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(54) ANTI-SERUM ALBUMIN BINDING VARIANTS

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(57) ABSTRACT

The invention relates to improved variants of the anti-serum albumin immunoglobulin single variable domain DOM7h-11, as well as ligands and drug conjugates comprising such variants, compositions, nucleic acids, vectors and hosts.

16 Claims, 6 Drawing Sheets

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				acute	low affinity	KD: 2000-10000	Kd:0.08 to 0.1; Ka: 5e4 to 1e4	KD: 2000-6000	Kd:0.08 to 0.1 ; Ka: 5e4 to 2e4	DOM7h-11
lineage (ranges supported by data)	overali range	KD: 1 to 10000	Kd:1.5e-4 to 0.1 ; Ka:2e6 to 1e4	intermediate	medium affinity	KD: 400-2000	Kd: 8e-3 to 0.08; Ka: 2e4 to 5e4	KD: 400-1500	Kd:8e-3 to 0.08; Ka: 2e4 to 6e4	DMS7325, DMS7326; DMS7323
kinetics based on DOM/n-14 and DOM/n-11				chronic	high affinity	KD: 0.1-400	Kd:1.5e-4 to 8e-3 ; Ka:1e6 to 5e4	KD: 1-200	Kd:3e-4 to 2e-3; Ka: 1e6 to 5e4	DOM7h-11-15, DOM7h-14, DOM7h-14- 10, DOM7h-14-18, DOM7h-14-19, DOM7h-11-18, DOM7h-11-19 DMS7321, DMS7322; DMS7324, DMS7321, DMS7327;
numan				therapeutic ranges				optional ranges		Examples

2A	
Figure	

c chroni high affi kD: 0.1- kD: 0.1- kD: 1.2 kD: 1-2 kD: 1-2 kD: 1-2 hom7h-14-10; DOM7h-14 14-19, DOM7h-14-28
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2B	
Figure	

Rat			
		overall range	
		KD: 1 to 10000	
		Kd: 2e-3 to 0.15 ; Ka: 2e6 to 1e4	
therapeutic ranges	chronic	intermediate	acute
	high affinity	medium affinity	low affinity
	KD: 1-300	KD: 300-2000	KD: 2000-10000
	Kd:2e-3 to 5e-2 ; Ka:2e6 to 2e5	Kd:5e-2 to 0.09; Ka:2e5 to 4.5e4	Kd:0.09 to 0.15 ; Ka: 4.5e4 to 1.5e4
optional ranges	KD: 20-200	KD: 400-1800	KD: 2000-6000
	Kd:9e-3 to 2e-2; Ka: 1e6 to 1e5	Kd: 4e-2 to 0.09; Ka:1e5 to 5e4	Kd: 0.1 to 0.14; Ka: 5e4 to 3e4
Examples	DOM7h-11-15; DOM7h-11-12; DOM7h- 11-18, DOM7h-11-19, DOM7h-14-28, DOM7h-14-36, DOM7h-14 DMS7327; DMS7322	DOM7h-14-18; DOM7h-14-19; DMS7321; DMS7323, DMS7324, DMS7326;,	DMS7325; DOM7h-11;

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Mouse			
		overall range	
		KD: 1 to 10000	
		Kd: 2e-3 to 0.15 ; Ka: 2e6 to 1e4	
therapeutic ranges	chronic	intermediate	acute
	hígh affinity	medium affinity	low affinity
	KD: 1-100	KD: 100-2000	KD: 2000-10000
	Kd:2e-3 to 1e-2 ; Ka:2e6 to 1e5	Kd:1e-2 to 0.07 ; Ka: 1e5 to 3e4	Kd: 0.08 to 0.15; Ka: 4e4 to 1.5e4
optional ranges	KD: 1 to 80	KD: 120-2000	KD: 4000-10000
	Kd:2e-3 to 1e-2; Ka: 2e6 to 1.5e5	Kd: 9e-3 to 0.07 ; Ka: 1.3e5 to 3e4	Kd:0.1 to 0.15; Ka: 2.5e4 to 1.5e4
Examples	DOM7h-11-15;; DOM7h-14; DOM7h-14- 10, DOM7h-14-18, DOM7h-14-19, DOM7h-11-18, DOM7h-11-19, DOM7h- 14-28, DOM7h-14-36 DMS7322, DMS7327	DMS7321; DMS7323; DMS7324; DOM7h-11-12; DMS7326	DMS7325; DOM7h-11

2D	
Figure	

ANTI-SERUM ALBUMIN BINDING VARIANTS

This application is a 371 of International Application No. PCT/EP2010/052008, filed 17 Feb. 2010, which claims the ⁵ benefit of U.S. Provisional Application Nos. 61/153,746, filed 19 Feb. 2009, 61/163,987, filed 27 Mar. 2009 and 61/247,136, filed 30 Sep. 2009, which are incorporated herein in their entirety.

The invention relates to improved variants of the antiserum albumin immunoglobulin single variable domain DOM7h-11, as well as ligands and drug conjugates comprising such variants, compositions, nucleic acids, vectors and hosts.

BACKGROUND OF THE INVENTION

WO04003019 and WO2008/096158 disclose anti-serum albumin (SA) binding moieties, such as anti-SA immunoglobulin single variable domains (dAbs), which have therapeutically-useful half-lives. These documents disclose monomer anti-SA dAbs as well as multi-specific ligands comprising such dAbs, eg, ligands comprising an anti-SA dAb and a dAb that specifically binds a target antigen, such 25 as TNFR1. Binding moieties are disclosed that specifically bind serum albumins from more than one species, eg human/ mouse cross-reactive anti-SA dAbs.

WO05118642 and WO2006/059106 disclose the concept of conjugating or associating an anti-SA binding moiety, ³⁰ such as an anti-SA immunoglobulin single variable domain, to a drug, in order to increase the half-life of the drug. Protein, peptide and NCE (new chemical entity) drugs are disclosed and exemplified. WO2006/059106 discloses the use of this concept to increase the half-life of insulintropic agents, eg, incretin hormones such as glucagon-like peptide (GLP)-1.

Reference is also made to Holt et al, "Anti-Serum albumin domain antibodies for extending the half-lives of short lived drugs", Protein Engineering, Design & Selection, vol 21, no 5, pp 283-288, 2008. It is conceivable that a molecule with an appropriately high affinity and specificity for serum albumin would stay in circulation long enough to have the desired therapeutic effect (Tomlinson, *Nature Biotechnology* 22, 521-522

WO2008/096158 discloses DOM7h-11, which is a good anti-SA dAb. It would be desirable to provide improved dAbs that are variants of DOM7h-11 and that specifically 45 bind serum albumin, preferably albumins from human and non-human species, which would provide utility in animal models of disease as well as for human therapy and/or diagnosis. It would also be desirable to provide for the choice between relatively modest- and high-affinity anti-SA 50 binding moieties (dAbs). Such moieties could be linked to drugs, the anti-SA binding moiety being chosen according to the contemplated end-application. This would allow the drug to be better tailored to treating and/or preventing chronic or acute indications, depending upon the choice of anti-SA binding moiety. It would also be desirable to provide anti-dAbs, that are monomeric or substantially so in solution. This would especially be advantageous when the anti-SA dAb is linked to a binding moiety, eg, a dAb, that 60 specifically binds a cell-surface receptor, such as TNFR1, with the aim of antagonizing the receptor. The monomeric state of the anti-SA dAb is useful in reducing the chance of receptor cross-linking, since multimers are less likely to form which could bind and cross-link receptors (eg, TNFR1) 65 on the cell surface, thus increasing the likelihood of receptor agonism and detrimental receptor signaling.

SUMMARY OF THE INVENTION

Aspects of the present invention solve these problems. To this end, the present inventors surprisingly found that beneficial mutations can be targeted to the FW2/CDR2 junction (positions 49 to 51, numbering according to Kabat) of DOM7h-11.

In one aspect the invention, therefore, provides an antiserum albumin (SA) immunoglobulin single variable domain variant of DOM7h-11, wherein the variant comprises at least one mutation in the FW2/CDR2 junction (positions 49 to 51, numbering according to Kabat) compared to DOM7h-11, and wherein the variant has from 2 to 8 changes compared to the amino acid sequence of DOM7h-11.

In one aspect the invention provides an anti-serum albumin (SA) immunoglobulin single variable domain variant of DOM7h-11, wherein the variant comprises a Met at position 32 (numbering according to Kabat) compared to DOM7h-11, and wherein the variant has from 0 to 4 further changes compared to the amino acid sequence of DOM7h-11.

Embodiments of either aspect of the invention provide DOM7h-11 variants of good anti-serum albumin affinities. The choice of variant can allow for tailoring of half-life according to the desired therapeutic and/or prophylactic setting. For example, in one embodiment, the affinity of the variant for serum albumin is relatively high, such that the variant would be useful for inclusion in products that find utility in treating and/or preventing chronic or persistent diseases, conditions, toxicity or other chronic indications. In one embodiment, the affinity of the variant for serum albumin is relatively modest, such that the variant would be useful for inclusion in products that find utility in treating and/or preventing acute diseases, conditions, toxicity or other acute indications. In one embodiment, the affinity of the variant for serum albumin is intermediate, such that the variant would be useful for inclusion in products that find utility in treating and/or preventing acute or chronic diseases, conditions, toxicity or other acute or chronic indications.

It is conceivable that a molecule with an appropriately high affinity and specificity for serum albumin would stay in circulation long enough to have the desired therapeutic effect (Tomlinson, *Nature Biotechnology* 22, 521-522 (2004)). Here, a high affinity anti-SA variant would stay in serum circulation matching that of the species' serum albumin (WO2008096158). Once in circulation, any fused therapeutic agent to the ALBUDABTM variant (an ALBUDABTM is an anti-serum albumin dAb or immunoglobulin single variable domain), be it NCE, peptide or protein, consequently would be able to act longer on its target and exhibit a longer lasting therapeutic effect. This would allow for targeting chronic or persistent diseases without the need of frequent dosing.

A variant with moderate affinity (but specificity to SA) would only stay in serum circulation for a short time (eg, for a few hours or a few days) allowing for the specific targeting of therapeutic targets involved in acute diseases by the fused therapeutic agent.

This way it is possible to tailor the anti-SA-containing product to the therapeutic disease area by choosing an anti-SA variant with the appropriate albumin binding affinity and/or serum half-life.

An aspect of the invention provides a multispecific ligand comprising any anti-SA variant as described above and a binding moiety that specifically binds a target antigen other than SA.

An aspect of the invention provides a fusion product, eg, a fusion protein or fusion with a peptide or NCE (new chemical entity) drug, comprising a polypeptide, protein, peptide or NCE drug fused or conjugated (for an NCE) to any variant as described above, wherein the variant is DOM7h-11-15 or $DOM7h-11-15^{S12P}$ (or a variant having an amino acid that is at least 95, 96, 97, 98 or 99% identical to the amino acid sequence of DOM7h-11-15) or DOM7h-11-5 12 (or a variant having an amino acid that is at least 95, 96, 97, 98 or 99% identical to the amino acid sequence of DOM7h-11-12). DOM7h-11-15 and DOM7h-11-12 give only a modest drop in affinity when fused or conjugated to partner making them useful in fusion products. DOM7h-11- 10 15^{S12P} is identical to DOM7h-11-15, with the exception that position 12 (numbering according to Kabat) is a proline instead of a serine. This provides advantages set out in WO08052933, including to reduce binding to Protein-L of fusion proteins containing this domain antibody and to 15 facilitate purification. The entire disclosure of WO08052933 is incorporated herein by reference. Similarly, the invention provides a DOM7h-11 variant as disclosed herein wherein the variant comprises an amino acid sequence as set out below with the exception that position 12 (numbering 20 according to Kabat) is a proline. The invention also provides fusion proteins, conjugates or composition comprising such DOM7h-11 variants.

One aspect of the invention provides a variant of DOM7h-11 that comprises an amino acid sequence that is identical to ²⁵ the amino acid sequence of DOM7h-11-15^{S12P} or has up to 4 changes compared to the amino acid sequence of DOM7h-11-15^{S12P}, provided that the amino acid sequence of the variant has at least one mutation in the FW2/CDR2 junction (positions 49 to 51, numbering according to Kabat). ³⁰

An aspect of the invention provides a composition comprising a variant, fusion protein or ligand of any preceding aspect and a pharmaceutically acceptable diluent, carrier, excipient or vehicle.

An aspect of the invention provides a method of treating ³⁵ or preventing a disease or disorder in a patient, comprising administering at least one dose of a variant according to any aspect or embodiment of the invention to said patient.

