
 VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
 5 ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
 SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK
TVAAPSTVAAPSGSDIQMTQSPSSLSASVGDRVTITCRASRPISDWLHWYQQKPGKAPKLLIAWA
 10 SSLQGGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCCQEGWGPPTFGQGTKVEIKR

SEQ ID NO:124

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
 GRVTITADESTSTAYMELSSLRSED TAVYYCARS IYDDYHVDDYYAMDYWGQGTLVTVSSASTKG
 PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
 15 VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
 ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
 SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK
TVAAPSTVAAPSGSDIQMTQSPSSLSASVGDRVTITCRASRPISDWLHWYQQKPGKAPKLLIAWA
 20 SSLQGGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCRQEGWGPPTFGQGTKVEIKR

SEQ ID NO:125

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
 GRVTITADESTSTAYMELSSLRSED TAVYYCARS IYDDYHVDDYYAMDYWGQGTLVTVSSASTKG
 25 PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
 VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
 ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
 SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK
 30 **TVAAPSTVAAPSG**SDIQMTQSPSSLSASVGDRVTITCRASRPISDWLHWYQQKPGKAPKLLIAWA
 SSLQGGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCWQEGWGPPTFGQGTKVEIKR

SEQ ID NO:126

QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
 35 GRVTITADESTSTAYMELSSLRSED TAVYYCARS IYDDYHVDDYYAMDYWGQGTLVTVSSASTKG
 PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
 VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
 ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
 40 SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK
TVAAPSTVAAPSGSDIQMTQSPSSLSASVGDRVTITCRASRPISDWLHWYQQKPGKAPKLLIAWA
 SSLQGGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCEQEGWGPPTFGQGTKVEIKR

SEQ ID NO:127

45 QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
 GRVTITADESTSTAYMELSSLRSED TAVYYCARS IYDDYHVDDYYAMDYWGQGTLVTVSSASTKG

PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
 VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
 ISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
 5 SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK
TVAAPSTVAAPSGSDIQMTQSPSSLSASVGDRVTITCRASRPISDWLHWYQQKPGKAPKLLIAWA
 SSLQGGVPSRFSGSGSGTDFTLTISLQPEDFATYYCKQEGWGPPTFGQGTKVEIKR

SEQ ID NO:128

10 QVQLVQSGAEVKKPGSSVKV SCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
 GRVTITADESTSTAYMELSSLRSED TAVYYCARS IYDDYHVDDYYAMDYWGQGT LVTVSSASTKG
 PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
 VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
 ISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
 15 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
 SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK
TVAAPSTVAAPSGSDIQMTQSPSSLSASVGDRVTITCRASRPISDWLHWYQQKPGKAPKLLIAWA
 SSLQGGVPSRFSGSGSGTDFTLTISLQPEDFATYYCDQEGWGPPTFGQGTKVEIKR

SEQ ID NO:129

20 QVQLVQSGAEVKKPGSSVKV SCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
 GRVTITADESTSTAYMELSSLRSED TAVYYCARS IYDDYHVDDYYAMDYWGQGT LVTVSSASTKG
 PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
 VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
 25 ISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
 SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK
TVAAPSTVAAPSGSDIQMTQSPSSLSASVGDRVTITCRASRPISDWLHWYQQKPGKAPKLLIAWA
 SSLQGGVPSRFSGSGSGTDFTLTISLQPEDFATYYCNQEGWGPPTFGQGTKVEIKR

30

SEQ ID NO:130

QVQLVQSGAEVKKPGSSVKV SCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
 GRVTITADESTSTAYMELSSLRSED TAVYYCARS IYDDYHVDDYYAMDYWGQGT LVTVSSASTKG
 PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
 35 VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
 ISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
 SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK
TVAAPSTVAAPSGSDIQMTQSPSSLSASVGDRVTITCRASRPISDWLHWYQQKPGKAPKLLIAWA
 40 SSLQGGVPSRFSGSGSGTDFTLTISLQPEDFATYYCYQEGWGPPTFGQGTKVEIKR

SEQ ID NO:131

QVQLVQSGAEVKKPGSSVKV SCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
 45 GRVTITADESTSTAYMELSSLRSED TAVYYCARS IYDDYHVDDYYAMDYWGQGT LVTVSSASTKG

PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
 VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
 ISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
 5 SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK
TVAAPSTVAAPSGSDIQMTQSPSSLSASVGDRVITICRASRPISDWLHWYQQKPGKAPKLLIAWA
 SSLQGGVPSRFSGSGSGTDFTLTISLQPEDFATYYCVQEGWGPPTFGQGTKVEIKR

SEQ ID NO:132

10 QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
 GRVTITADESTSTAYMELSSLRSEDVAVYYCARSYDDYHVDDYYAMDYWGQGLTVTVSSASTKG
 PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
 VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
 ISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
 15 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
 SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK
TVAAPSTVAAPSGSDIQMTQSPSSLSASVGDRVITICRASRPISDWLHWYQQKPGKAPKLLIAWA
 SSLQGGVPSRFSGSGSGTDFTLTISLQPEDFATYYCIQEGWGPPTFGQGTKVEIKR

SEQ ID NO:133

20 QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
 GRVTITADESTSTAYMELSSLRSEDVAVYYCARSYDDYHVDDYYAMDYWGQGLTVTVSSASTKG
 PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
 VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
 25 ISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
 SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK
TVAAPSTVAAPSGSDIQMTQSPSSLSASVGDRVITICRASRPISDWLHWYQQKPGKAPKLLIAWA
 SSLQGGVPSRFSGSGSGTDFTLTISLQPEDFATYYCFQEGWGPPTFGQGTKVEIKR

SEQ ID NO:134

30 QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
 GRVTITADESTSTAYMELSSLRSEDVAVYYCARSYDDYHVDDYYAMDYWGQGLTVTVSSASTKG
 PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
 35 VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
 ISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
 SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK
TVAAPSTVAAPSGSDIQMTQSPSSLSASVGDRVITICRASRPISDWLHWYQQKPGKAPKLLIAWA
 40 SSLQGGVPSRFSGSGSGTDFTLTISLQPEDFATYYCPQEGWGPPTFGQGTKVEIKR

SEQ ID NO:135

45 QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
 GRVTITADESTSTAYMELSSLRSEDVAVYYCARSYDDYHYDDYYAMDYWGQGLTVTVSSASTKG
 PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT

VPSSSLGTQTYICNVNHHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
 ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
 SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK
 5 **GSTVAAPSGS**DIQMTQSPSSLSASVGDRVTITCRASRPISDWLHWYQQKPGKAPKLLIAWASSLQ
 GGVPSRFSGSGSGTDFTLTISLQPEDFATYYCLQEGWGPPTFGQGTKVEIKR

SEQ ID NO:136

10 QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
 GRVTITADESTSTAYMELSSLRSED TAVYYCARS IYDDYHYDDYYAMDYWGQGT LVT VSSASTKG
 PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
 VPSSSLGTQTYICNVNHHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
 ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
 15 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
 SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK
GSTVAAPSGSTVAAPSGSDIQMTQSPSSLSASVGDRVTITCRASRPISDWLHWYQQKPGKAPKLL
 IAWASSLQGGVPSRFSGSGSGTDFTLTISLQPEDFATYYCLQEGWGPPTFGQGTKVEIKR

SEQ ID NO:137

20 QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
 GRVTITADESTSTAYMELSSLRSED TAVYYCARS IYDDYHYDDYYAMDYWGQGT LVT VSSASTKG
 PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
 VPSSSLGTQTYICNVNHHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
 25 ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
 SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK
GSTVAAPSGSTVAAPSGSTVAAPSGSDIQMTQSPSSLSASVGDRVTITCRASRPISDWLHWYQQK
 PGKAPKLLIAWASSLQGGVPSRFSGSGSGTDFTLTISLQPEDFATYYCLQEGWGPPTFGQGTKV
 30 EIKR

SEQ ID NO:138

35 QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQ
 GRVTITADESTSTAYMELSSLRSED TAVYYCARS IYDDYHYDDYYAMDYWGQGT LVT VSSASTKG
 PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
 VPSSSLGTQTYICNVNHHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
 ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE
 SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK
 40 **GSTVAAPSGSTVAAPSGSTVAAPSGSTVAAPSGS**DIQMTQSPSSLSASVGDRVTITCRASRPISD
 WLHWYQQKPGKAPKLLIAWASSLQGGVPSRFSGSGSGTDFTLTISLQPEDFATYYCLQEGWGP
 TFGQGTKVEIKR

SEQ ID NO:139

GSTVAAPSGS

SEQ ID NO:140

GSTVAAPSGSTVAAPSGS

5 SEQ ID NO:141

GSTVAAPSGSTVAAPSGSTVAAPSGS

SEQ ID NO:142

GSTVAAPSGSTVAAPSGSTVAAPSGSTVAAPSGS

10

SEQ ID NO:143

GSTVAAPSGSTVAAPSGSTVAAPSGSTVAAPSGSTVAAPSGS

SEQ ID NO:144

15 GSTVAAPSGSTVAAPSGSTVAAPSGSTVAAPSGSTVAAPSGSTVAAPSGS

SEQ ID NO:145

TVAAPSTVAAPSGS

20 SEQ ID NO:146

TVAAPSTVAAPSTVAAPSGS

SEQ ID NO:147

25 QVQLVQSGAEVKKPGSSVKVSCKASGFYIKDTYMHWVRQAPGQGLEWMGTIDPANGNTKYVPKFQGRVTITA
DESTSTAYMELSSLRSEDSAVYYCARSITYDDYHVDYAMDYLGQGLTVTVSSASTKGPSVFPLAPSSKSTS
GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSN
TKVDDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL
30 PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFS
CSVMHEALHNHYTQKSLSLSPGKTVAAPSTVAAPSGSDIQMTQSPSSLSASVGDRVTITCRASRPISDWLHW
YQQKPGKAPKLLIAWASSLQGGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCMQEGWGPPTFGQGTKVEIK
R