An aspect of the invention provides a polypeptide fusion or conjugate comprising an anti-serum albumin dAb as ⁴⁰ disclosed herein (eg, DOM7h-11-15 or DOM7h-11-3 or DOM7h-11-15^{S12P} or DOM7h-11-15^{S12P} with up to 4 changes compared to the amino acid sequence of DOM7h-11-15^{S12P}) and an incretin or insulinotropic agent, eg, exendin-4, GLP-1(7-37), GLP-1(6-36) or any incretin or insulito tropic agent disclosed in WO06/059106, these agents being explicitly incorporated herein by reference as though written herein for inclusion in the present invention and claims below.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1: Amino-acid sequence alignment for DOM7h-11 (SEQ ID NO: 421) variant dAbs. A "." at a particular position indicates the same amino as found in DOM7h-11 at 55 that position. The CDRs are indicated by underlining and bold text (the first underlined sequence is CDR1, the second underlined sequence is CDR2 and the third underlined sequence is CDR3). The figure comprises the following variants: DOM 7h-11-12 (SEQ ID NO:1), DOM 7h-11-15 60 (SEQ ID NO:2), DOM 7h-11-18 (SEQ ID NO:3), DOM 7h-11-19 (SEQ ID NO:4), and DOM 7h-11-3 (SEQ ID NO: 5).

FIG. 2: Kinetic parameters of DOM7h-11 variants. KD units=nM; Kd units=sec⁻¹; Ka units= M^{-1} sec⁻¹. The notation A e-B means A×10^{-B} and C e D means C×10^D. The overall kinetic ranges in various species, as supported by the

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examples below, are indicated. Optional ranges are also provided for use in particular therapeutic settings (acute or chronic indications, conditions or diseases and "intermediate" for use in both chronic and acute settings). High affinity dAbs and products comprising these are useful for chronic settings. Medium affinity dAbs and products comprising these are useful for intermediate settings. Low affinity dAbs and products comprising these are useful for acute settings. The affinity in this respect is the affinity for serum albumin. Various example anti-serum dAbs and fusion proteins are listed, and these support the ranges disclosed. Many of the examples have favourable kinetics in human and one or more non-human animals (eg, in human and Cynomolgus monkey and/or mouse). Choice of dAb or product comprising this can be tailored, according to the invention, depending on the setting (eg, chronic or acute) to be treated therapeutically.

DETAILED DESCRIPTION OF THE INVENTION

Within this specification the invention has been described, with reference to embodiments, in a way which enables a clear and concise specification to be written. It is intended and should be appreciated that embodiments may be variously combined or separated without parting from the invention.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art (e.g., in cell culture, molecular genetics, nucleic acid chemistry, hybridization techniques and biochemistry). Standard techniques are used for molecular, genetic and biochemical methods (see generally, Sambrook et al., Molecular Cloning: A Laboratory Manual, 2d ed. (1989) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. and Ausubel et al., Short Protocols in Molecular Biology (1999) 4th Ed, John Wiley & Sons, Inc. which are incorporated herein by reference) and chemical methods.

As used herein, the term "antagonist of Tumor Necrosis Factor Receptor 1 (TNFR1)" or "anti-TNFR1 antagonist" or the like refers to an agent (e.g., a molecule, a compound) which binds TNFR1 and can inhibit a (i.e., one or more)
45 function of TNFR1. For example, an antagonist of TNFR1 can inhibit the binding of TNFα to TNFR1 and/or inhibit signal transduction mediated through TNFR1. Accordingly, TNFR1-mediated processes and cellular responses (e.g., TNFα-induced cell death in a standard L929 cytotoxicity
50 assay) can be inhibited with an antagonist of TNFR1.

A "patient" is any animal, eg, a mammal, eg, a non-human primate (such as a baboon, rhesus monkey or Cynomolgus monkey), mouse, human, rabbit, rat, dog, cat or pig. In one embodiment, the patient is a human.

As used herein, "peptide" refers to about two to about 50 amino acids that are joined together via peptide bonds.

As used herein, "polypeptide" refers to at least about 50 amino acids that are joined together by peptide bonds. Polypeptides generally comprise tertiary structure and fold into functional domains.

As used herein an antibody refers to IgG, IgM, IgA, IgD or IgE or a fragment (such as a Fab, $F(ab')_2$, Fv, disulphide linked Fv, scFv, closed conformation multispecific antibody, disulphide-linked scFv, diabody) whether derived from any species naturally producing an antibody, or created by recombinant DNA technology; whether isolated from serum, B-cells, hybridomas, transfectomas, yeast or bacteria.

As used herein, "antibody format" refers to any suitable polypeptide structure in which one or more antibody variable domains can be incorporated so as to confer binding specificity for antigen on the structure. A variety of suitable antibody formats are known in the art, such as, chimeric 5 antibodies, humanized antibodies, human antibodies, single chain antibodies, bispecific antibodies, antibody heavy chains, antibody light chains, homodimers and heterodimers of antibody heavy chains and/or light chains, antigen-binding fragments of any of the foregoing (e.g., a Fv fragment 10 (e.g., single chain Fv (scFv), a disulfide bonded Fv), a Fab fragment, a Fab' fragment, a F(ab')₂ fragment), a single antibody variable domain (e.g., a dAb, V_H, V_{HH}, V_L), and modified versions of any of the foregoing (e.g., modified by the covalent attachment of polyethylene glycol or other 15 suitable polymer or a humanized V_{HH}).

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 different V regions or domains. An immunoglobulin single 20 variable domain can be present in a format (e.g., homo- or hetero-multimer) with other variable regions or variable domains where the other regions or domains are not required for antigen binding by the single immunoglobulin variable domain (i.e., where the immunoglobulin single variable 25 domain binds antigen independently of the additional variable domains). A "domain antibody" or "dAb" is the same as an "immunoglobulin single variable domain" as the term is used herein. A "single immunoglobulin variable domain" is the same as an "immunoglobulin single variable domain" 30 as the term is used herein. A "single antibody variable domain" or an "antibody single variable domain" is the same as an "immunoglobulin single variable domain" as the term is used herein. An immunoglobulin single variable domain is in one embodiment a human antibody variable domain, 35 but also includes single antibody variable domains from other species such as rodent (for example, as disclosed in WO 00/29004, the contents of which are incorporated herein by reference in their entirety), nurse shark and Camelid $\mathrm{V}_{H\!H}$ dAbs. Camelid V_{HH} are immunoglobulin single variable 40 domain polypeptides that are derived from species including camel, llama, alpaca, dromedary, and guanaco, which produce heavy chain antibodies naturally devoid of light chains. The V_{HH} may be humanized.

A "domain" is a folded protein structure which has 45 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 transferred to other proteins without loss of function of the remainder of the protein and/or of the 50 domain. A "single antibody 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 55 by sequences which are not 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 60 domain.

In the instant application, the term "prevention" and "preventing" involves administration of the protective composition prior to the induction of the disease or condition. "Treatment" and "treating" involves administration of the 65 protective composition after disease or condition symptoms become manifest. "Suppression" or "suppressing" refers to 6

administration of the composition after an inductive event, but prior to the clinical appearance of the disease or condition.

As used herein, the term "dose" refers to the quantity of ligand administered to a subject all at one time (unit dose), or in two or more administrations over a defined time interval. For example, dose can refer to the quantity of ligand (e.g., ligand comprising an immunoglobulin single variable domain that binds target antigen) administered to a subject over the course of one day (24 hours) (daily dose), two days, one week, two weeks, three weeks or one or more months (e.g., by a single administration, or by two or more administrations). The interval between doses can be any desired amount of time. The term "pharmaceutically effective" when referring to a dose means sufficient amount of the ligand, domain or pharmaceutically active agent to provide the desired effect. The amount that is "effective" will vary from subject to subject, depending on the age and general condition of the individual, the particular drug or pharmaceutically active agent and the like. Thus, it is not always possible to specify an exact "effective" amount applicable for all patients. However, an appropriate "effective" dose in any individual case may be determined by one of ordinary skill in the art using routine experimentation.

Methods for pharmacokinetic analysis and determination of ligand (eg, single variable domain, fusion protein or multi-specific ligand) half-life will be familiar to those skilled in the art. Details may be found in Kenneth, A et al: Chemical Stability of Pharmaceuticals: A Handbook for Pharmacists and in Peters et al, Pharmacokinetc analysis: A Practical Approach (1996). Reference is also made to "Pharmacokinetics", M Gibaldi & D Perron, published by Marcel Dekker, 2^{nd} Rev. ex edition (1982), which describes pharmacokinetic parameters such as t alpha and t beta half lives and area under the curve (AUC). Optionally, all pharmacokinetic parameters and values quoted herein are to be read as being values in a human. Optionally, all pharmacokinetic parameters and values quoted herein are to be read as being values in a mouse or rat or Cynomolgus monkey.

Half lives (t1/2 alpha and t1/2 beta) and AUC can be determined from a curve of serum concentration of ligand against time. The WinNonlin analysis package, eg version 5.1 (available from Pharsight Corp., Mountain View, Calif. 94040, USA) can be used, for example, to model the curve. When two-compartment modeling is used, in a first phase (the alpha phase) the ligand is undergoing mainly distribution in the patient, with some elimination. A second phase (beta phase) is the phase when the ligand has been distributed and the serum concentration is decreasing as the ligand is cleared from the patient. The t alpha half life is the half life of the first phase and the t beta half life is the half life of the second phase. Thus, in one embodiment, in the context of the present invention, the variable domain, fusion protein or ligand has a t α half-life in the range of (or of about) 15 minutes or more. In one embodiment, the lower end of the range is (or is about) 30 minutes, 45 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 10 hours, 11 hours or 12 hours. In addition, or alternatively, the variable domain, fusion protein or ligand according to the invention will have a ta half life in the range of up to and including 12 hours (or about 12 hours). In one embodiment, the upper end of the range is (or is about) 11, 10, 9, 8, 7, 6 or 5 hours. An example of a suitable range is (or is about) 1 to 6 hours, 2 to 5 hours or 3 to 4 hours.

In one embodiment, the present invention provides the variable domain, fusion protein or ligand according to the invention has a $t\beta$ half-life in the range of (or of about) 2.5

hours or more. In one embodiment, the lower end of the range is (or is about) 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 10 hours, 11 hours, or 12 hours. In addition, or alternatively, the t β half-life is (or is about) up to and including 21 or 25 days. In one embodiment, the upper end 5 of the range is (or is about) 12 hours, 24 hours, 2 days, 3 days, 5 days, 10 days, 15 days, 19 days, 20 days, 21 days or 22 days. For example, the variable domain, fusion protein or ligand according to the invention will have a t β half life in the range 12 to 60 hours (or about 12 to 60 hours). In a 10 further embodiment, it will be in the range 12 to 26 hours).

As an alternative to using two-compartment modeling, the skilled person will be familiar with the use of non-compart- 15 mental modeling, which can be used to determine terminal half-lives (in this respect, the term "terminal half-life" as used herein means a terminal half-life determined using non-compartmental modeling). The WinNonlin analysis package, eg version 5.1 (available from Pharsight Corp., 20 Mountain View, Calif. 94040, USA) can be used, for example, to model the curve in this way. In this instance, in one embodiment the single variable domain, fusion protein or ligand has a terminal half life of at least (or at least about) 8 hours, 10 hours, 12 hours, 15 hours, 28 hours, 20 hours, 1 25 day, 2 days, 3 days, 7 days, 14 days, 15 days, 16 days, 17 days, 18 days, 19 days, 20 days, 21 days, 22 days, 23 days, 24 days or 25 days. In one embodiment, the upper end of this range is (or is about) 24 hours, 48 hours, 60 hours or 72 hours or 120 hours. For example, the terminal half-life is (or 30 is about) from 8 hours to 60 hours, or 8 hours to 48 hours or 12 to 120 hours, eg, in man.

In addition, or alternatively to the above criteria, the variable domain, fusion protein or ligand according to the invention has an AUC value (area under the curve) in the range of (or of about) 1 mg·min/ml or more. In one embodiment, the lower end of the range is (or is about) 5, 10, 15, 20, 30, 100, 200 or 300 mg·min/ml. In addition, or alternatively, the variable domain, fusion protein or ligand according to the invention has an AUC in the range of (or of about) 40, 200, 300, 200, 150, 100, 75 or 50 mg·min/ml. Advantageously the variable domain, fusion protein or ligand will have an AUC in (or about in) the range selected from the group consisting of the following: 15 to 100 mg·min/ml, 15 to 75 mg·min/ml, and 15 to 50 mg·min/ml.

"Surface Plasmon Resonance": Competition assays can be used to determine if a specific antigen or epitope, such as human serum albumin, competes with another antigen or 50 epitope, such as cynomolgus serum albumin, for binding to a serum albumin binding ligand described herein, such as a specific dAb. Similarly competition assays can be used to determine if a first ligand such as dAb, competes with a second ligand such as a dAb for binding to a target antigen 55 or epitope. The term "competes" as used herein refers to substance, such as a molecule, compound, preferably a protein, which is able to interfere to any extent with the specific binding interaction between two or more molecules. The phrase "does not competitively inhibit" means that 60 substance, such as a molecule, compound, preferably a protein, does not interfere to any measurable or significant extent with the specific binding interaction between two or more molecules. The specific binding interaction between two or more molecules preferably includes the specific 65 binding interaction between a single variable domain and its cognate partner or target. The interfering or competing

molecule can be another single variable domain or it can be a molecule that is structurally and/or functionally similar to a cognate partner or target.

The term "binding moiety" refers to a domain that specifically binds an antigen or epitope independently of a different epitope or antigen binding domain. A binding moiety may be a domain antibody (dAb) or may be a domain which is a derivative of a non-immunoglobulin protein scaffold, eg, a scaffold selected from the group consisting of CTLA-4, lipocalin, SpA, an adnectin, affibody, an avimer, GroE1, transferrin, GroES and fibronectin, which binds to a ligand other than the natural ligand (in the case of the present invention, the moiety binds serum albumin). See WO2008/ 096158, which discloses examples of protein scaffolds and methods for selecting antigen or epitope-specific binding domains from repertoires (see Examples 17 to 25). These specific disclosures of WO2008/096158 are expressly incorporated herein by reference as though explicitly written herein and for use with the present invention, and it is contemplated that any part of such disclosure can be incorporated into one or more claims herein).

In one aspect, the invention provides an anti-serum albumin (SA) immunoglobulin single variable domain variant of DOM7h-11, wherein the variant comprises at least one mutation in the FW2/CDR2 junction (positions 49 to 51, numbering according to Kabat) compared to DOM7h-11, and wherein the variant has from 2 to 8 changes compared to the amino acid sequence of DOM7h-11. Optionally, position 49 (according to Kabat) is Leu. Additionally or alternatively, position 50 (according to Kabat) is optionally Ala or Trp. Additionally or alternatively, position 51 (according to Kabat) is optionally Phe or Asn. In one embodiment, the variant comprises a mutation at each of positions 49, 50 and 51 (numbering according to Kabat) compared to DOM7h-11. In one embodiment, the variant comprises a LFG motif, where L is at position 49 (numbering according to Kabat), wherein L, F and G are Leu, Phe and Gly respectively.

In one embodiment, the variant comprises an amino acid single variable domain selected from DOM7h-11-3, DOM7h-11-15, DOM7h-11-12 and DOM7h-11-19 or has up to 4 changes compared to the selected amino acid sequence, provided that the amino acid sequence of the variant has at least one mutation in the FW2/CDR2 junction as defined above. In one embodiment, the variant comprises an amino acid sequence that is identical to the amino acid sequence of DOM7h-11-15^{S12P} or has up to 4 changes compared to the amino acid sequence of DOM7h-11-15^{S12P}, provided that the amino acid sequence of the variant has at least one mutation in the FW2/CDR2 junction (positions 49 to 51, numbering according to Kabat). In one embodiment, the variant comprises an amino acid sequence that is identical to the amino acid sequence of a single variable domain selected from DOM7h-11-3, or has up to 4 changes compared to the selected amino acid sequence, provided that the amino acid sequence of the variant has L at position 49, W at position 50 and N at position 51. In one embodiment, the variant comprises an amino acid sequence that is identical to the amino acid sequence of a single variable domain selected from DOM7h-11-12, or has up to 4 changes compared to the selected amino acid sequence, provided that the amino acid sequence of the variant has M at position 32 and L at position 49. In one embodiment, the variant comprises an amino acid sequence that is identical to the amino acid sequence of a single variable domain selected from DOM7h-11-15 or DOM7h-11-15^{S12P}, or has up to 4 changes com-

pared to the selected amino acid sequence, provided that the amino acid sequence of the variant has M at position 32, L at position 49, A at position 50 and F at position 51. In one embodiment, the variant comprises an amino acid sequence that is identical to the amino acid sequence of a single variable domain selected from DOM7h-11-18, or has up to 4 changes compared to the selected amino acid sequence, provided that the amino acid sequence of the variant has M at position 32 and H at position 87. In one embodiment, the variant comprises an amino acid sequence that is identical to 10 the amino acid sequence of a single variable domain selected from DOM7h-11-19, or has up to 4 changes compared to the selected amino acid sequence, provided that the amino acid sequence of the variant has M at position 32, L at position 49 and T at position 91. All numbering in this paragraph is 15 according to Kabat.

An aspect of the invention provides an anti-serum albumin (SA) immunoglobulin single variable domain variant of DOM7h-11, wherein the variant comprises a Met at position 32 (numbering according to Kabat) compared to DOM7h- 20 11, and wherein the variant has from 0 to 4 further changes compared to the amino acid sequence of DOM7h-11. Optionally, the variant comprises at least one mutation in the FW2/CDR2 junction (positions 49 to 51, numbering according to Kabat) compared to DOM7h-11. 25

In one embodiment of any aspect of the invention, the variant comprises at least one mutation compared to DOM7h-11 selected from the following

Position 49=L,

Position 50=A or W,

Position 51=F or N,

Position 87=H, and

Position 91=T.

In one embodiment, the variant comprises an amino acid sequence that is identical to the amino acid sequence of a 35 single variable domain selected from DOM7h-11-12, DOM7h-11-15, DOM7h-11-15^{S12P}, DOM7h-11-18 and DOM7h-11-19 or has up to 4 changes compared to the selected amino acid sequence, provided that the amino acid sequence of the variant has Met at position 32. 40

In one embodiment, the variant comprises one or more of the following kinetic characteristics:—

- (a) The variant comprises a binding site that specifically binds human SA with a dissociation constant (KD) from (or from about) 0.1 to (or to about) 10000 nM, 45 optionally from (or from about) 1 to (or to about) 6000 nM, as determined by surface plasmon resonance;
- (b) The variant comprises a binding site that specifically binds human SA with an off-rate constant (KO from (or from about) 1.5×10^{-4} to (or to about) 0.1 sec^{-1} , option- 50 ally from (or from about) 3×10^{-4} to (or to about) 0.1 sec⁻¹ as determined by surface plasmon resonance;
- (c) The variant comprises a binding site that specifically binds human SA with an on-rate constant (K_a) from (or from about) 2×10^6 to (or to about) $1 \times 10^4 M^{-1} \text{ sec}^{-1}$, 55 optionally from (or from about) 1×10^6 to (or to about) $2 \times 10^4 M^{-1} \text{ sec}^{-1}$ as determined by surface plasmon resonance;
- (d) The variant comprises a binding site that specifically binds Cynomolgus monkey SA with a dissociation 60 constant (KD) from (or from about) 0.1 to (or to about) 10000 nM, optionally from (or from about) 1 to (or to about) 6000 nM, as determined by surface plasmon resonance;
- (e) The variant of any preceding claim, wherein the 65 variant comprises a binding site that specifically binds Cynomolgus monkey SA with an off-rate constant (KO

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from (or from about) 1.5×10^{-4} to (or to about) 0.1 sec⁻¹, optionally from (or from about) 3×10^{-4} to (or to about) 0.1 sec⁻¹ as determined by surface plasmon resonance;

- (f) The variant of any preceding claim, wherein the variant comprises a binding site that specifically binds Cynomolgus monkey SA with an on-rate constant (K_a) from (or from about) 2×10^6 to (or to about) $1 \times 10^4 M^{-1}$ sec⁻¹, optionally from (or from about) 1×10^6 to (or to about) $5 \times 10^3 M^{-1}$ sec⁻¹ as determined by surface plasmon resonance;
- (g) The variant comprises a binding site that specifically binds rat SA with a dissociation constant (KD) from (or from about) 1 to (or to about) 10000 nM, optionally from (or from about) 20 to (or to about) 6000 nM, as determined by surface plasmon resonance;
- (h) The variant comprises a binding site that specifically binds rat SA with an off-rate constant (K_d) from (or from about) 2×10^{-3} to (or to about) 0.15 sec^{-1} , optionally from (or from about) 9×10^{-3} to (or to about) 0.14 sec⁻¹ as determined by surface plasmon resonance;
- (i) The variant comprises a binding site that specifically binds rat SA with an on-rate constant (K_a) from (or from about) 2×10^6 to (or to about) $1 \times 10^4 M^{-1}$ sec⁻¹, optionally from (or from about) 1×10^6 to (or to about) $3 \times 10^4 M^{-1}$ sec⁻¹ as determined by surface plasmon resonance;
- (j) The variant comprises a binding site that specifically binds mouse SA with a dissociation constant (KD) from (or from about) 1 to (or to about) 10000 nM as determined by surface plasmon resonance;
- (k) The variant comprises a binding site that specifically binds mouse SA with an off-rate constant (K_d) from (or from about) 2×10^{-3} to (or to about) 0.15 sec⁻¹ as determined by surface plasmon resonance; and/or
- (1) The variant comprises a binding site that specifically binds mouse SA with an on-rate constant (K_a) from (or from about) 2×10^6 to (or to about) $1\times10^4M^{-1}$ sec⁻¹, optionally from (or from about) 2×10^6 to (or to about) 1.5×10^4 M⁻¹ sec⁻¹ as determined by surface plasmon resonance.

Optionally, the variant has

- I: a KD according to (a) and (d), a K_d according to (b) and (e), and a K_a according to (c) and (f); or
- II: a KD according to (a) and (g), a K_{d} according to (b) and (h), and a K_{d} according to (c) and (i); or
- III: a KD according to (a) and (j), a K_d according to (b) and (k), and a K_a according to (c) and (l); or
- IV: kinetics according to I and II; or
- V: kinetics according to I and III; or
- VI: kinetics according to I, II and III.

The invention also provides a ligand comprising a variant of any preceding aspect or embodiment of the invention. For example, the ligand can be a dual-specific ligand (see WO04003019 for examples of dual-specific ligands). In one aspect, the invention provides a multispecific ligand comprising an anti-SA variant of any preceding aspect or embodiment of the invention and a binding moiety that specifically binds a target antigen other than SA. The binding moiety can be any binding moiety that specifically binds a target, eg, the moiety is an antibody, antibody fragment, scFv, Fab, dAb or a binding moiety comprising a nonimmunoglobulin protein scaffold. Such moieties are disclosed in detail in WO2008/096158 (see examples 17 to 25, which disclosure is incorporated herein by reference). Examples of non-immunoglobulin scaffolds are CTLA-4, lipocallin, staphylococcal protein A (spA), Affibody[™], Avimers[™], adnectins, GroEL and fibronectin.

In one embodiment, a linker is provided between the anti-target binding moiety and the anti-SA single variant, the linker comprising the amino acid sequence AST, optionally 5 ASTSGPS. Alternative linkers are described in WO2007085814 (incorporated herein by reference) and WO2008/096158 (see the passage at page 135, line 12 to page 140, line 14, which disclosure and all sequences of linkers are expressly incorporated herein by reference as 10 though explicitly written herein and for use with the present invention, and it is contemplated that any part of such disclosure can be incorporated into one or more claims herein).