CLAIMS

1. An antigen binding protein which binds human IL-13 and which comprises the CDRH3
SIYDDYHYDDYYAMDY (SEQ ID NO: 3), wherein CDRH3 comprises one or more of the
5 following substitutions:
 - g) S95 in position 1 is substituted for tryptophan (W)
 - h) I96 in position 2 is substituted for valine (V)
 - i) Y97 in position 3 is substituted for phenylalanine (F)
 - j) D98 in position 4 is substituted for glutamine (E)
 - 10 k) H100A in position 7 is substituted for alanine (A), glutamic acid (E), glutamine (Q),
Arginine (R), Serine (S), threonine (T) or valine (V), and
 - l) Y100B in position 8 is substituted for alanine (A), isoleucine, (I), tryptophan (W) or
valine (V).
- 15 2. The antigen binding protein according to claim 1 wherein CDRH3 is substituted at
Y100B in position 8 to an amino acid selected from alanine (A), isoleucine, (I),
tryptophan (W) or valine (V).
- 20 3. The antigen binding protein according to claim 1 or 2 which binds human IL-13 and
which comprises a CDRH3 sequence selected from those set out in SEQ ID NO: 4, SEQ
ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8 and SEQ ID NO: 9, SEQ ID NO:
10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14 and SEQ ID NO:
15, SEQ ID NO: 16, SEQ ID NO: 17 and SEQ ID NO: 18.
- 25 4. The antigen binding protein according to any one of claims 1 to 3 wherein said antigen
binding protein further comprises the following CDR sequences:
CDRH1: SEQ ID NO: 1,
CDRH2: SEQ ID NO: 2;
CDRL1: SEQ ID NO: 19;
30 CDRL2: SEQ ID NO: 20; and
CDRL3: SEQ ID NO: 21.
- 35 5. The antigen binding protein according to any one of claims 1 to 3 wherein said antigen
binding protein comprises the following CDRs:
CDRH1: SEQ ID NO: 1,
CDRH2: SEQ ID NO: 2;
CDRH3: SEQ ID NO: 18
CDRL1: SEQ ID NO: 19;
CDRL2: SEQ ID NO: 20; and
40 CDRL3: SEQ ID NO: 21.
- 45 6. The antigen binding protein according to any one of claims 1 to 3 wherein said
antigen binding protein comprises the following CDRs:
CDRH1: SEQ ID NO: 1,
CDRH2: SEQ ID NO: 2;

CDRH3: SEQ ID NO: 17
 CDRL1: SEQ ID NO:19;
 CDRL2: SEQ ID NO:20; and
 CDRL3: SEQ ID NO:21.

5

7. The antigen binding protein according to any one of claims 1 to 3 wherein said antigen binding protein comprises the following CDRs:

CDRH1: SEQ ID NO:1,
 CDRH2: SEQ ID NO: 2;
 CDRH3: SEQ ID NO:16
 CDRL1: SEQ ID NO:19;
 CDRL2: SEQ ID NO:20; and
 CDRL3: SEQ ID NO:21.

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8. The antigen binding protein according to any one of claims 1 to 3 wherein said antigen binding protein comprises the following CDRs:

CDRH1: SEQ ID NO:1,
 CDRH2: SEQ ID NO: 2;
 CDRH3: SEQ ID NO:15
 CDRL1: SEQ ID NO:19;
 CDRL2: SEQ ID NO:20; and
 CDRL3: SEQ ID NO:21.

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9. The antigen binding protein according to any preceding claim wherein the antigen binding protein comprises an antibody.

10. The antibody according to claim 9 wherein the antibody is a humanised antibody.

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11. The antigen binding protein of claim 10 wherein the antibody is of IgG isotype.

35

12. The antigen binding protein according to any preceding claim comprising a heavy chain selected from SEQ ID NO: 26, SEQ ID NO: 28, SEQ ID NO: 30, SEQ ID NO: 32, SEQ ID NO: 34, SEQ ID NO: 36, SEQ ID NO: 38, SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 50, SEQ ID NO: 52 and SEQ ID NO: 54; and the light chain of SEQ ID NO: 24, 108, 110, 112 and 114.

40

13. The antigen binding protein according to claim 13 comprising a heavy chain selected from SEQ ID NO: 48, SEQ ID NO: 50, SEQ ID NO: 52 and SEQ ID NO: 54; and the light chain of SEQ ID NO:108 and 110.

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14. The antigen binding protein according to claim 13 comprising the heavy chain of SEQ ID NO: 54 and the light chain of SEQ ID NO:108.

15. The antigen binding protein according to claim 13 comprising the heavy chain of SEQ ID NO: 54 and the light chain of SEQ ID NO:110.

16. The antibody according to any one of claims 10 to 15 comprising a mutated Fc region such that said antibody has reduced ADCC and/or complement activation.

5 17. The antigen binding protein according to any preceding claim which is capable of binding to IL-13 and which is also capable of binding to at least one of IL-4 and IL-5.

18. The antigen binding protein according to claim 17 which comprises at least one dAb selected from SEQ ID NO: 78, 79, 80, 81 and 94.

10

19. The antigen binding protein according to claim 18 which comprises a heavy chain selected from any one of SEQ ID NO: 62, 64, 66, 68, 70, 72, 74, 76, 96, 98, 100, 102, 104, 106, and 117-138 and the light of SEQ ID NO: 24, 108, 110, 112 and 114.

15

20. The antigen binding protein according to claim 19 which comprises a heavy chain selected from any one of SEQ ID NO: 96, 98, 100, 102, 104, 106 and the light of SEQ ID NO: 24, 108 and 110.

20

21. The antigen binding protein according to claim 20 comprising the heavy chain of SEQ ID NO: 96 and the light chain of SEQ ID NO: 24, or the SEQ ID NO: 96 and the light chain of SEQ ID NO: 108, or the SEQ ID NO: 96 and the light chain of SEQ ID NO: 110, or the SEQ ID NO: 98 and the light chain of SEQ ID NO: 24, or the SEQ ID NO: 98 and the light chain of SEQ ID NO: 108, or the SEQ ID NO: 98 and the light chain of SEQ ID NO: 110, or the SEQ ID NO: 100 and the light chain of SEQ ID NO: 24, or the SEQ ID NO: 100 and the light chain of SEQ ID NO: 108, or the SEQ ID NO: 100 and the light chain of SEQ ID NO: 110.

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22. A recombinant transformed or transfected host cell comprising a first and second vector, said first vector comprising a polynucleotide encoding a heavy chain of an antibody according to any preceding claim and said second vector comprising a polynucleotide encoding a light chain of any preceding claim.

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23. A pharmaceutical composition comprising an antigen binding protein of any one of claims 1 to 21 and a pharmaceutically acceptable carrier.

40

24. A method of treating a human patient with allergic asthma, severe asthma, difficult asthma, brittle asthma, nocturnal asthma, premenstrual asthma, steroid resistant asthma, steroid dependent asthma, aspirin induced asthma, adult-onset asthma, paediatric asthma, atopic dermatitis, allergic rhinitis, Crohn's disease, COPD, fibrotic diseases or disorders such as idiopathic pulmonary fibrosis, progressive systemic sclerosis, hepatic fibrosis, hepatic granulomas, schistosomiasis, leishmaniasis, diseases of cell cycle regulation such as Hodgkins disease, B cell chronic lymphocytic leukaemia which method comprises the step of administering a therapeutically effective amount of an antigen binding protein of 1 to 21.

45

25. Use of an antigen binding protein according to any one of claims 1 to 21 in the preparation of a medicament for treatment or prophylaxis of Allergic asthma, severe asthma, difficult asthma, brittle asthma, nocturnal asthma, premenstrual asthma, steroid resistant asthma, steroid dependent asthma, aspirin induced asthma, adult-onset
- 5 asthma, paediatric asthma, atopic dermatitis, allergic rhinitis, Crohn's disease, COPD, fibrotic diseases or disorders such as idiopathic pulmonary fibrosis, progressive systemic sclerosis, hepatic fibrosis, hepatic granulomas, schistosomiasis, leishmaniasis, diseases of cell cycle regulation such as Hodgkins disease, B cell chronic lymphocytic leukaemia.
- 10 26. The antigen binding protein according to any one of claims 1 to 21 for use in the treatment or prophylaxis of Allergic asthma, severe asthma, difficult asthma, brittle asthma, nocturnal asthma, premenstrual asthma, steroid resistant asthma, steroid dependent asthma, aspirin induced asthma, adult-onset asthma, paediatric asthma, atopic dermatitis, allergic rhinitis, Crohn's disease, COPD, fibrotic diseases or disorders
- 15 such as idiopathic pulmonary fibrosis, progressive systemic sclerosis, hepatic fibrosis, hepatic granulomas, schistosomiasis, leishmaniasis, diseases of cell cycle regulation such as Hodgkins disease, B cell chronic lymphocytic leukaemia.
- 20 27. A method for reducing the aggregation of an immunoglobulin single variable domain comprising the steps of
- a) measuring the aggregation levels of an immunoglobulin single variable domain
- b) mutating kabat position 89 to a residue selected from 'Q' (glutamine), 'G' (glycine), 'S' (serine), 'M' (methionine), 'A' (alanine), 'T' (threonine) and 'E' (glutamic acid),
- c) measuring the aggregation levels of a the mutated immunoglobulin single variable
- 25 domain;
- wherein the binding activity is retained and aggregation levels of the mutated immunoglobulin single variable domain are lower than the aggregation levels of the un-mutated immunoglobulin single variable domain.
- 30 28. The method according to claim 27 wherein the kabat residue 89 is mutated to a residue selected from 'Q' (glutamine), 'G' (glycine), 'S' (serine), 'M' (methionine) and 'E' (glutamic acid).
- 35 29. The method according to claim 28 wherein the kabat residue 89 is mutated to 'Q' (glutamine).
- 40 30. A human VK dAb derived from a germline framework selected from IGKV1-17, IGKV1D-17, IGKV1/OR2-108, IGKV1-6, IGKV5-2, IGKV1D-42, IGKV2-24, IGKV2-28, IGKV2-30, IGKV2-40, IGKV2D-29, IGKV2D-30, IGKV2D-24 and IGKV6-21 wherein residue 89 (kabat numbering) of the human VK dAb is Glutamine.
31. An Immunoglobulin single variable domain comprising the sequence of SEQ ID NO:94.