In one embodiment of the multispecific ligand, the target 15 antigen may be, or be part of, polypeptides, proteins or nucleic acids, which may be naturally occurring or synthetic. In this respect, the ligand of the invention may bind the target antigen and act as an antagonist or agonist (e.g., EPO receptor agonist). One skilled in the art will appreciate that 20 the choice is large and varied. They may be for instance, human or animal proteins, cytokines, cytokine receptors, where cytokine receptors include receptors for cytokines, enzymes, co-factors for enzymes or DNA binding proteins. Suitable cytokines and growth factors include, but are pref-25 erably not limited to: ApoE, Apo-SAA, BDNF, Cardiotrophin-1, EGF, EGF receptor, ENA-78, Eotaxin, Eotaxin-2, Exodus-2, EpoR, FGF-acidic, FGF-basic, fibroblast growth factor-10, FLT3 ligand, Fractalkine (CX3C), GDNF, G-CSF, GM-CSF, GF- β 1, insulin, IFN- γ , IGF-I, IGF-II, IL-1 α , 30 IL-113, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8 (72 a.a.), IL-8 (77 a.a.), IL-9, IL-10, IL-11, IL-12, IL-13, IL-15, IL-16, IL-17, IL-18 (IGIF), Inhibin α , Inhibin β , IP-10, keratinocyte growth factor-2 (KGF-2), KGF, Leptin, LIF, Lymphotactin, Mullerian inhibitory substance, monocyte colony 35 inhibitory factor, monocyte attractant protein, M-CSF, MDC (67 a.a.), MDC (69 a.a.), MCP-1 (MCAF), MCP-2, MCP-3, MCP-4, MDC (67 a.a.), MDC (69 a.a.), MIG, MIP-1a, MIP-1 β , MIP-3 α , MIP-3 β , MIP-4, myeloid progenitor inhibitor factor-1 (MPIF-1), NAP-2, Neurturin, Nerve 40 growth factor, β-NGF, NT-3, NT-4, Oncostatin M, PDGF-AA, PDGF-AB, PDGF-BB, PF-4, RANTES, SDF1a, SDF1 β , SCF, SCGF, stem cell factor (SCF), TARC, TGF- α , TGF-β, TGF-β2, TGF-β3, tumour necrosis factor (TNF), TNF-α, TNF-β, TNF receptor I, TNF receptor II, TNIL-1, 45 TPO, VEGF, VEGF receptor 1, VEGF receptor 2, VEGF receptor 3, GCP-2, GRO/MGSA, GRO-B, GRO-y, HCC1, 1-309, HER 1, HER 2, HER 3 and HER 4, CD4, human chemokine receptors CXCR4 or CCR5, non-structural protein type 3 (NS3) from the hepatitis C virus, TNF-alpha, IgE, 50 IFN-gamma, MMP-12, CEA, H. pylori, TB, influenza, Hepatitis E, MMP-12, internalizing receptors that are overexpressed on certain cells, such as the epidermal growth factor receptor (EGFR), ErBb2 receptor on tumor cells, an internalising cellular receptor, LDL receptor, FGF2 receptor, 55 ErbB2 receptor, transferrin receptor, PDGF receptor, VEGF receptor, PsmAr, an extracellular matrix protein, elastin, fibronectin, laminin, α 1-antitrypsin, tissue factor protease inhibitor, PDK1, GSK1, Bad, caspase-9, Forkhead, an antigen of Helicobacter pylori, an antigen of Mycobacterium 60 tuberculosis, and an antigen of influenza virus. It will be appreciated that this list is by no means exhaustive.

In one embodiment, the multispecific ligand comprises an anti-SA dAb variant of the invention and an anti-TNFR1 binding moiety, eg, an anti-TNFR1 dAb. Optionally, the 65 ligand has only one anti-TNFR1 binding moiety (eg, dAb) to reduce the chance of receptor cross-linking. In one

embodiment, the anti-SA dAb variant is DOM7h-11-3 or DOM7h-11-15 or DOM7h-11-15 S12P .

In one embodiment, the anti-TNFR1 binding moiety is DOM1h-131-206 disclosed in WO2008149148 (the amino acid sequence of which and the nucleotide sequence of which, as disclosed in that PCT application, are expressly incorporated herein by reference as though explicitly written herein and for use with the present invention, and it is contemplated that any part of such disclosure can be incorporated into one or more claims herein). In one embodiment, the multispecific ligand comprises or consists of the amino acid sequence of DOM1h-131-206 and the amino acid sequence of DOM7h-11-3 or DOM7h-11-15 or DOM7h-11- 15^{S12P} .

In one embodiment, the anti-TNFR1 binding moiety or dAb is any such moiety or dAb disclosed in co-pending application U.S. Ser. No. 61/153,746, the disclosure of which is incorporated herein by reference. In one embodiment, the anti-TNFR1 binding moiety comprises an amino acid sequence that is at least 95% identical to the amino acid sequence of DOM1h-574-156, DOM1h-574-72, DOM1h-574-109, DOM1h-574-138, DOM1h-574-162 or DOM1h-574-180 or the amino acid sequence of any anti-TNFR1 dAb disclosed in Table 3. In one embodiment, the multispecific ligand comprises or consists of the amino acid sequence of DOM1h-574-156 and the amino acid sequence of DOM7h-11-15^{S12P}.

In one embodiment, the ligand of the invention is a fusion protein comprising a variant of the invention fused directly or indirectly to one or more polypeptides. For example, the fusion protein can be a "drug fusion" as disclosed in WO2005/118642 (the disclosure of which is incorporated herein by reference), comprising a variant of the invention and a polypeptide drug as defined in that PCT application.

As used herein, "drug" refers to any compound (e.g., small organic molecule, nucleic acid, polypeptide) that can be administered to an individual to produce a beneficial, therapeutic or diagnostic effect through binding to and/or altering the function of a biological target molecule in the individual. The target molecule can be an endogenous target molecule encoded by the individual's genome (e.g. an enzyme, receptor, growth factor, cytokine encoded by the individual's genome) or an exogenous target molecule encoded by the genome of a pathogen (e. g. an enzyme encoded by the genome of a virus, bacterium, fungus, nematode or other pathogen). Suitable drugs for use in fusion proteins and conjugates comprising an anti-SA dAb variant of the invention are disclosed in WO2005/118642 and WO2006/059106 (the entire disclosures of which are incorporated herein by reference, and including the entire list of specific drugs as though this list were expressly written herein, and it is contemplated that such incorporation provides disclosure of specific drugs for inclusion in claims herein). For example, the drug can be glucagon-like peptide 1 (GLP-1) or a variant, interferon alpha 2b or a variant or exendin-4 or a variant.

In one embodiment, the invention provides a drug conjugate as defined and disclosed in WO2005/118642 and WO2006/059106, wherein the conjugate comprises a variant of the invention. In one example, the drug is covalently linked to the variant (eg, the variant and the drug are expressed as part of a single polypeptide). Alternatively, in an example, the drug is non-covalently bonded or associated with the variant. The drug can be covalently or noncovalently bonded to the variant directly or indirectly (e.g., through a suitable linker and/or noncovalent binding of complementary binding partners (e.g., biotin and avidin)).

When complementary binding partners are employed, one of the binding partners can be covalently bonded to the drug directly or through a suitable linker moiety, and the complementary binding partner can be covalently bonded to the variant directly or through a suitable linker moiety. When 5 the drug is a polypeptide or peptide, the drug composition can be a fusion protein, wherein the polypeptide or peptide, drug and the polypeptide binding moiety are discrete parts (moieties) of a continuous polypeptide chain. As described herein, the polypeptide binding moieties and polypeptide drug moieties can be directly bonded to each other through a peptide bond, or linked through a suitable amino acid, or peptide or polypeptide linker.

A ligand which contains one single variable domain (monomer) variant of the invention or more than one single 15 variable domain (multimer, fusion protein, conjugate, and dual specific ligand as defined herein) which specifically binds to serum albumin, can further comprise one or more entities selected from, but preferably not limited to a label, a tag, an additional single variable domain, a dAb, an 20 antibody, an antibody fragment, a marker and a drug. One or more of these entities can be located at either the COOH terminus or at the N terminus or at both the N terminus and the COOH terminus of the ligand comprising the single variable domain, (either immunoglobulin or non-immuno- 25 globulin single variable domain). One or more of these entities can be located at either the COOH terminus, or the N terminus, or both the N terminus and the COOH terminus of the single variable domain which specifically binds serum albumin of the ligand which contains one single variable 30 domain (monomer) or more than one single variable domains (multimer, fusion protein, conjugate, and dual specific ligand as defined herein). Non-limiting examples of tags which can be positioned at one or both of these termini include a HA, his or a myc tag. The entities, including one 35 or more tags, labels and drugs, can be bound to the ligand which contains one single variable domain (monomer) or more than one single variable domain (multimer, fusion protein, conjugate, and dual specific ligand as defined herein), which binds serum albumin, either directly or 40 through linkers as described above.

An aspect of the invention provides a fusion product, eg, a fusion protein or fusion with a peptide or conjugate with an NCE (new chemical entity) drug, comprising a polypeptide drug fused or conjugated (for an NCE) to any variant as 45 described above, optionally wherein the variant is DOM7h-11-15 or DOM7h-11-15^{S12P} (or a variant having an amino acid that is at least 95, 96, 97, 98 or 99% identical to the amino acid sequence of DOM7h-11-15 or DOM7h-11- 15^{S12P}) or DOM7h-11-12 (or a variant having an amino acid 50 that is at least 95, 96, 97, 98 or 99% identical to the amino acid sequence of DOM7h-11-15 or DOM7h-11-15^{S12P}). DOM7h-11-15, DOM7h-11-15^{S12P} and DOM7h-11-12 give only a modest drop in affinity when fused or conjugated to partner, making them useful in fusion products. 55

The invention provides a composition comprising a variant, fusion protein, conjugate or ligand of any aspect of the invention and a pharmaceutically acceptable diluent, carrier, excipient or vehicle.

Also encompassed herein is an isolated nucleic acid 60 encoding any of the variants, fusion proteins, conjugates or ligands described herein, e.g., a ligand which contains one single variable domain (monomer) variant of the invention or more than one single variable domain (e.g., multimer, fusion protein, conjugate, and dual specific ligand as defined 65 herein) variant which specifically binds to serum albumin, or which specifically binds both human serum albumin and at

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least one non-human serum albumin, or functionally active fragments thereof. Also encompassed herein is a vector and/or an expression vector, a host cell comprising the vector, e.g., a plant or animal cell and/or cell line transformed with a vector, a method of expressing and/or producing one or more variants, fusion proteins or ligands which contains one single variable domain (monomer) variant or more than one single variable domain variants (e.g., multimer, fusion protein, conjugate, and dual specific ligand as defined herein) which specifically binds to serum albumin, or fragment(s) thereof encoded by said vectors, including in some instances culturing the host cell so that the one or more variants, fusion proteins or ligands or fragments thereof are expressed and optionally recovering the ligand which contains one single variable domain (monomer) or more than one single variable domain (e.g., multimer, fusion protein, conjugate, and dual specific ligand as defined herein) which specifically binds to serum albumin, from the host cell culture medium. Also encompassed are methods of contacting a ligand described herein with serum albumin, including serum albumin and/or non-human serum albumin(s), and/or one or more targets other than serum albumin, where the targets include biologically active molecules, and include animal proteins, cytokines as listed above, and include methods where the contacting is in vitro as well as administering any of the variants, fusion proteins or ligands described herein to an individual host animal or cell in vivo and/or ex vivo. Preferably, administering ligands described herein which comprises a single variable domain (immunoglobulin or non-immunoglobulin) directed to serum albumin and/or non-human serum albumin(s), and one or more domains directed to one or more targets other than serum albumin, will increase the half life, including the T beta and/or terminal half life, of the anti-target ligand. Nucleic acid molecules encoding the variants, fusion proteins or single domain containing ligands or fragments thereof, including functional fragments thereof, are contemplated herein. Vectors encoding the nucleic acid molecules, including but preferably not limited to expression vectors, are contemplated herein, as are host cells from a cell line or organism containing one or more of these expression vectors. Also contemplated are methods of producing any variant, fusion protein or ligand, including, but preferably not limited to any of the aforementioned nucleic acids, vectors and host cells.

An aspect of the invention provides a nucleic acid comprising a nucleotide sequence encoding a variant according to the invention or a multispecific ligand of the invention or fusion protein of the invention.

An aspect of the invention provides a nucleic acid comprising the nucleotide sequence of a DOM7h-11 variant selected from DOM7h-11-3, DOM7h-11-15, DOM7h-11-15^{S12P}, DOM7h-11-12, DOM7h-11-18 and DOM7h-11-19 or a nucleotide sequence that is at least 70, 75, 80, 85, 90, 95, 96, 97, 98 or 99% identical to said selected sequence.

An aspect of the invention provides a vector comprising the nucleic acid of the invention. An aspect of the invention provides an isolated host cell comprising the vector.

Reference is made to WO2008/096158 for details of library vector systems, combining single variable domains, characterization of dual specific ligands, structure of dual specific ligands, scaffolds for use in constructing dual specific ligands, uses of anti-serum albumin dAbs and multispecific ligands and half-life-enhanced ligands, and compositions and formulations of comprising anti-serum albumin dAbs. These disclosures are incorporated herein by reference to provide guidance for use with the present invention,

including for variants, ligands, fusion proteins, conjugates, nucleic acids, vectors, hosts and compositions of the present invention.