1 / 9

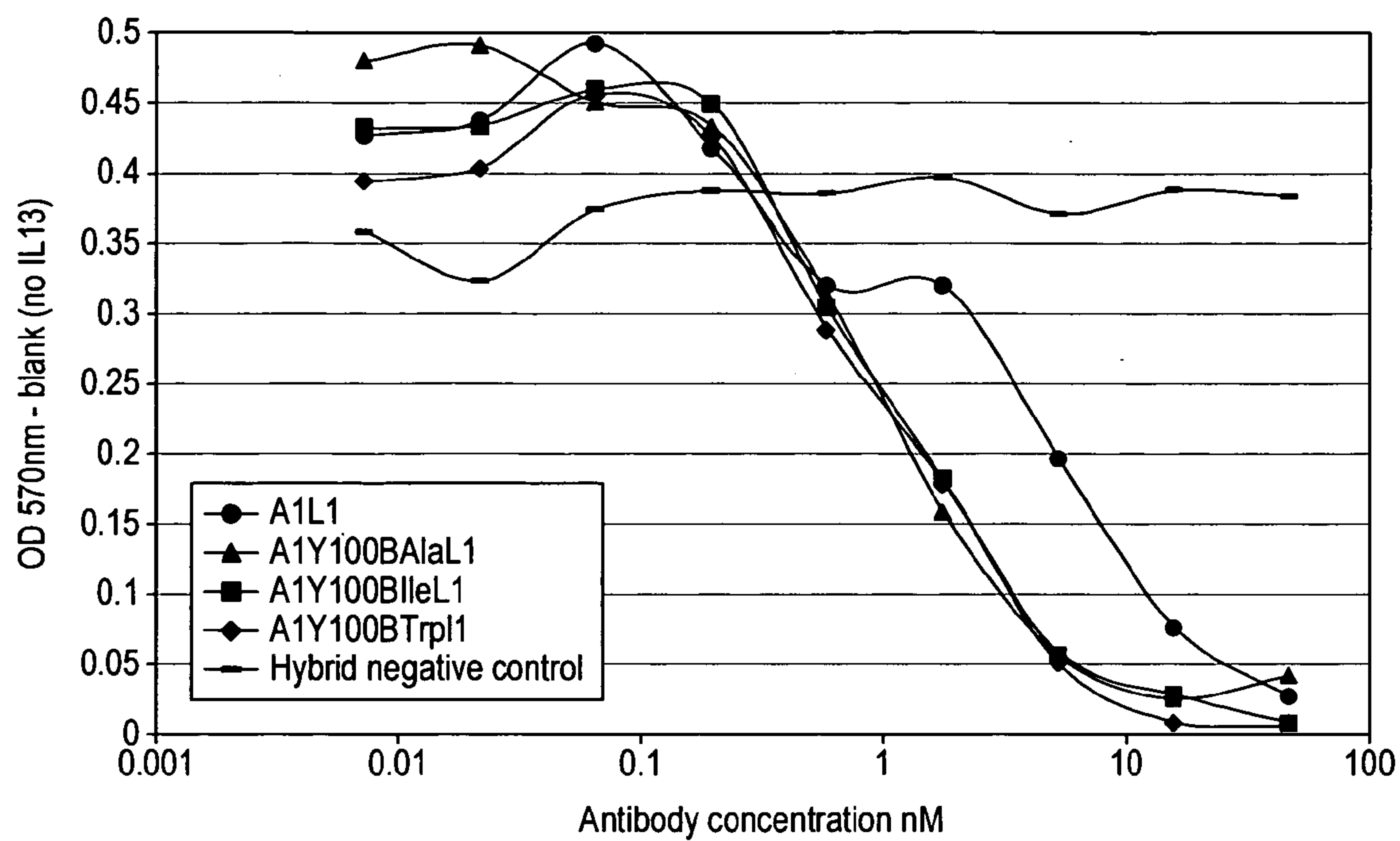


FIG. 1

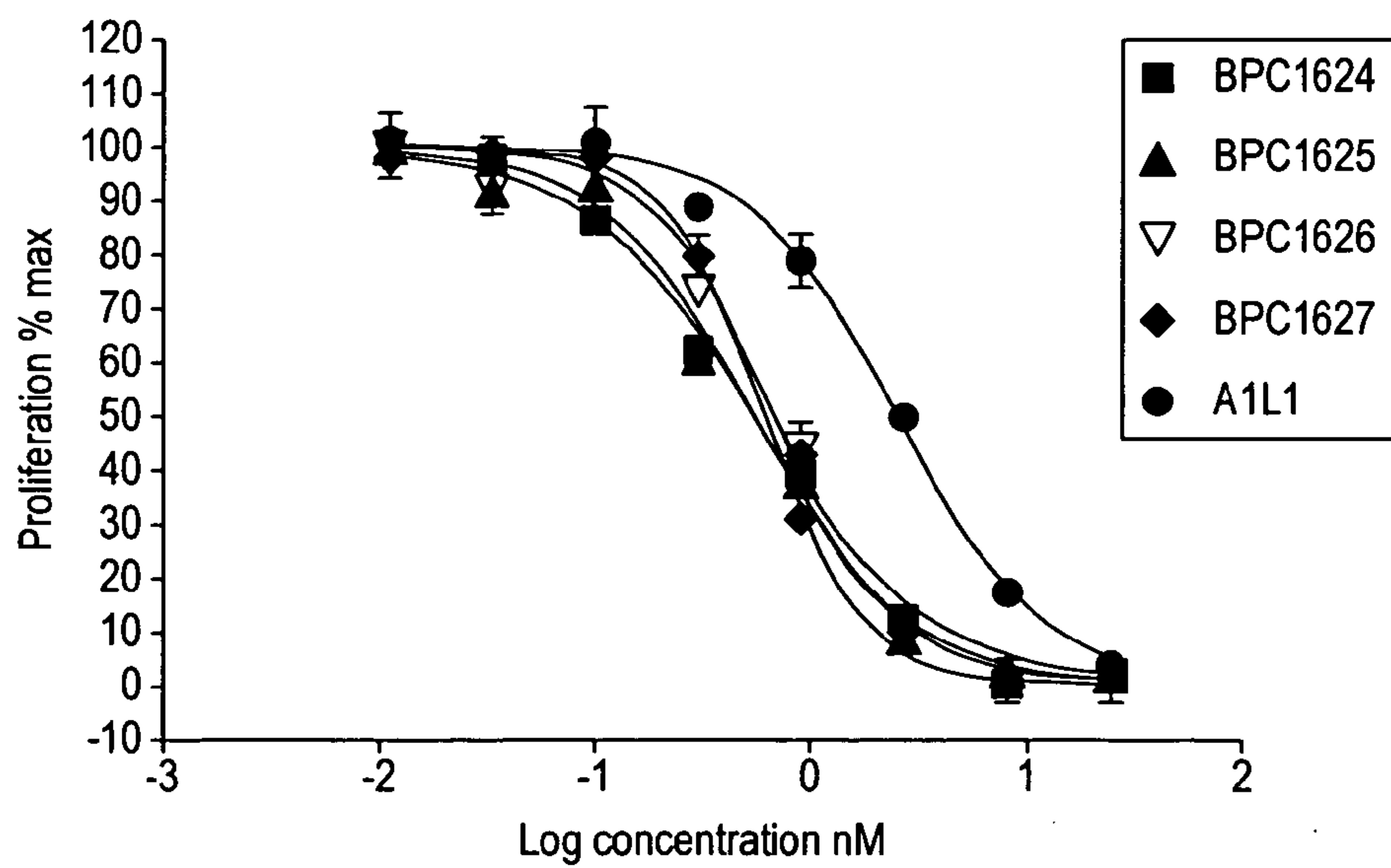


FIG. 2

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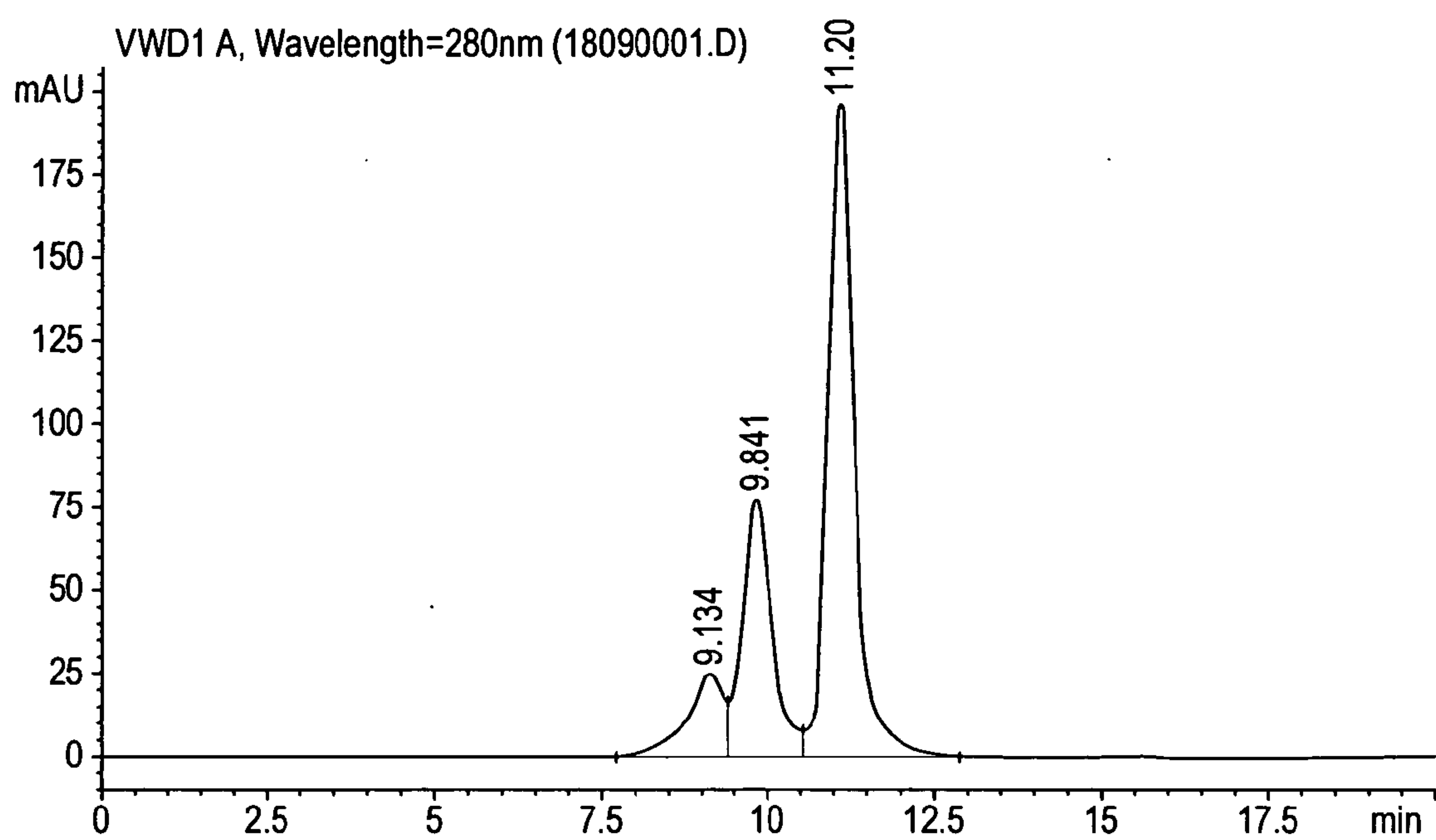


FIG. 3

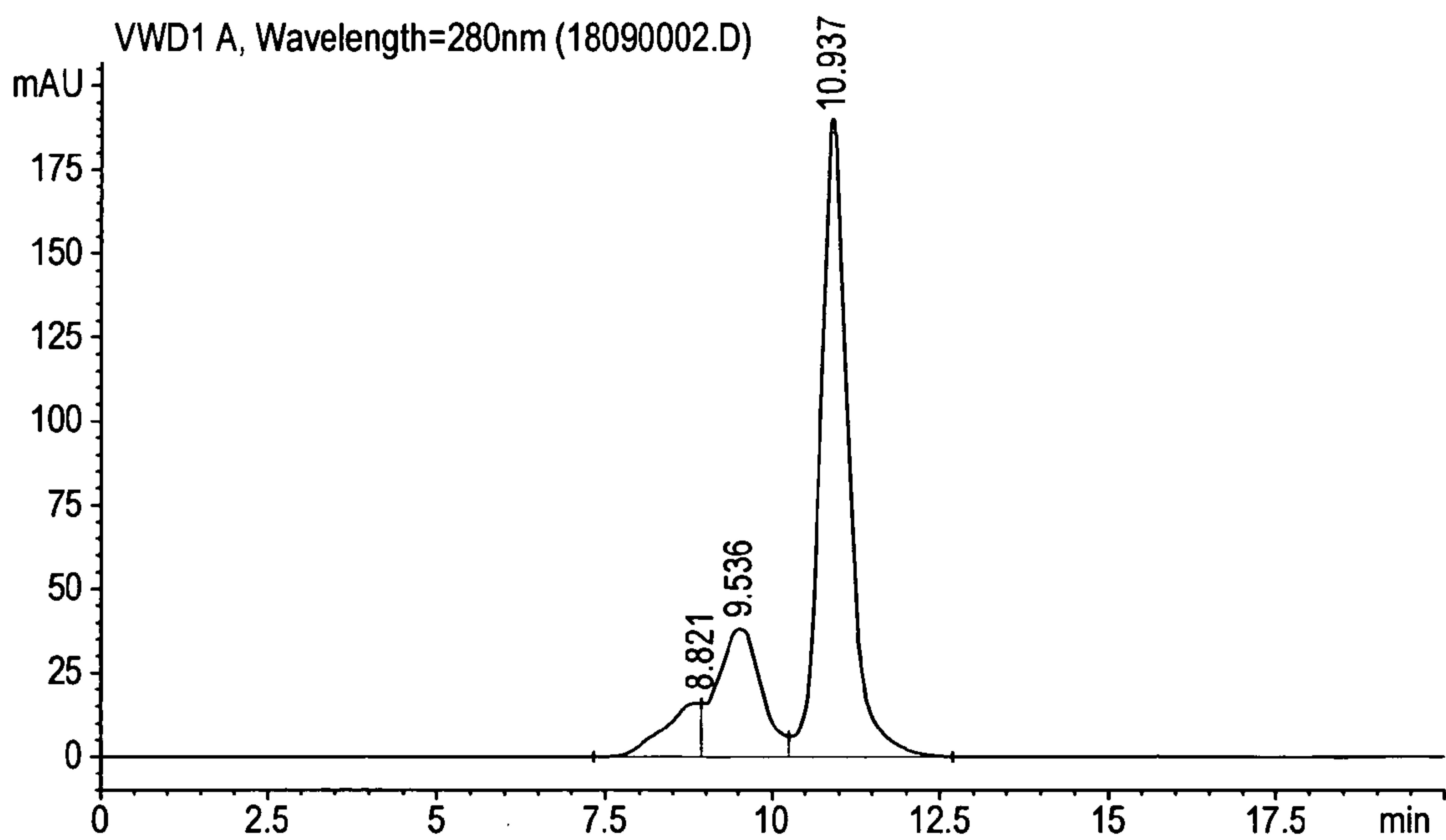


FIG. 4

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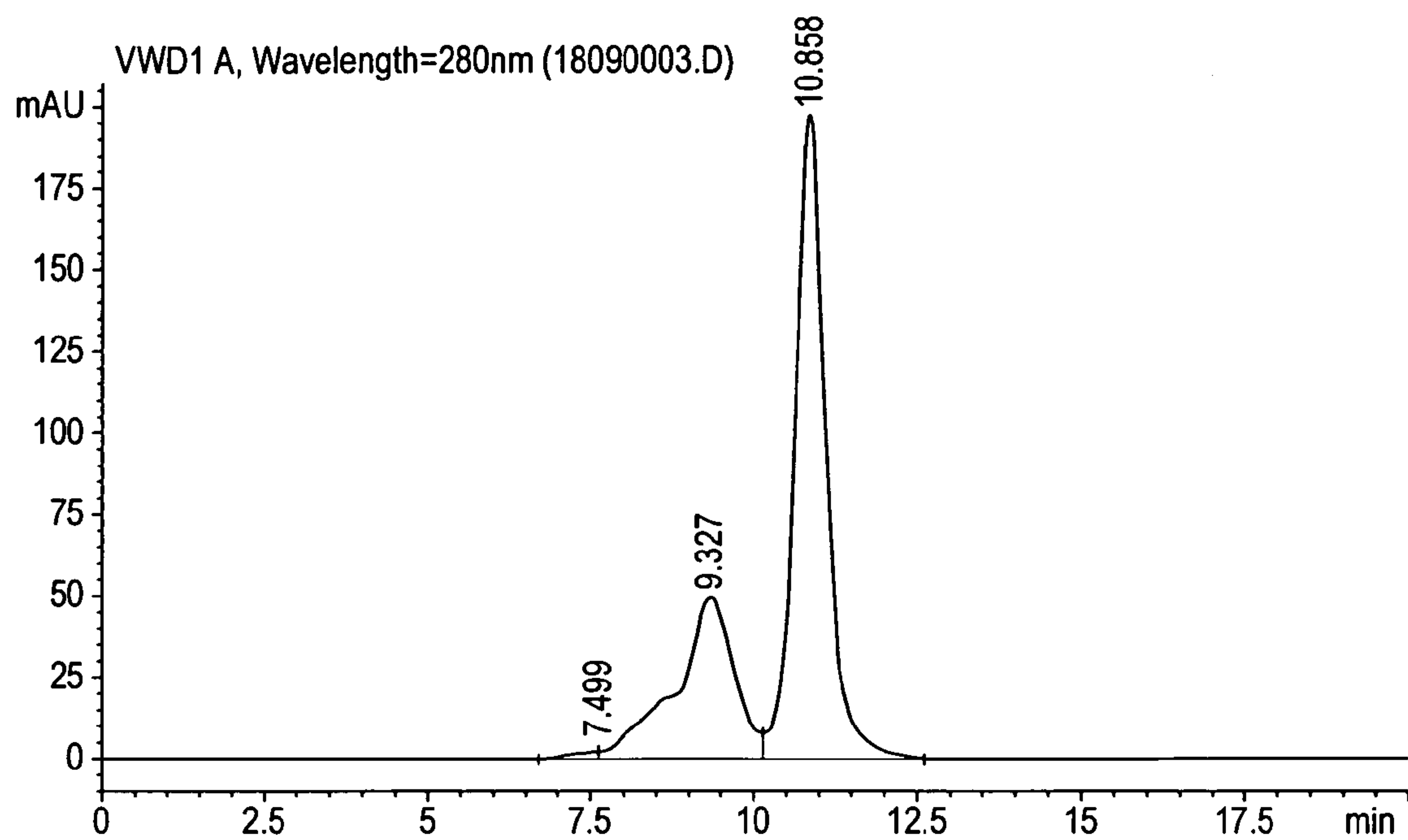