DOM7h-14 variant sequences, which are not according the invention, are disclosed in a co-pending US provision patent application entitled IMPROVED ANTI-SERU ALBUMIN BINDING VARIANTS, filed on the same day the present application. These sequences of DOM7hvariants (SEQ ID NO:s 1-10 in the co-pending application are incorporated herein by reference as though explicit written herein.

Sequences

TABLE 1

Amino	Acid	Sequences	of	DOM7h-11	Variant	dAbs
1 100 110	11010	begaeneeb	<u> </u>	DOU/UL TT	tar ranc	an mon

DOM7h-11-12 (SEQ ID NO: 1) DIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLIL

GSRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFG

GTKVEIKR

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TABLE	1-cont	cinu	ed

un		Amino Acid Sequences of DOM7h-11 Variant dAbs
to nal	5	DOM7h-11-15 (SEQ ID NO: 2) DIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLILA
М		FSRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQ
as 14		GTKVEIKR
on) tly	10	DOM7h-11-18 (SEQ ID NO: 3) DIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLIWF
		${\tt GSRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYHCAQAGTHPTTFGQ}$
		GTKVEIKR
	15	DOM7h-11-19 (SEQ ID NO: 4) DIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLILF
		${\tt GSRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQTGTHPTTFGQ}$
-	20	GTKVEIKR
F O		DOM7h-11-3 (SEQ ID NO: 5) DIQMTQSPSSLSASVGDRVTITCRASRPIGTTLSWYQQKPGKAPKLLILW
×		${\tt NSRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQ}$
	25	GTKVEIKR

TABLE 2

ATCCTACGAC GTTCGGCCAA GGGACCAAGG TGGAAATCAA ACGG

ATCCTACGAC GTTCGGCCAA GGGACCAAGG TGGAAATCAA ACGG

ATCCTACGAC GTTCGGCCAA GGGACCAAGG TGGAAATCAA ACGG

DOM7h-11-12 (SEQ ID NO: 6)

DOM7h-11-15 (SEQ ID NO: 7)

DOM7h-11-18 (SEQ ID NO: 8)

DOM7h-11-19 (SEQ ID NO: 9)

Nucleotide Sequences of DOM7h-11 Variant dAbs

GACATCCAGA TGACCCAGTC TCCATCCTCC CTGTCTGCAT CTGTAGGAGA CCGTGT CACC ATCACTTGCC GGGCAAGTCG TCCGATTGGG ACGATGTTAA GTTGGTACCA GC AGAAACCA GGGAAAGCCC CTAAGCTCCT GATCTTGTTT GGTTCCCGGT TGCAAAGT GG GGTCCCATCA CGTTTCAGTG GCAGTGGATC TGGGACAGAT TTCACTCTCA CCAT CAGCAG TCTGCAACCT GAAGATTTTG CTACGTACTA CTGTGCGCAG GCTGGGACGC

GACATCCAGA TGACCCAGTC TCCATCCTCC CTGTCTGCAT CTGTAGGAGA CCGTGT CACC ATCACTTGCC GGGCAAGTCG TCCGATTGGG ACGATGTTAA GTTGGTACCA GC AGAAACCA GGGAAAGCCC CTAAGCTCCT GATCCTTGCT TTTTCCCGTT TGCAAAGT GG GGTCCCATCA CGTTTCAGTG GCAGTGGATC TGGGACAGAT TTCACTCTCA CCAT CAGCAG TCTGCAACCT GAAGATTTTG CTACGTACTA CTGCGCGCAG GCTGGGACGC

GACATCCAGA TGACCCAGTC TCCATCCTCC CTGTCTGCAT CTGTAGGAGA CCGTGT CACC ATCACTTGCC GGGCAAGTCG TCCGATTGGG ACGATGTTAA GTTGGTACCA GC AGAAACCA GGGAAAGCCC CAAAGCTCCT GATCTGGTTT GGTTCCCGGT TGCAAAGT GG GGTCCCATCA CGTTTCAGTG GCAGTGGATC TGGGACAGAT TTCACTCTCA CCAT CAGCAG TCTGCAACCT GAAGATTTTG CTACGTACCA CTGTGCGCAG GCGGGGACGC

GACATCCAGA TGACCCAGTC TCCATCCTCC CTGTCTGCAT CTGTAGGAGA CCGTGT CACC ATCACTTGCC GGGCAAGTCG TCCGATTGGG ACGATGTTAA GTTGGTACCA GC

TABLE 2-continued

Nucleotide Sequences of DOM7h-11 Variant dAbs
AGAAACCA GGGAAAGCCC CTAAGCTCCT GATCTTGTTT GGTTCCCGGT TGCAAAGT
GG GGTCCCATCA CGTTTCAGTG GCAGTGGATC TGGGACGGAT TTCACTCTCA CCAT
CAGCAG TCTGCAACCT GAAGATTTTG CTACGTACTA CTGTGCGCAG ACTGGGACGC
ATCCCACGAC GTTCGGCCAA GGGACCAAGG TGGAAATCAA ACGG
DOM7h-11-3 (SEQ ID NO: 10) GACATCCAGA TGACCCAGTC TCCATCCTCC CTGTCTGCAT CTGTAGGAGA CCGTGT
CACC ATCACTTGCC GGGCAAGTCG TCCGATTGGG ACGACGTTAA GTTGGTACCA GC
AGAAACCA GGGAAAGCCC CTAAGCTCCT GATCCTTTGG AATTCCCGTT TGCAAAGT
GG GGTCCCATCA CGTTTCAGTG GCAGTGGATC TGGGACAGAT TTCACTCTCA CCAT
CAGCAG TCTGCAACCT GAAGATTTTG CTACGTACTA CTGTGCGCAG GCTGGGACGC
ATCCTACGAC GTTCGGCCAA GGGACCAAGG TGGAAATCAA ACGG
TABLE 3
Amino Acid Sequences of anti-TNFR1 dAbs
>DOM1h-509 (SEQ ID NO: 11) EVQLLESGGGLVQPGGSLRLSCAASGFTFSQYRMHWVRQAPGKSLEWVSSIDTRGSST
YYADPVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKAVTMFSPFFDYWGQGTLV
TVSS
>DOM1h-510 (SEQ ID NO: 12) EVQLLESGGGLVQPGGSLRLSCAASGFTFADYGMRWVRQAPGKGLEWVSSITRTGRVT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKWRNRHGEYLADFDYWGQG

TLVTVSS

>DOM1h-543 (SEQ ID NO: 13) EVQLLESGGGLVQPGGSLRLSCAASGFTFMRYRMHWVRQAPGKGLEWVSSIDSNGSST

 $\verb|YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDRTERSPVFDYWGQGTLV||$

EVQLLESGGGLVQPGGSLRLSCAASGFTFVDYEMHWVRQAPGKGLEWVSSISESGTTT $\verb|YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKRRFSASTFDYWGQGTLVT||$

 ${\tt EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGGHT}$ $\verb|YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKYTGHwePFDYwGQGTLVT||$

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGGHT YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKYTGRWEPYDYWGQGTLVT

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGGHT $\verb|YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKYTGRWEPFDYWGQGTLVT||$

TVSS

VSS

VSS

VSS

VSS

>DOM1h-549 (SEQ ID NO: 14)

>DOM1h-574 (SEQ ID NO: 15)

>DOM1h-574-1 (SEQ ID NO: 16)

>DOM1h-574-2 (SEQ ID NO: 17)

 $\verb|YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT||$

>DOM1h-574-17 (SEQ ID NO: 28) ${\tt EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISNTGDHT}$

VSS

YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT

>DOM1h-574-16 (SEQ ID NO: 27) EVOLLESGGGLVOPGGSLRLSCAASGFTFVKYSMGWVROAPGKGPEWVSOISNTGDRT

VSS

YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT

>DOM1h-574-15 (SEQ ID NO: 26) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDHT

VSS

YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT

>DOM1h-574-14 (SEQ ID NO: 25) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRT

VSS

 $\verb|YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKYTGRWEPFDYWGQGTLVT||$

>DOM1h-574-13 (SEQ ID NO: 24) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRT

VSS

 $\verb|YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKYTGRWEPFDYWGQGTLVT||$

>DOM1h-574-12 (SEQ ID NO: 23) ${\tt EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDHT}$

VSS

 $\verb|YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKYTGRWEPFDHWGQGTLVT|| \\$

>DOM1h-574-11 (SEQ ID NO: 22) ${\tt EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGGHT}$

VSS

YYADSVKGRFTI SRDNSKNTLYLOMNSLRAEDTAVYYCAI YTGRWEPFDYWGOGTLVT

>DOM1h-574-10 (SEQ ID NO: 21) ${\tt EVQLLESGGGLVQPGGSLRLSCAASGFTFGKYSMGWVRQAPGKDLEWVSQISNTGGHT}$

VSS

VSS

YYADSVKGRFTISRDNSKNTLYMQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT

>DOM1h-574-9 (SEO ID NO: 20) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGGHT

VSS

YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT

19

TABLE 3-continued Amino Acid Sequences of anti-TNFR1 dAbs

>DOM1h-574-7 (SEQ ID NO: 18)

>DOM1h-574-8 (SEQ ID NO: 19) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISNTGGHT

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGGHT YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT

YYADSVKGRFTISRDNSKNSLYLQMNSLRAEDTAVYYCAIYTGRWVPFDNWGQGTLVT

>DOM1h-574-33 (SEQ ID NO: 39) ${\tt EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRT}$

VSS

YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT

>DOM1h-574-32 (SEQ ID NO: 38) EVOLLESGGGLVOPGGSLRLSCAASGFTFVKYSMGWVROAPGKGLEWVSOISNTGDRT

VSS

YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFNYWGQGTLVT

>DOM1h-574-31 (SEQ ID NO: 37) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTADRT

VSS

YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAAYYCAIYTGRWEPFDYWGQGTLVT

>DOM1h-574-30 (SEQ ID NO: 36) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTGDRR

VSS

YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWRPFEYWGQGTLVT

>DOM1h-574-29 (SEQ ID NO: 35) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRT

VSS

YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT

>DOM1h-574-28 (SEQ ID NO: 34) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRT

VSS

 $\verb|YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWKPFEYWGQGTLVT|| \\$

>DOM1h-574-27 (SEQ ID NO: 33) ${\tt EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRT$

VSS

YYADSVKGRFTI SRDNSKNTLYLOMNSLRAEDTAVYYCAI YTGRWEPFEYWGOGTLVT

>DOM1h-574-26 (SEQ ID NO: 32) ${\tt EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRT$

VSS

YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT

>DOM1h-574-25 (SEO ID NO: 31) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRT

VSS

VSS

YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT

>DOM1h-574-18 (SEQ ID NO: 29)

EVQLLESGGGLVQPGGSLRLSCAASGFTFGKYSMGWVRQAPGKDLEWVSQISNTGDHT

21

TABLE 3-continued Amino Acid Sequences of anti-TNFR1 dAbs

>DOM1h-574-19 (SEQ ID NO: 30)

EVQLLESGGGLVQPGGSLRLSCAASGFTFGKYSMGWVRQAPGKDLEWVSQISNTGDRT YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT 22

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 $\verb|YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT||$

>DOM1h-574-67 (SEQ ID NO: 50) ${\tt EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTGDRR}$

VSS

YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWKPFEYWGQGTLVT

>DOM1h-574-66 (SEQ ID NO: 49) EVOLLESGGGLVOPGGSLRLSCAASGFTFVKYSMGWVROAPGKGLEWVSOIANTGDRR

VSS

YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT

>DOM1h-574-65 (SEQ ID NO: 48) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTGDRR

VTS

YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPYEYWGQGTLVT

>DOM1h-574-54 (SEQ ID NO: 47) EVQLLESGGGLVQPGGSLRLSCAASGFTFVNYSMGWVRQAPGKGLEWVSQISNTGDRT

VSS

 $\verb|YADSVKGRFTISRDNPKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFEYWGQGTLVT||$

>DOM1h-574-53 (SEQ ID NO: 46) EVQLLESGGGLVQPGGSLRLSCAASGFTFSKYSMGWVRQAPGKGLEWVSQISNTGERR

VSS

 $\verb|YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFKYWGQGTLVT||$

>DOM1h-574-40 (SEQ ID NO: 45) ${\tt EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRT$