FIG. 5

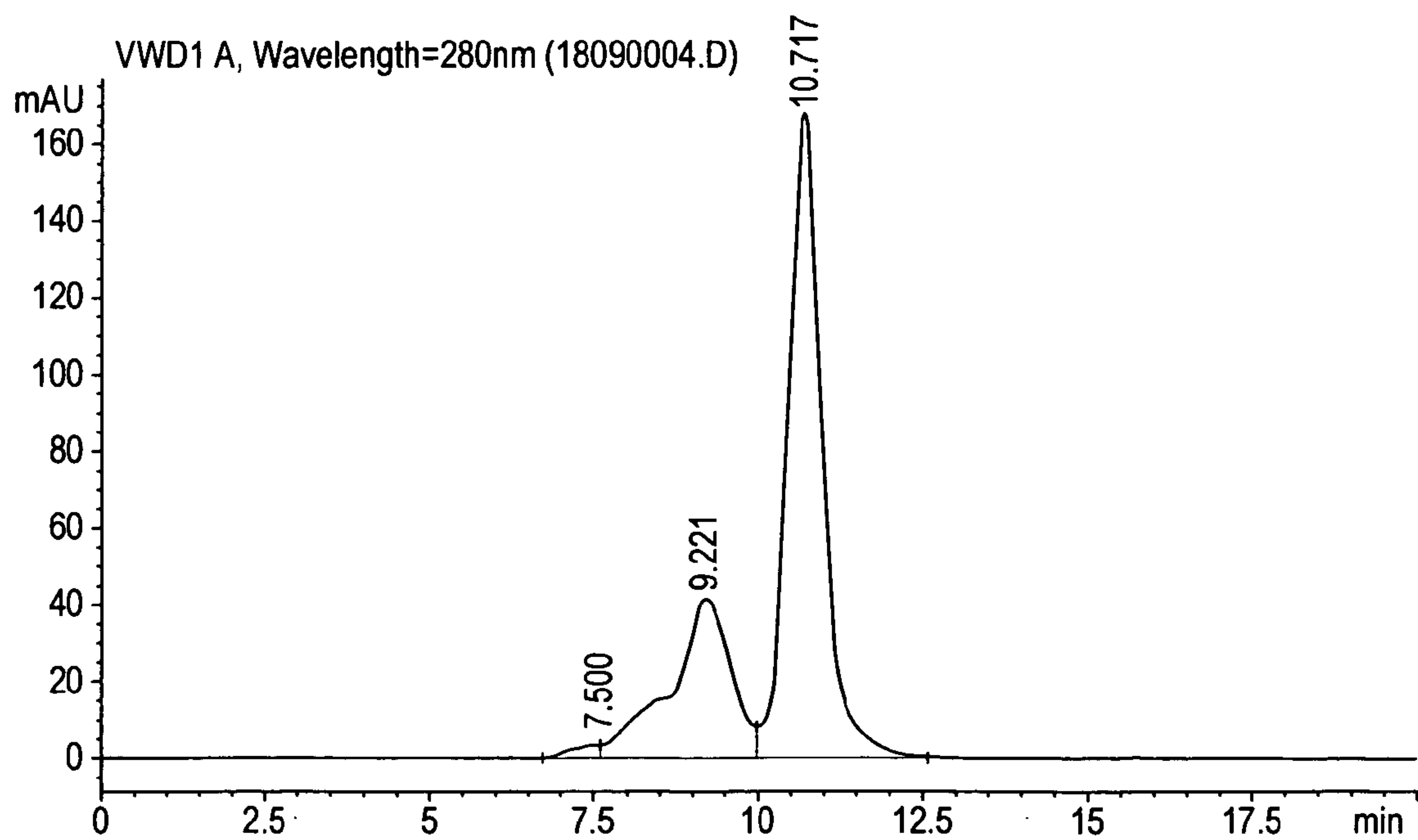


FIG. 6

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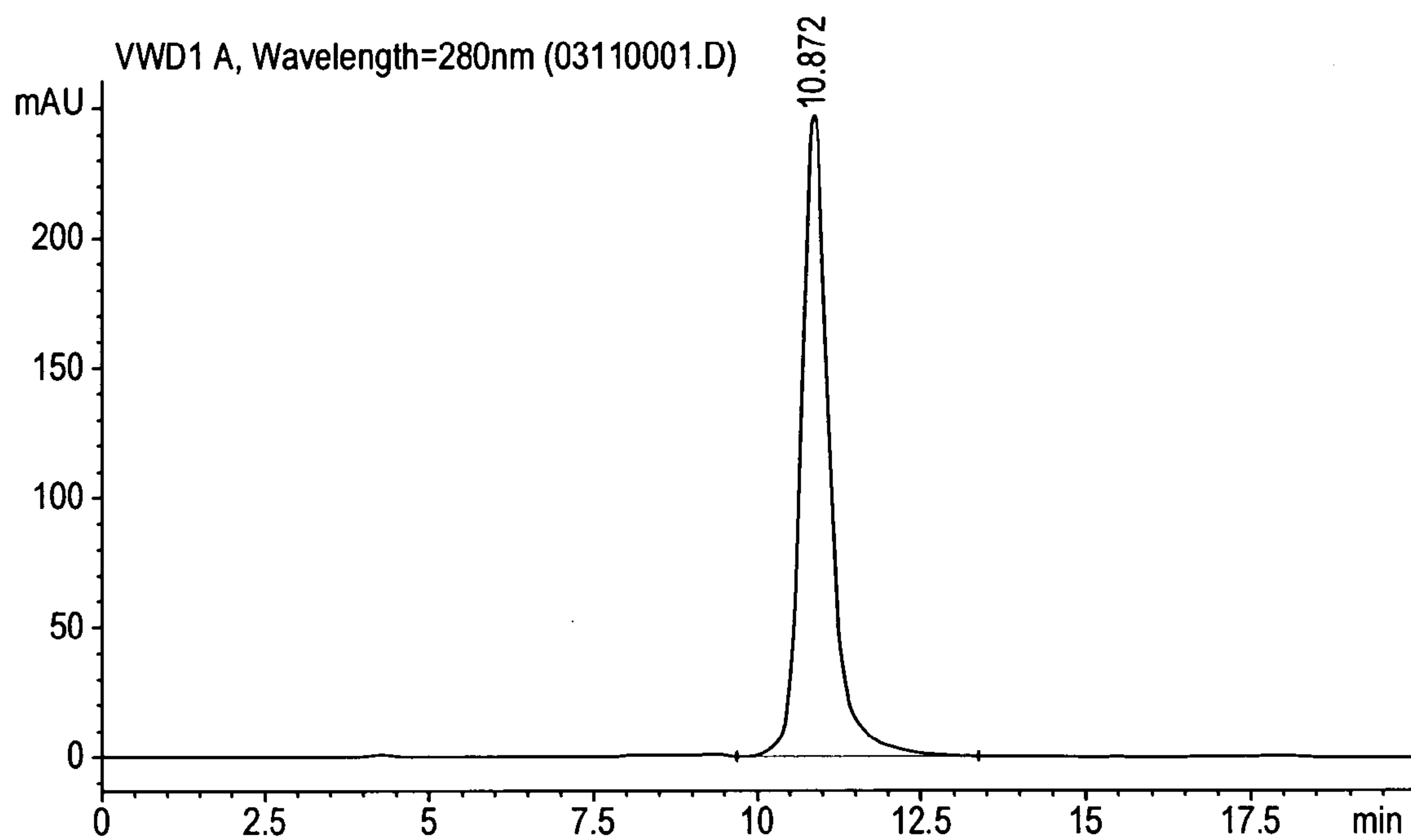


FIG. 7

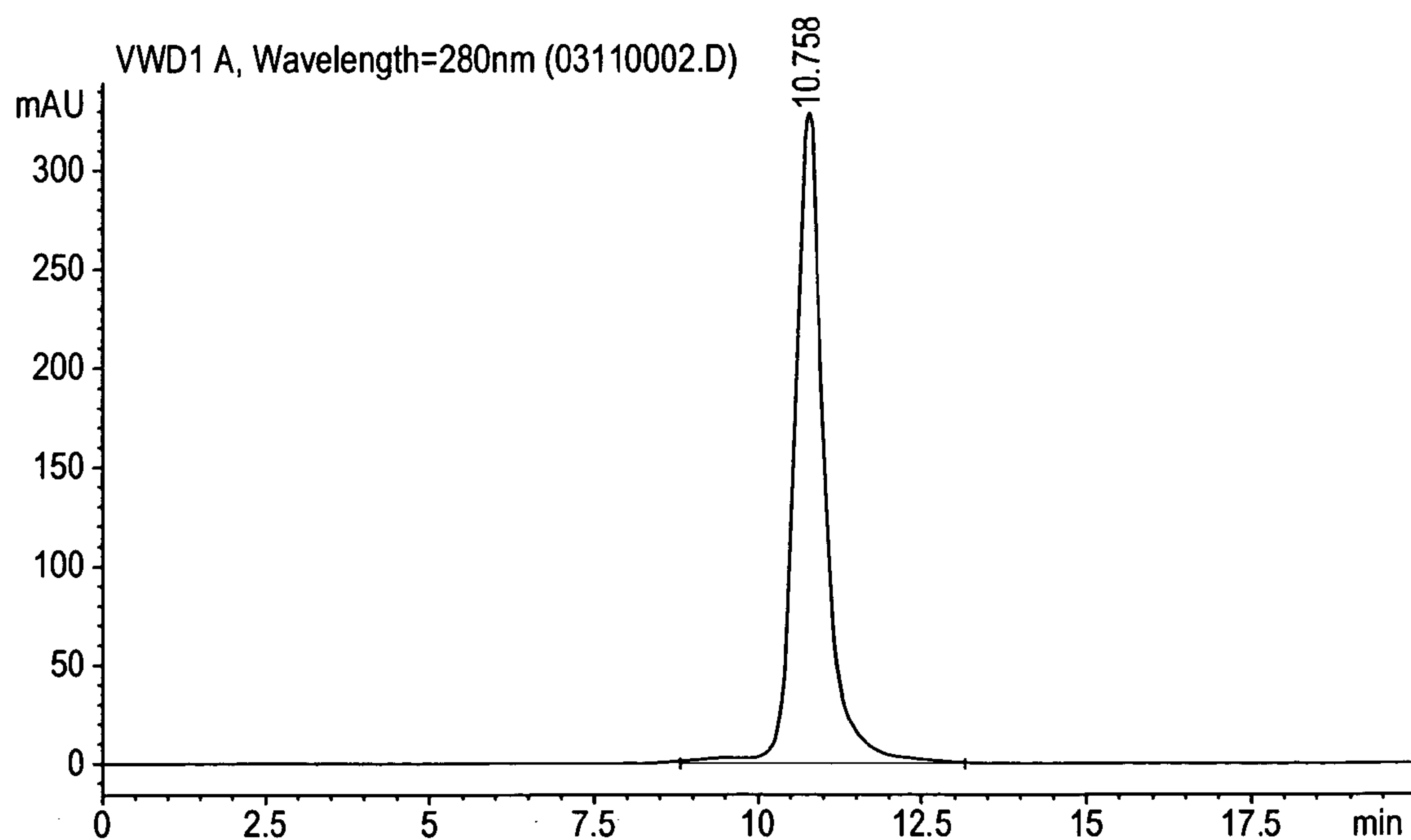


FIG. 8

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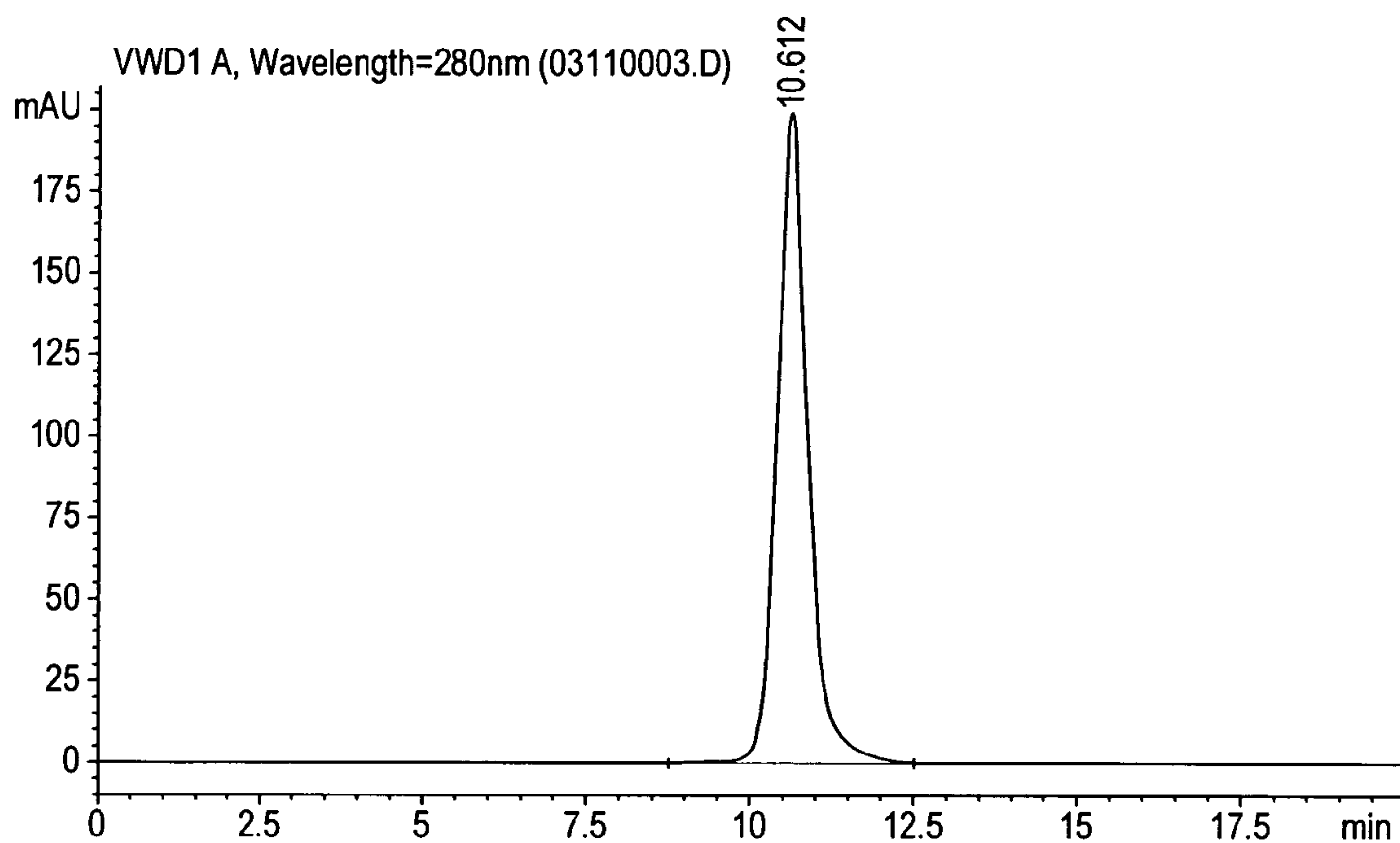


FIG. 9

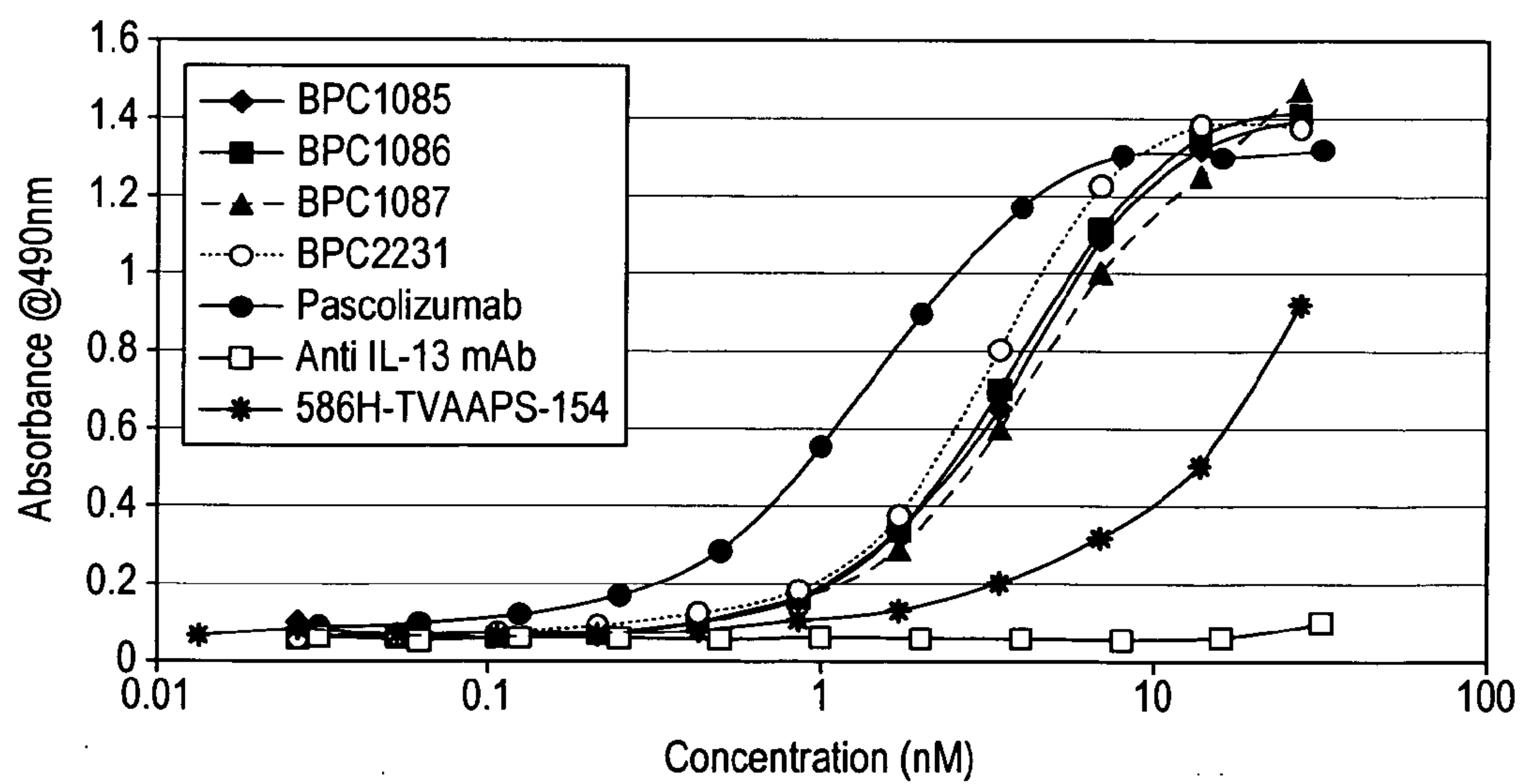


FIG. 10

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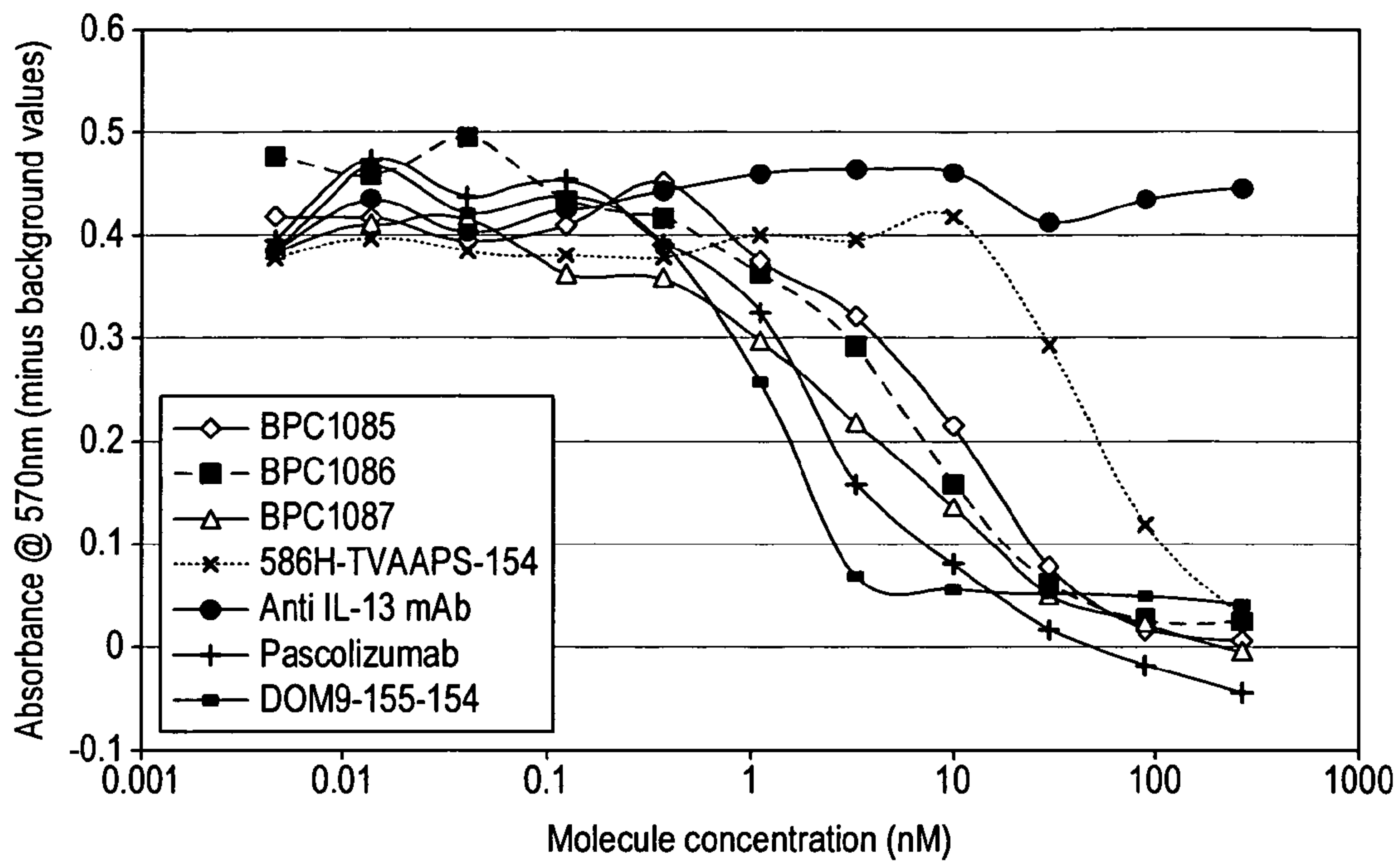