VSS

 $\verb|YADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT|| \\$

>DOM1h-574-39 (SEQ ID NO: 44) ${\tt EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRR}$

VSS

YYDDSVKGRFTI SRDNSKNTLYLOMNSLRAEDTAVYYCAI YTGRWEPFDYWGOGTLVT

>DOM1h-574-38 (SEQ ID NO: 43) ${\tt EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTGDRR}$

VSS

YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT

>DOM1h-574-37 (SEQ ID NO: 42) EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISNTGDRT

VSS

YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT

VSS

>DOM1h-574-35 (SEQ ID NO: 40)

>DOM1h-574-36 (SEQ ID NO: 41)

EVQLLESGGGLVQPGGSLRLSCAASGFTFGKYSMGWVRQAPGKGLEWVSQISNTGDRT

23

TABLE 3-continued Amino Acid Sequences of anti-TNFR1 dAbs

EVQLLESGGGLVQPGGSLRLSCAASGFTFITYSMGWVRQAPGKGLEWVSQISNTGDRT YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFQYWGQGTLVT

 $\verb|YYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWRPFEYWGQGTLVT||$

>DOM1h-574-78 (SEQ ID NO: 61) ${\tt EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTGDRR}$

VSS

YYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT

>DOM1h-574-77 (SEQ ID NO: 60) EVOLLESGGGLVOPGGSLRLSCAASGFTFVKYSMGWVROAPGKGLEWVSOISDTGDRR

VSS

YYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWKPFEYWGQGTLVT

>DOM1h-574-76 (SEQ ID NO: 59) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTGDRR

VSS

YYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT

>DOM1h-574-75 (SEQ ID NO: 58) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTGDRR

VSS

YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT

>DOM1h-574-74 (SEQ ID NO: 57) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTADRT

VSS

YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWRPFEYWGQGTLVT

>DOM1h-574-73 (SEQ ID NO: 56) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTADRT

VSS

 ${\tt YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT}$

>DOM1h-574-72 (SEQ ID NO: 55) ${\tt EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTADRT}$

VSS

YYAHSVKGRFTI SRDNSKNTLYLOMNSLRAEDTAVYYCAI YTGRWKPFEYWGOGTLVT

>DOM1h-574-71 (SEQ ID NO: 54) ${\tt EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTADRT}$

VSS

YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAVYTGRWEPFVYWGQGTLVT

>DOM1h-574-70 (SEO ID NO: 53) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTADRT

VSS

YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTGDRR

>DOM1h-574-69 (SEQ ID NO: 52)

VSS

YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWRPFEYWGQGTLVT

25

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTGDRR

Amino Acid Sequences of anti-TNFR1 dAbs >DOM1h-574-68 (SEQ ID NO: 51)

TABLE 3-continued

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 $\verb|YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAAYYCAIYTGRWPDFDYWGQGTLVT||$

>DOM1h-574-94 (SEQ ID NO: 72) ${\tt EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTGDRR}$

VSS

YYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT

>DOM1h-574-93 (SEQ ID NO: 71) ${\tt EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISDTGDRR}$

VSS

YYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT

>DOM1h-574-92 (SEQ ID NO: 70) EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTGDRR

VSS

YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT

>DOM1h-574-91 (SEQ ID NO: 69) EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISNTADRT

VSS

YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT

>DOM1h-574-90 (SEQ ID NO: 68) EVQLLESGGGLVQPGGSLRLSCAASGFTFLKFSMGWVRQAPGKGLEWVSQIANTGDRR

VSS

YYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT

>DOM1h-574-88 (SEQ ID NO: 67) ${\tt EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRR}$

VSS

 $\verb|YADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWRPFEYWGQGTLVT|| \\$

>DOM1h-574-87 (SEQ ID NO: 66) ${\tt EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRR}$

VSS

YYADAVKGRFTI SRDNSKNTLYLOMNSLRAEDTAVYYCAI YTGRWVPFEYWGOGTLVT

>DOM1h-574-86 (SEQ ID NO: 65) ${\tt EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRR}$

VSS

YYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWKPFEYWGQGTLVT

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRR

YYADAVKGRFTI SRDNSKNTLYLQMNSLRAEDTAVYYCAI YTGRWEPFVYWGQGTLVT

>DOM1h-574-85 (SEO ID NO: 64)

VSS

>DOM1h-574-79 (SEQ ID NO: 62)

>DOM1h-574-84 (SEQ ID NO: 63)

VSS

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRR

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TABLE 3-continued Amino Acid Sequences of anti-TNFR1 dAbs

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTGDRR YYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT

 $\verb|YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT||$

>DOM1h-574-105 (SEQ ID NO: 83) ${\tt EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISETGRRT}$

VSS

YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT

>DOM1h-574-104 (SEQ ID NO: 82) EVOLLESGGGLVOPGGSLRLSCAASGFTFVKYSMGWVROAPGKGPEWVSOISDKGTRT

VSS

YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT

>DOM1h-574-103 (SEQ ID NO: 81) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISDGGTRT

VSS

YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT

>DOM1h-574-102 (SEQ ID NO: 80) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISDSGYRT

VSS

 ${\tt YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT}$

>DOM1h-574-101 (SEQ ID NO: 79) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISDGGQRT

VSS

 $\verb|YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT||$

>DOM1h-574-100 (SEQ ID NO: 78) ${\tt EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISAWGDRT$

VSS

 $\verb|YYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWPDFEYWGQGTLVT|| \\$

>DOM1h-574-99 (SEQ ID NO: 77) ${\tt EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTGDRR}$

VSS

YYDDSVKGRFTI SRDNSKNTLYLOMNSLRAEDTAVYYCAI YTGRWPDFDYWGOGTLVT

>DOM1h-574-98 (SEQ ID NO: 76) ${\tt EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTGDRR}$

VSS

YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWPDFEYWGQGTLVT

>DOM1h-574-97 (SEQ ID NO: 75) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTADRT

VSS

YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWPDFDYWGQGTLVT

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTADRT

YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAAYYCAIYTGRWPDFEYWGQGTLVT VSS

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTGDRR

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>DOM1h-574-95 (SEQ ID NO: 73)

>DOM1h-574-96 (SEQ ID NO: 74)

TABLE 3-continued Amino Acid Sequences of anti-TNFR1 dAbs

 $\verb|YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT||$

>DOM1h-574-116 (SEQ ID NO: 94) ${\tt EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRR}$

VSS

YYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT

>DOM1h-574-115 (SEQ ID NO: 93) EVOLLESGGGLVOPGGSLRLSCAASGFTFVKYSMGWVROAPGKGLEWVSOISNTADRT

VSS

YYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT

>DOM1h-574-114 (SEQ ID NO: 92) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQILNTADRT

VSS

YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT

>DOM1h-574-113 (SEQ ID NO: 91) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTADRR

VSS

YYTHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT

>DOM1h-574-112 (SEQ ID NO: 90) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRT

VSS

YYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWRPFEYWGQGTLVT

>DOM1h-574-111 (SEQ ID NO: 89) ${\tt EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRT}$

VSS

 ${\tt YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT}$

>DOM1h-574-110 (SEQ ID NO: 88) ${\tt EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRT}$

VSS

YYAHSVKGRFTI SRDNSKNTLYLOMNSLRAEDTAVYYCAI YTGRWVPFEYWGOGTLVT

>DOM1h-574-109 (SEO ID NO: 87) EVOLLESGGGLVOPGGSLRLSCAASGFTFVKYSMGWVROAPGKGLEWVSOISDTADRT

VSS

YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT

>DOM1h-574-108 (SEO ID NO: 86) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISNTADRT

VSS

YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISNTADRT

>DOM1h-574-107 (SEQ ID NO: 85)

VSS

YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT

31

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQINNTGSTT

>DOM1h-574-106 (SEQ ID NO: 84)

Amino Acid Sequences of anti-TNFR1 dAbs

TABLE 3-continued

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 $\verb|YYAHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT||$

>DOM1h-574-127 (SEQ ID NO: 105) ${\tt EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTADRR}$

VSS

YYAHAVKGRFTI SRDNSKNTLYLQMNSLRAEDTAVYYCAI YTGRWEPFVYWGQGTLVT

>DOM1h-574-126 (SEQ ID NO: 104) EVOLLESGGGLVOPGGSLRLSCAASGFTFVKYSMGWVROAPGKGLEWVSOIANTGDRR

VSS

YYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT

>DOM1h-574-125 (SEQ ID NO: 103) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTADRR

VSS

YYAHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT

>DOM1h-574-124 (SEQ ID NO: 102) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRR

VSS

 $\verb|YADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT||$

>DOM1h-574-123 (SEQ ID NO: 101) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTADRR

VSS

YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT

>DOM1h-574-122 (SEQ ID NO: 100) ${\tt EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTADRR}$

VSS

 $\verb|YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCALYTGRWVPFEYWGQGTLVT|| \\$

>DOM1h-574-121 (SEQ ID NO: 99) ${\tt EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTADRT}$

VSS

YYAHSVKGRFTI SRDNSKNTLYLOMNSLRAEDTAVYYCAVYTGRWVPFEYWGOGTLVT

>DOM1h-574-120 (SEO ID NO: 98) EVOLLESGGGLVOPGGSLRLSCAASGFTFVKYSMGWVROAPGKGLEWVSOISNTADRT

VSS

YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCALYTGRWVSFEYWGQGTLVT

>DOM1h-574-119 (SEO ID NO: 97) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTADRT

VSS

YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAVYTGRWVSFEYWGQGTLVT

VSS

>DOM1h-574-118 (SEQ ID NO: 96) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTADRT

>DOM1h-574-117 (SEQ ID NO: 95) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRR

YYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT

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Amino Acid Sequences of anti-TNFR1 dAbs

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 $\verb|YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT||$

>DOM1h-574-139 (SEQ ID NO: 116) ${\tt EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISDTADRT$

VSS

YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT

>DOM1h-574-138 (SEQ ID NO: 115) EVOLLESGGGLVOPGGSLRLSCAASGFTFFKYSMGWVROAPGKGLEWVSOISDTADRT

VSS

YYTDAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT

>DOM1h-574-137 (SEQ ID NO: 114) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRT

VSS

YYTHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT

>DOM1h-574-135 (SEQ ID NO: 113) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRT

VSS

YYSHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT

>DOM1h-574-134 (SEQ ID NO: 112) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRT

VSS

YYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT

>DOM1h-574-133 (SEQ ID NO: 111) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRT

VSS

 $\verb|YYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWRPFEYWGQGTLVT||$

>DOM1h-574-132 (SEQ ID NO: 110) ${\tt EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRT}$

VSS

YYDHSVKGRFTI SRDNSKNTLYLOMNSLRAEDTAVYYCAI YTGRWAPFEYWGOGTLVT

>DOM1h-574-131 (SEO ID NO: 109) ${\tt EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRT}$

VSS

YYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT

>DOM1h-574-130 (SEO ID NO: 108) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTGDRR

VSS

VSS

YYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT

>DOM1h-574-128 (SEQ ID NO: 106)

>DOM1h-574-129 (SEQ ID NO: 107) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIVNTGDRR

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TABLE 3-continued Amino Acid Sequences of anti-TNFR1 dAbs

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTADRR YYAHAVKGRFTI SRDNSKNTLYLQMNSLRAEDTAVYYCAI YTGRWEPFVYWGQGTLVT

>DOM1h-574-150 (SEQ ID NO: 127) ${\tt EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRT$

VSS

YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWGPFQYWGQGTLVT

>DOM1h-574-149 (SEQ ID NO: 126) EVOLLESGGGLVOPGGSLRLSCAASGFTFVKYSMGWVROAPGKGLEWVSOISDTADRT

VSS

YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFAYWGQGTLVT

>DOM1h-574-148 (SEQ ID NO: 125) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRT

VSS

YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWGPFVYWGQGTLVT

>DOM1h-574-147 (SEQ ID NO: 124) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRT

VSS

 $\verb|YVDDAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT||$

>DOM1h-574-146 (SEQ ID NO: 123) EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQIADTGDRR

VSS

 $\verb|YYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT||$

>DOM1h-574-145 (SEQ ID NO: 122) ${\tt EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQIADTGDRR}$

VSS

>DOM1h-574-144 (SEQ ID NO: 121) ${\tt EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQIADTADRR}$

VSS

YYDDAVKGRFTI SRDNSKNTLYLOMNSLRAEDTAVYYCAI YTGRWEPFVYWGOGTLVT

>DOM1h-574-143 (SEO ID NO: 120) ${\tt EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTGDRR}$

VSS

YYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT

EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTGDRR

>DOM1h-574-142 (SEO ID NO: 119)

VSS

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TABLE 3-continued Amino Acid Sequences of anti-TNFR1 dAbs

YYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT

VSS

EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTADRR

>DOM1h-574-140 (SEQ ID NO: 117)

>DOM1h-574-141 (SEQ ID NO: 118)

EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQIADTGDRR YYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT

>DOM1h-574-161 (SEQ ID NO: 138) ${\tt EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISDTADRT$

VSS

YYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT

>DOM1h-574-160 (SEQ ID NO: 137) EVOLLESGGGLVOPGGSLRLSCAASGFTFLKYSMGWVROAPGKGLEWVSOISDTADRT

VSS

YYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT

>DOM1h-574-159 (SEQ ID NO: 136) EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTADRT

VSS

YYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWRPFEYWGQGTLVT

>DOM1h-574-158 (SEQ ID NO: 135) EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTADRT

VSS

YYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWRPFEYWGQGTLVT

>DOM1h-574-157 (SEQ ID NO: 134) EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISDTADRT

VSS

YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT

>DOM1h-574-156 (SEQ ID NO: 133) ${\tt EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTADRT}$

VSS

 ${\tt YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT}$

>DOM1h-574-155 (SEQ ID NO: 132) ${\tt EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISDTADRT}$

VSS

YYDHSVKGRFTI SRDNSKNTLYLOMNSLRAEDTAVYYCAI YTGRWAPFEYWGOGTLVT

>DOM1h-574-154 (SEO ID NO: 131) ${\tt EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTGDRR}$

VSS

YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFQYWGQGTLVT

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRT

>DOM1h-574-153 (SEO ID NO: 130)

VSS

YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFQYWGQGTLVT

>DOM1h-574-152 (SEQ ID NO: 129) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRT

>DOM1h-574-151 (SEQ ID NO: 128)

39

YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRT

TABLE 3-continued Amino Acid Sequences of anti-TNFR1 dAbs

VSS

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YYAHSVKGRFTISRDNSKNTLYLOMNSLRAEDTAVYYCAIYTGRWAPFEYWGOGTLVT

>DOM1h-574-173 (SEQ ID NO: 149) ${\tt EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIADTADRR}$

VSS

YYDHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT

>DOM1h-574-172 (SEQ ID NO: 148) EVOLLESGGGLVOPGGSLRLSCAASGFTFVKYSMGWVROAPGKGLEWVSOIADTADRT

VSS

YYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT

>DOM1h-574-171 (SEQ ID NO: 147) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIADTADRT

VSS

YYAHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT

>DOM1h-574-170 (SEQ ID NO: 146) EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTADRT

VSS

YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT

>DOM1h-574-169 (SEQ ID NO: 145) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIADTADRT

VSS

YYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT

>DOM1h-574-167 (SEQ ID NO: 144) ${\tt EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISDTGDRR}$

VSS

 $\verb|YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT||$

>DOM1h-574-166 (SEQ ID NO: 143) ${\tt EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISDTADRT}$

VSS

YYAHSVKGRFTI SRDNSKNTLYLOMNSLRAEDTAVYYCAI YTGRWAPFEYWGOGTLVT

>DOM1h-574-165 (SEO ID NO: 142) EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTADRT

VSS

YYTHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT

>DOM1h-574-164 (SEO ID NO: 141) EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISDTADRT

VSS

VSS

YYTHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT

EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTADRT

>DOM1h-574-163 (SEQ ID NO: 140)

TABLE 3-continued Amino Acid Sequences of anti-TNFR1 dAbs

YYSHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT

EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTADRT

41

>DOM1h-574-162 (SEQ ID NO: 139)

TABLE 3-continued

Amino Acid Sequences of anti-TNFR1 dAbs
>DOM1h-574-174 (SEQ ID NO: 150) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRR
$\verb YAHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT $
VSS
>DOM1h-574-175 (SEQ ID NO: 151) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIADTADRR
$\verb YAHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT $
VSS
>DOM1h-574-176 (SEQ ID NO: 152) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRR
YYDHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS
>DOM1h-574-177 (SEQ ID NO: 153) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIADTADRR
YYDHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
vss
>DOM1h-574-178 (SEQ ID NO: 154) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIADTADRR
$\verb YYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT $
VSS
>DOM1h-574-179 (SEQ ID NO: 155) EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTADRR
$\verb YYDDAVKGRFTITRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT $
VSS
>DOM1h-574-180 (SEQ ID NO: 156) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRT
YYAHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT
VSS
>DOM1h-574-4 (SEQ ID NO: 157) EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGGHT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKYTGRWEPFEYWGQGTLVT
VSS
>DOM1h-574-168 (SEQ ID NO: 158) EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTGDRR
YYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS
TARLE A
NUCLEOTIDE SEQUENCES OF ANTI-TNFKE GADS
>DOM1h-509 (SEQ ID NO: 417)

 ${\tt TCTCCTGTGCAGCCTCCGGATTCACCTTTAGTCAGTATAGGATGCATTGGGTCCGCCA$

 ${\tt GGCTCCAGGGAAGAGTCTAGAGTGGGTCTCAAGTATTGATACTAGGGGTTCGTCTACA}$

TACTACGCAGACCCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA

TABLE 4-continued Nucleotide sequences of anti-TNFR1 dAbs

CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC GAAAGCTGTGACGATGTTTTTCTCCCTTTTTTTGACTACTGGGGTCAGGGAACCCTGGTC ACCGTCTCGAGC >DOM1h-510 (SEQ ID NO: 418) GAGGTGCAGCTGTTGGAGTCTGGGGGGGGGGGGGCTTGGTACAGCCTGGGGGGGTCCCTGCGTC TCTCCTGTGCAGCCTCCGGATTCACCTTTGCTGATTATGGGATGCGTTGGGTCCGCCA GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCATCTATTACGCGGACTGGTCGTGTTACA TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC GAAATGGCGGAATCGGCATGGTGAGTATCTTGCTGATTTTGACTACTGGGGTCAGGGA ACCCTGGTCACCGTCTCGAGC >DOM1h-543 (SEQ ID NO: 159) GAGGTGCAGCTGTTGGAGTCTGGGGGGGGGGGGCTTGGTACAGCCTGGGGGGGTCCCTGCGTC TCTCCTGTGCAGCCTCCGGATTCACCTTTATGAGGTATAGGATGCATTGGGTCCGCCA TACTACGCAGACTCCGTGAAGGGCCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC ${\tt GAAAGATCGTACGGAGCGTTCGCCGGTTTTTGACTACTGGGGTCAGGGAACCCTGGTC$ ACCGTCTCGAGC >DOM1h-549 (SEQ ID NO: 160) TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTGATTATGAGATGCATTGGGTCCGCCA GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCATCTATTAGTGAGAGTGGTACGACGACA TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC GAAACGTCGTTTTTCTGCTTCTACGTTTGACTACTGGGGTCAGGGAACCCTGGTCACC GTCTCGAGC >DOM1h-574 (SEQ ID NO: 161) GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGGTCATACA TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC GAAATATACGGGTCATTGGGAGCCTTTTGACTACTGGGGTCAGGGAACCCTGGTCACC GTCTCGAGC >DOM1h-574-1 (SEQ ID NO: 162) GAGGTGCAGCTGTTGGAGTCTGGGGGGGGGGGCTTGGTACAGCCTGGGGGGGTCCCTGCGTC

CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC

TABLE 4-continued

Nucleotide sequences of anti-TNFR1 dAbs
GAAATATACGGGTCGTTGGGAGCCTTATGACTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC
>DOM1h-574-2 (SEQ ID NO: 163) GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGGG
TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGGTCATACA
TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GAAATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC
>DOM1h-574-4 (SEQ ID NO: 164) GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGGG
TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGGTCATACA
TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GAAATATACGGGTCGTTGGGAGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC
>DOM1h-574-180 (SEQ ID NO: 165) GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGGG
TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTACA
TACTACGCACACGCGGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGTGC
GATATATACTGGGCGTTGGGTGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC
>DOM1h-574-7 (SEQ ID NO: 166) GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGGG
TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGGTCATACA
TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC
>DOM1h-574-8 (SEQ ID NO: 167) GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGGG

TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGATGGGTCCGCCA GGCTCCAGGGAAAGGTCCAGAGTGGGTCTCACAGATTTCGAATACGGGTGGTCATACA TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA CGCTGTATCTGCAAATGAACAGCCTGCGGGGCCGAGGAACCCGCGGTATATTACTGTGC GATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTCAGGGAACCCTGGTCACA GTCTCGAGC TABLE 4-continued

Nucleotide sequences of anti-TNFR1 dAbs >DOM1h-574-9 (SEQ ID NO: 168) GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGGTCATACA TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATATCCCGCGACAATTCCAAGAACA CGCTGTATATGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC GATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTCAGGGAACCCTGGTCACC GTCTCGAGC >DOM1h-574-10 (SEO ID NO: 169) GAGGTGCAGCTGTTGGAGTCTGGGGGGGGGGGGCTTGGTACAGCCTGGGGGGGTCCCTGCGTC

GGCTCCAGGGAAGGATCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGGTCATACA TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC GATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTCAGGGAACCCTGGTCACC GTCTCGAGC >DOM1h-574-11 (SEQ ID NO: 170)

 ${\tt GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGGTCATACA}$ TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA ${\tt CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC}$ ${\tt GAAATATACGGGTCGTTGGGAGCCTTTTGACCACTGGGGTCAGGGGACCCTGGTCACC}$

>DOM1h-574-12 (SEQ ID NO: 171) GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGATCATACA TACTACGCAGACTCCGTGAAGGGCCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA ${\tt CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC}$ GAAATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTCAGGGAACCCTGGTCACC

GTCTCGAGC

GTCTCGAGC >DOM1h-574-13 (SEQ ID NO: 172) GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGATCGTACA ${\tt TACTACGCAGACTCCGTGAAGGGCCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA}$ ${\tt CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC}$ GAAATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTCAGGGAACCCTGGTCACC

GTCTCGAGC

>DOM1h-574-18 (SEQ ID NO: 177)

GTCTCGAGC

GTCTCGAGC

>DOMIh-574-15 (SEQ ID NO: 174) GAGGTGCAGCTGTTGGAGTCTGGGGGGGGGCTTGGTACAGCCTGGGGGGGCCCGCGCC TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGGTGGGGTCCGCCA GGCTCCAGGGAAGGGTCTAGAGTGGGGTCTCACAGATTCCGAATACCGGGTGATCATACA TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGGTATATTACTGTGC

GATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTCAGGGAACCCTGGTCACC

Nucleotide sequences of anti-TNFR1 dAbs

GTCTCGAGC

GTCTCGAGC

GTCTCGAGC

GATATATACGGGTCGTTGGGAGCCTTTTGTCTACTGGGGTCAGGGAACCCTGGTCACC

TABLE 4-continued Nucleotide sequences of anti-TNFR1 dAbs

53

GTCTCGAGC

GTCTCGAGC

GATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTCAGGGAACCCTGGTCACC

Nucleotide sequences of anti-TNFR1 dAbs

55
GTCTCGAGC

GTCTCGAGC

GATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTCAGGGAACCCTGGTCACC

TABLE 4-continued Nucleotide sequences of anti-TNFR1 dAbs

>DOM1h-574-66 (SEQ ID NO: 197) GAGGTGCAGCTGTTGGAGTCTGGGGGGGGGGGGCTTGGTACAGCCTGGGGGGGTCCCTGCGTC GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGAATACGGGTGATCGTAGA ${\tt TACTACGCAGACTCTGTGAAGGGCCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA}$ CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC GATATATACGGGTCGTTGGAAGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC GTCTCGAGC

GTCTCGAGC

>DOM1h-574-65 (SEQ ID NO: 196) GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGAATACGGGTGATCGTAGA TACTACGCAGACTCTGTGAAGGGCCCGGTTCACCATCTCCCGCGATAATTCCAAGAACA ${\tt Cactgtatctgcaaatgaacagcctgcgtgccgaggacaccgcggtatattactgtgc}$ GATATATACGGGTCGTTGGGAGCCTTTTGTCTACTGGGGTCAGGGAACCCTGGTCACC