FIG. 11

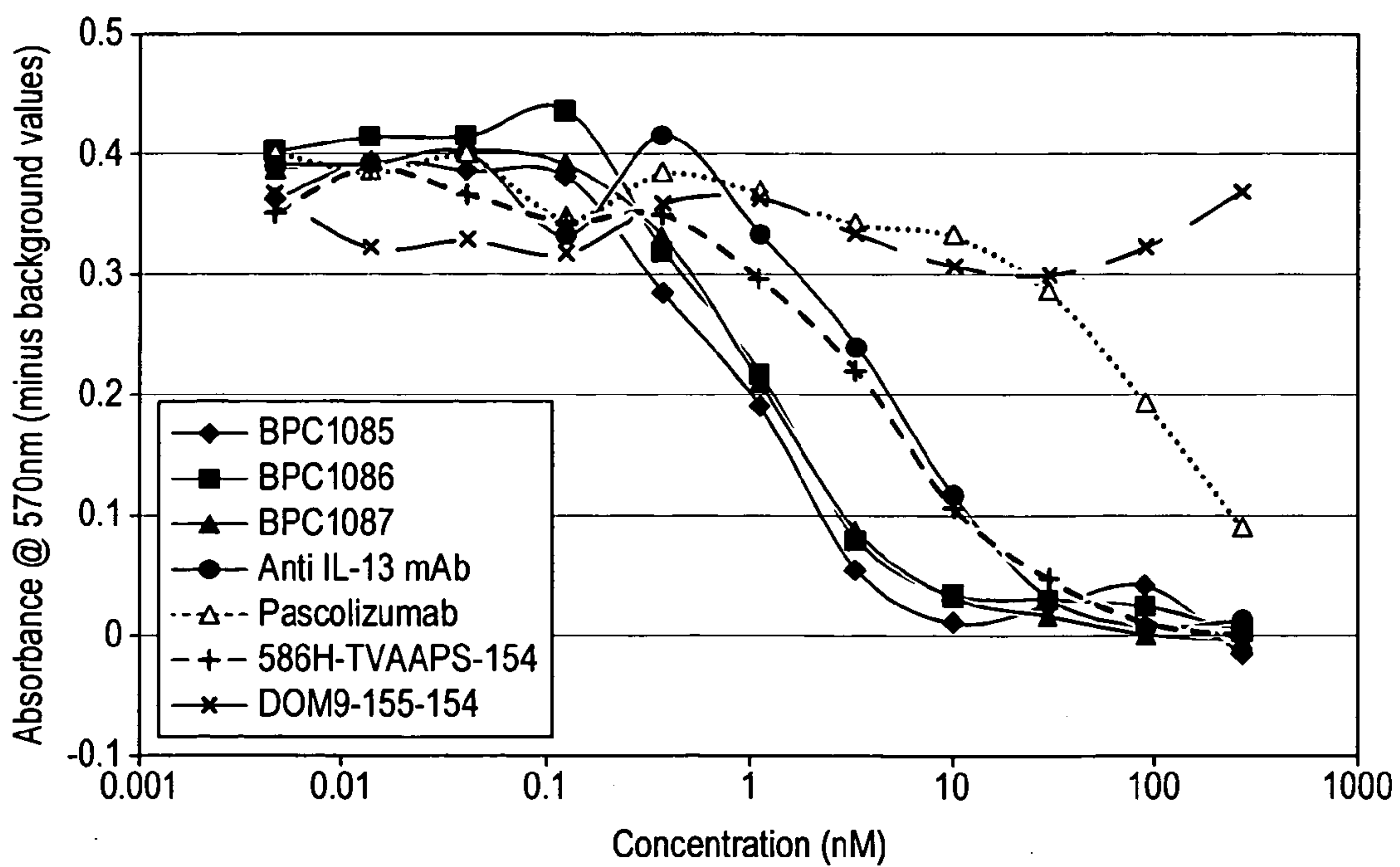


FIG. 12

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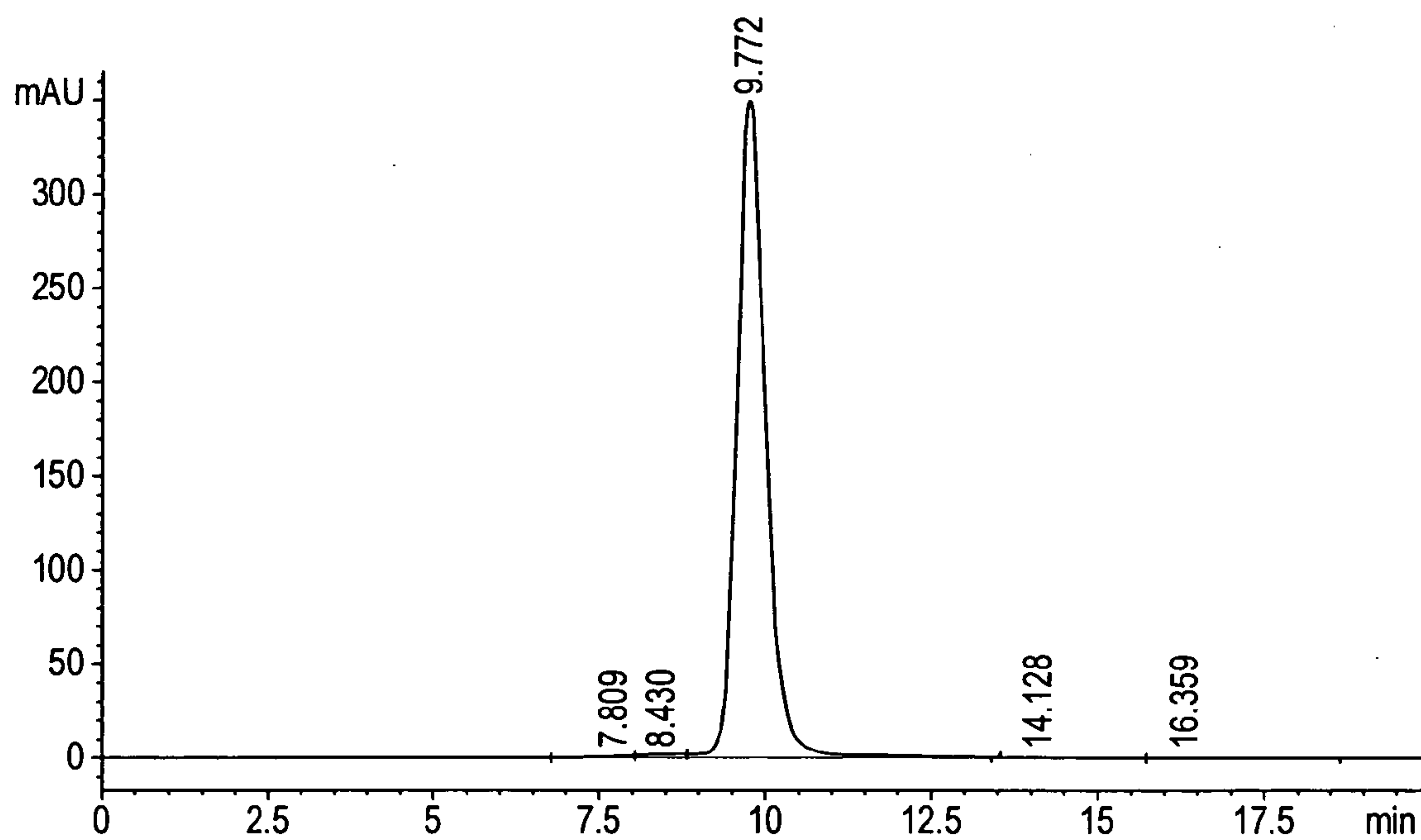


FIG. 13

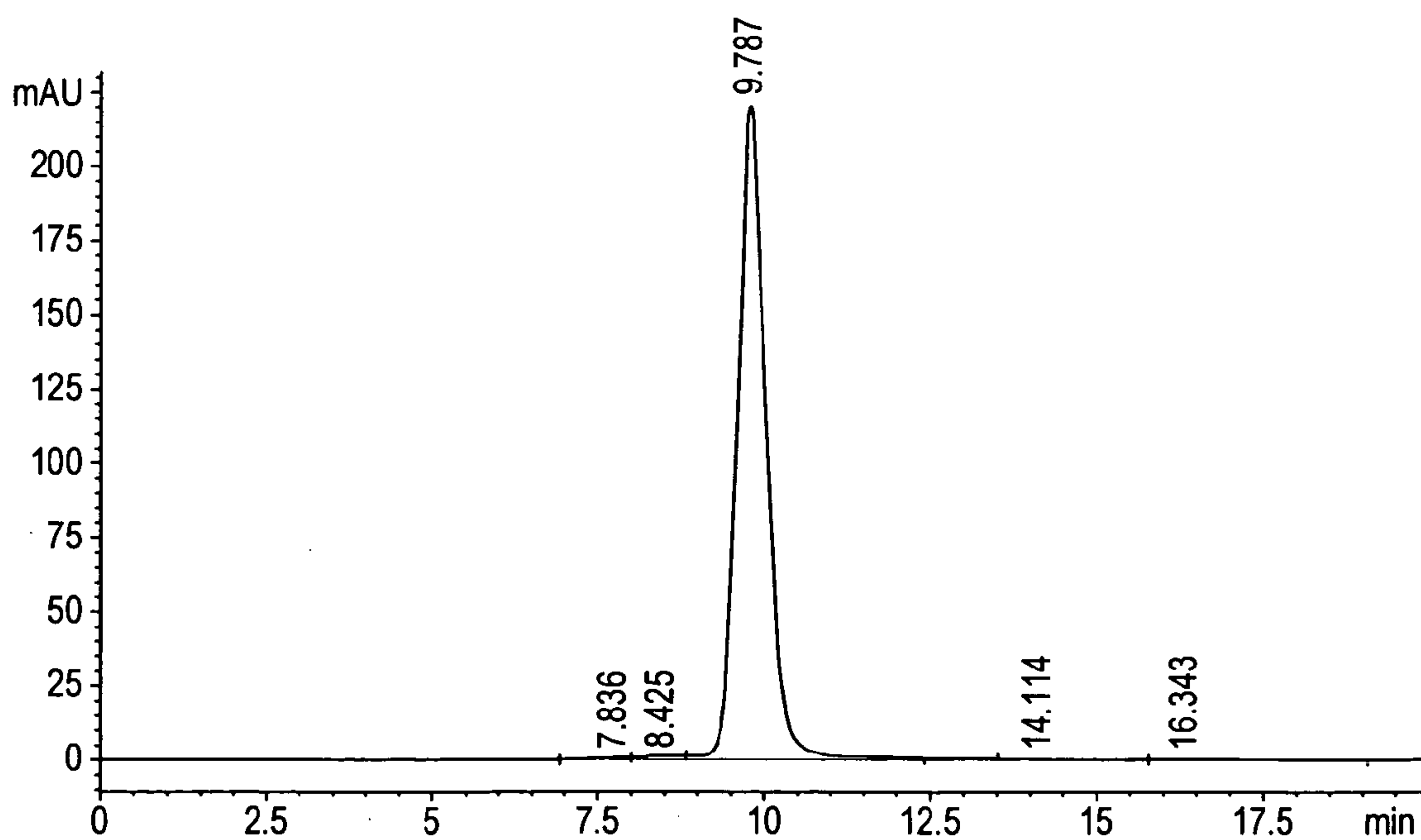


FIG. 14

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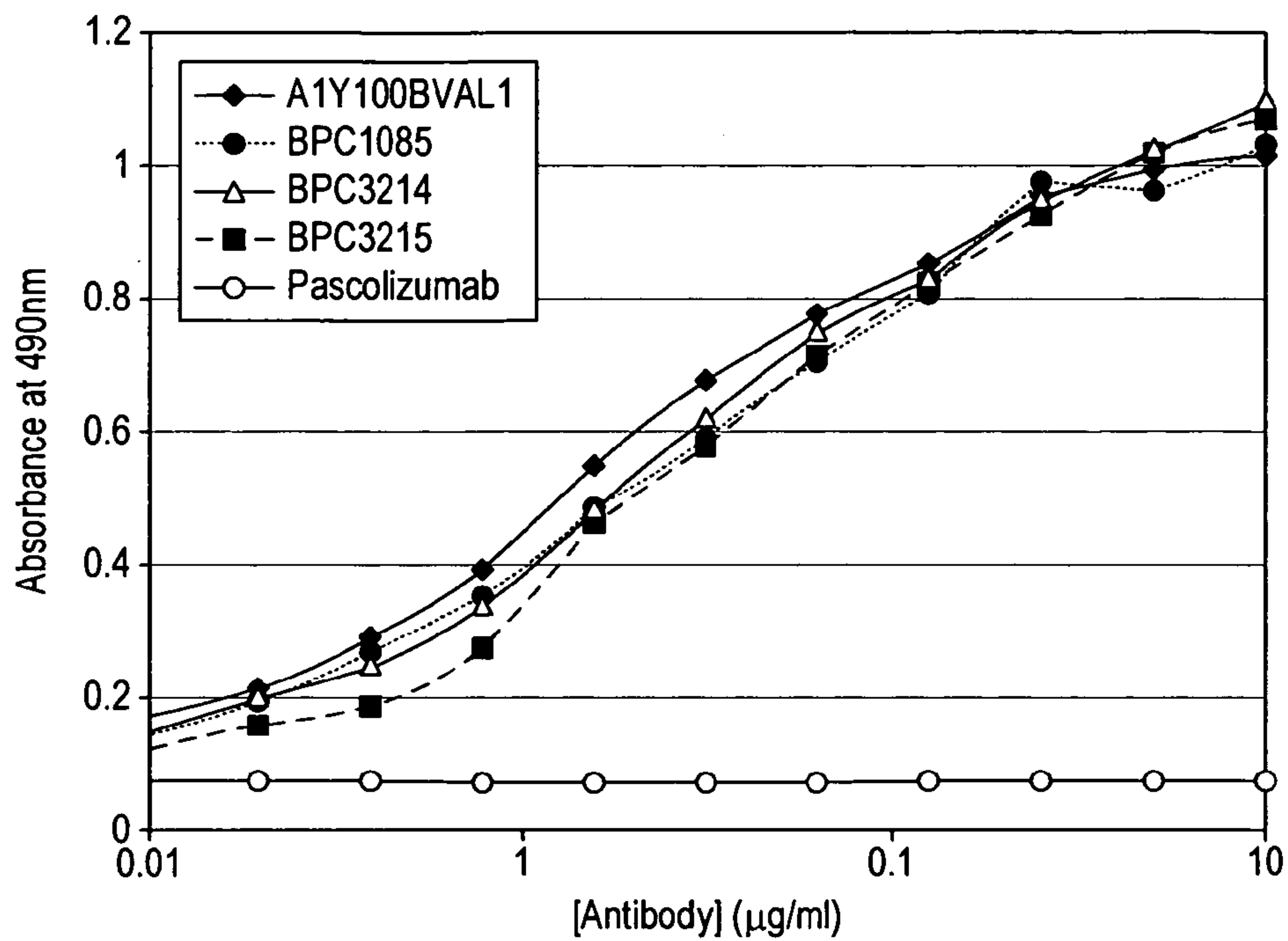


FIG. 15

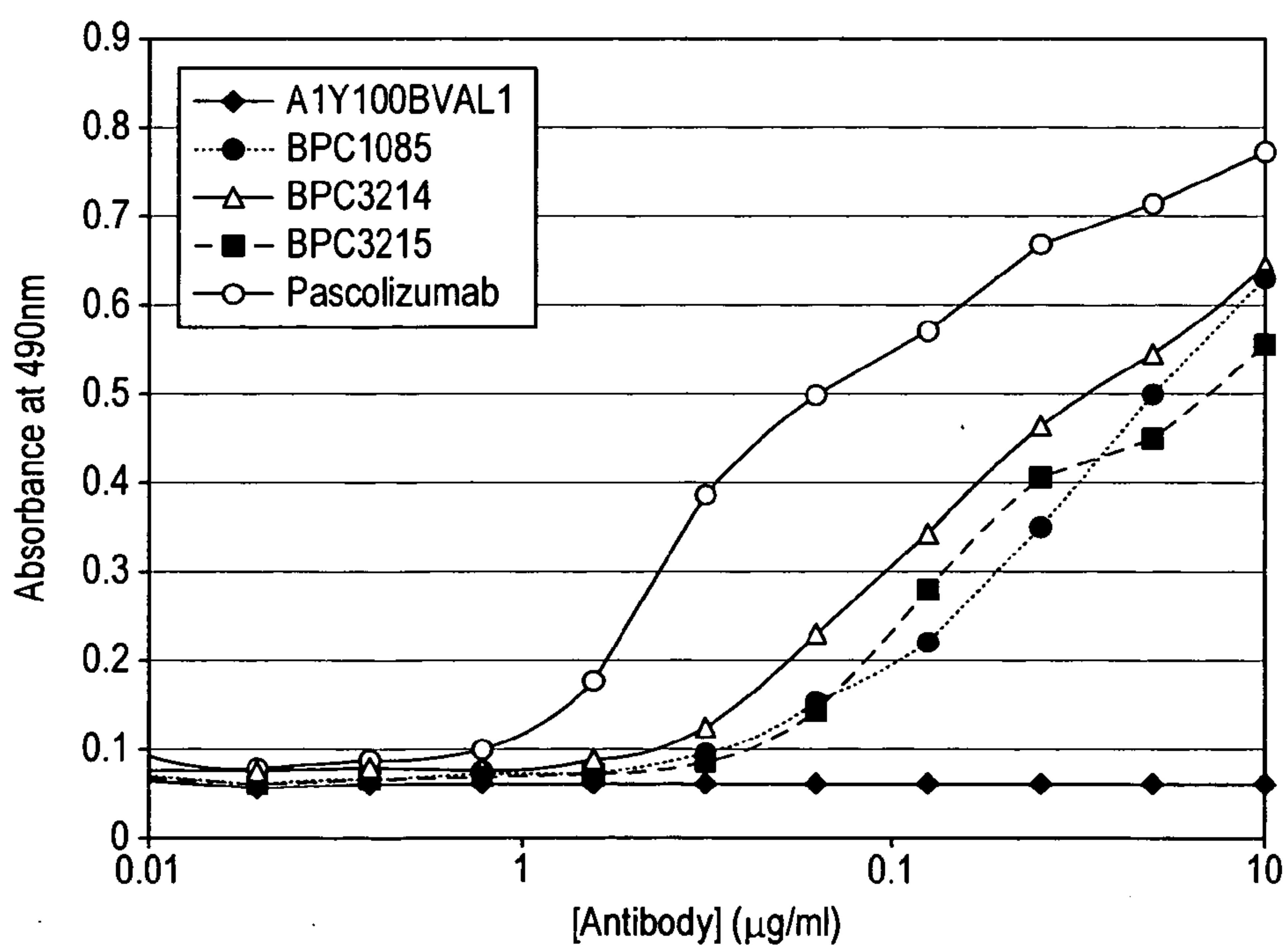


FIG. 16

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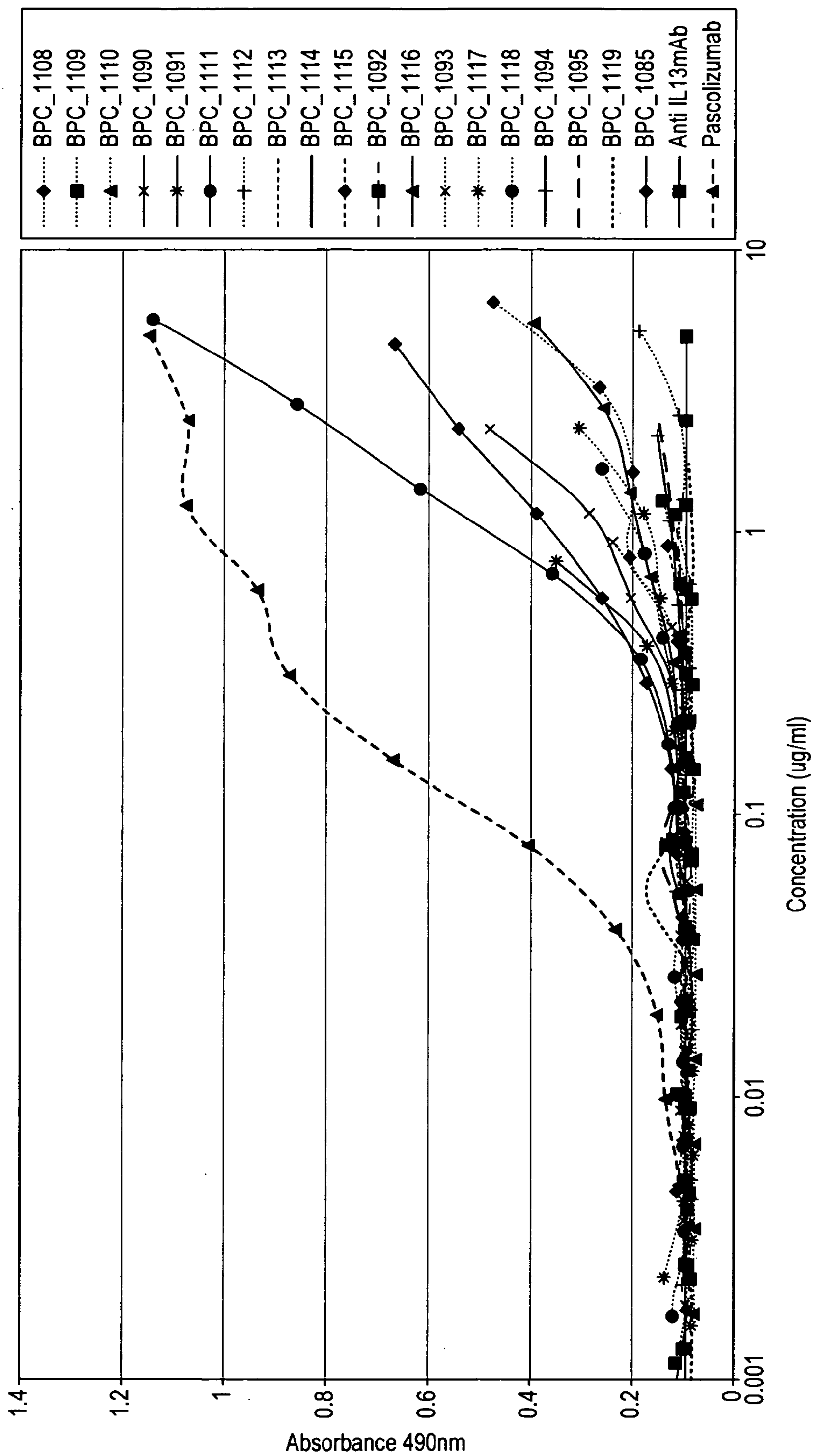


FIG. 17