GTCACGAGC

GTCTCGAGC >DOM1h-574-54 (SEQ ID NO: 195) GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGATCGTACA TACTACGCGGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA ${\tt CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC}$ ${\tt GATATATACGGGTCGTTGGGAGCCTTATGAGTACTGGGGTCAGGGAACCCTGGTCACC}$

GTCTCGAGC >DOM1h-574-53 (SEQ ID NO: 194) GAGGTGCAGCTGTTGGAGTCTGGGGGGGGGGGGGCTTGGTACAGCCTGGGGGGGTCCCTGCGTC GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGAGCGTAGA TACTACGCAGACTCAGTGAAGGGCCGGTTCACCATCTCCCGCGACAATCCCAAGAACA

CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAAGGACACCGCGGTATATTACTGTGC GATATATACGGGTCGGTGGGAGCCTTTTGAATACTGGGGTCAGGGAACCCTGGTCACC

GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGATCGTACA TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA ${\tt CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGTGC}$ GATATATACGGGTCGTTGGGAGCCTTTTAAGTACTGGGGTCAGGGAACCCTGGTCACC

Nucleotide sequences of anti-TNFR1 dAbs >DOM1h-574-40 (SEQ ID NO: 193)

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GTCTCGAGC

GTCTCGAGC

TACTACGCAGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC GATATATACGGGTCGTTGGAGGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC

GTCTCGAGC

Nucleotide sequences of anti-TNFR1 dAbs

GTCTCGAGC

>DOM1h-574-76 (SEQ ID NO: 207) GGCCCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACGGGTGATCGTAGA TACTACGATGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA ${\tt CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGTGC}$ GATATATACGGGTCGTTGGAAGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC

GTCTCGAGC

>DOM1h-574-75 (SEQ ID NO: 206) GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACGGGTGATCGTAGA TACTACGATGACTCTGTGAAGGGCCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA ${\tt CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC}$ GATATATACGGGTCGTTGGGAGCCTTTTGTCTACTGGGGTCAGGGAACCCTGGTCACC

GTCTCGAGC

GTCTCGAGC >DOM1h-574-74 (SEQ ID NO: 205) GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACTGCTGATCGTACA TACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA ${\tt CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC}$ ${\tt GATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC}$

GTCTCGAGC >DOM1h-574-73 (SEQ ID NO: 204) GAGGTGCAGCTGTTGGAGTCTGGGGGGGGGGGGGCTTGGTACAGCCTGGGGGGGTCCCTGCGTC GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACTGCTGATCGTACA

TACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC GATATATACGGGTCGTTGGAGGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC

GAGGTGCAGCTGTTGGAGTCTGGGGGGGGGGGGTCCCTGCGGGGGGGCCCCGCGCC GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACTGCTGATCGTACA TACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA ${\tt CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGTGC}$ GATATATACTGGGCGTTGGGTGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC

TABLE 4-continued Nucleotide sequences of anti-TNFR1 dAbs

63

>DOM1h-574-72 (SEQ ID NO: 203)

GTCTCGAGC

GTCTCGAGC

CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC GATATATACGGGTCGTTGGAGGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC

GTCTCGAGC

Nucleotide sequences of anti-TNFR1 dAbs

65

>DOM1h-574-77 (SEQ ID NO: 208)

GTCTCGAGC

GTCTCGAGC

GATATATACGGGTCGTTGGAGGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC

Nucleotide sequences of anti-TNFR1 dAbs

GTCTCGAGC

GTCTCGAGC

GTCTCGAGC >DOMIh-574-94 (SEQ ID NO: 220) GAGGTGCAGCTGTGGAGTCTGGGGGGGGCTTGGTACAGCCTGGGGGGGCCCGCGCC TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGGTCCGCCA GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGAATACGGGTGGATCGTAGA TACTACGCAGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA CGCTGTATCTGCAAATGAACAGCCTGCGTGCCCGAGGACACCGCGGCATATTACTGTGC GATATATACGGGTCGGTGGCCCGACTTTGACTACTGGGGTCAGGGAACCCTGGTCACC

GATATATACGGGTCGTTGGGAGCCTTTTGTCTACTGGGGTCAGGGAACCCTGGTCACC

Nucleotide sequences of anti-TNFR1 dAbs

TABLE 4-continued

GTCTCGAGC

GTCTCGAGC

CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC GATATATACGGGTCGGTGGCCCGACTTTGACTACTGGGGTCAGGGAACCCTGGTCACC

TABLE 4-continued Nucleotide sequences of anti-TNFR1 dAbs

GAGGTGCAGCTGTTGGAGTCTGGGGGGGGGGGGTCCCTGCGGGGGGGCCCCGCGCC

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>DOM1h-574-106 (SEQ ID NO: 232) GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTAACAATACGGGTTCGACCACA ${\tt TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA}$ ${\tt CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC}$ GATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTCAGGGAACCCTGGTCACC

GTCTCGAGC

>DOM1h-574-105 (SEQ ID NO: 231) TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGATGGGTCCGCCA GGCTCCAGGGAAAGGTCCAGAGTGGGTCTCACAGATTTCGGAGACCGGTCGCAGGACA TACTACGCAGACTCCGTGAAGGGCCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA ${\tt CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC}$ GATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTCAGGGAACCCTGGTCACC

GTCTCGAGC

GTCTCGAGC >DOM1h-574-104 (SEQ ID NO: 230) TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGATGGGTCCGCCA GGCTCCAGGGAAAGGTCCAGAGTGGGTCTCACAGATTTCGGACAAGGGTACGCGCACA TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA ${\tt CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC}$ ${\tt GATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTCAGGGAACCCTGGTCACC}$

>DOM1h-574-103 (SEQ ID NO: 229) GAGGTGCAGCTGTTGGAGTCTGGGGGGGGGGGGGCTTGGTACAGCCTGGGGGGGTCCCTGCGTC GGCTCCAGGGAAGGGTCCAGAGTGGGTCTCACAGATTTCGGACGGGGGTACGCGGACA TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA

CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAAGGACACCGCGGTATATTACTGTGC GATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTCAGGGAACCCTGGTCACC

GTCTCGAGC

GGCTCCAGGGAAAGGTCCAGAGTGGGTCTCACAGATTTCGGACTCCGGTTACCGCACA TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA ${\tt CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC}$ GATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTCAGGGAACCCTGGTCACC

GAGGTGCAGCTGTTGGAGTCTGGGGGGGGGGGGTCCCTGCGGGGGGGCCCCGCGCC TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGATGGGTCCGCCA

73

>DOM1h-574-102 (SEQ ID NO: 228)

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GTCTCGAGC

>DOM1h-574-111 (SEQ ID NO: 237)

GTCTCGAGC

75

>DOM1h-574-107 (SEQ ID NO: 233)

>DOM1h-574-116 (SEQ ID NO: 242) GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTAGA TACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA ${\tt CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC}$ GATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC

GTCTCGAGC

>DOM1h-574-115 (SEQ ID NO: 241) GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACTGCTGATCGTACA TACTACGATCACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA ${\tt CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC}$ GATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC

GTCTCGAGC

GTCTCGAGC >DOM1h-574-114 (SEQ ID NO: 240) GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTTGAATACTGCTGATCGTACA TACTACGATCACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA ${\tt CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC}$ ${\tt GATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC}$

>DOM1h-574-113 (SEQ ID NO: 239) GAGGTGCAGCTGTTGGAGTCTGGGGGGGGGGGGGCTTGGTACAGCCTGGGGGGGTCCCTGCGTC GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACTGCTGATCGCAGA TACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC GATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC

GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTACA TACTACACACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA ${\tt CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC}$ GATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC GTCTCGAGC

Nucleotide sequences of anti-TNFR1 dAbs

GAGGTGCAGCTGTTGGAGTCTGGGGGGGGGGGGTCCCTGCGGGGGGGCCCCGCGCC

>DOM1h-574-112 (SEQ ID NO: 238)

US 9,534,043 B2

GTCTCGAGC

>DOM1h-574-121 (SEQ ID NO: 247)

GTCTCGAGC

TABLE 4-continued

Nucleotide sequences of anti-TNFR1 dAbs

79

>DOM1h-574-117 (SEQ ID NO: 243)

GTCTCGAGC

GTCTCGAGC

81

>DOM1h-574-122 (SEQ ID NO: 248)

GTCTCGAGC

GTCTCGAGC

GATATATACGGGTCGTTGGGAGCCTTTTGTCTACTGGGGTCAGGGAACCCTGGTCACC

GTCTCGAGC

GTCTCGAGC

GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTACA TACTACGATCACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC GATATATACGGGTCGTTGGAGGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC

TABLE 4-continued Nucleotide sequences of anti-TNFR1 dAbs

85

>DOM1h-574-132 (SEQ ID NO: 258)

GTCTCGAGC

>DOM1h-574-142 (SEQ ID NO: 267)

GTCTCGAGC

TABLE 4-continued

Nucleotide sequences of anti-TNFR1 dAbs

87

>DOM1h-574-138 (SEQ ID NO: 263)

GTCTCGAGC

GTCTCGAGC

GATATATACGGGTCGTTGGGAGCCTTTTGTCTACTGGGGTCAGGGAACCCTGGTCACC

Nucleotide sequences of anti-TNFR1 dAbs

89

>DOM1h-574-143 (SEQ ID NO: 268)

GTCTCGAGC

>DOM1h-574-151 (SEQ ID NO: 276)

Nucleotide sequences of anti-TNFR1 dAbs

91

US 9,534,043 B2

GTCTCGAGC

GTCTCGAGC

GATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC

Nucleotide sequences of anti-TNFR1 dAbs

GTCTCGAGC

GTCTCGAGC

Nucleotide sequences of anti-TNFR1 dAbs

GAGGTGCAGCTGTTGGAGTCTGGGGGGGGGGGGTCCCTGCGGGGGGGCCCCGCGCC

TABLE 4-continued

GTCTCGAGC

GTCTCGAGC

TABLE 4-continued Nucleotide sequences of anti-TNFR1 dAbs

97

>DOM1h-574-163 (SEQ ID NO: 288)

>DOM1h-574-172 (SEQ ID NO: 297) GAGGTGCAGCTGTTGGAGTCTGGGGGGGGGGGGCTTGGTACAGCCTGGGGGGGTCCCTGCGTC GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGGATACTGCTGATCGTACA ${\tt TACTACGATCACGCGGTGAAGGGCCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA}$ ${\tt CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGTGC}$ GATATATACTGGGCGTTGGGTGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC

GTCTCGAGC

>DOM1h-574-171 (SEQ ID NO: 296) GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGGATACTGCTGATCGTACA TACTACGATCACTCCGTGAAGGGCCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA ${\tt CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGTGC}$ GATATATACTGGGCGTTGGGTGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC

GTCTCGAGC

GTCTCGAGC >DOM1h-574-170 (SEQ ID NO: 295) GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTACA TACTACGCACACGCGGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA ${\tt CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGTGC}$ ${\tt GATATATACTGGGCGTTGGGTGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC}$

>DOM1h-574-169 (SEQ ID NO: 294) GAGGTGCAGCTGTTGGAGTCTGGGGGGGGGGGGGCTTGGTACAGCCTGGGGGGGTCCCTGCGTC GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGGATACTGCTGATCGTACA TACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGCGC GATATATACTGGGCGTTGGGTGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC

GAGGTGCAGCTGTTGGAGTCTGGGGGGGGGGGGTCCCTGCGGGGGGGCCCCGCGCC ${\tt GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACCGGTGATCGTAGA$ TACTACGATCACTCTGTGAAGGGCCGGTTCACTATCTCCCGCGACAATTCCAAGAACA ${\tt CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC}$ GATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC GTCTCGAGC

TABLE 4-continued Nucleotide sequences of anti-TNFR1 dAbs

99

>DOM1h-574-168 (SEQ ID NO: 293)

GTCTCGAGC

GTCTCGAGC

GTCTCGAGC >DOMIh-574-175 (SEQ ID NO: 300) GAGGTGCAGCTGTGGAGTCTGGGGGGGGCTTGGTACAGCCTGGGGGGGCCCGCGCC TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGGTGGGGTCCGCCA GGCTCCAGGGAAGGGTCTAGAGTGGGGTCTCACAGATTGCGGATACTGCTGATCGTAGA TACTACGCACACGCGGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC GATATATACGGGTCGGTGGGGCGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC

GATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC

GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGGATACTGCTGATCGTAGA TACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC GATATATACGGGTCGGTGGGCGGCCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC

TABLE 4-continued

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	υ	

TABLE 4-continued

Nucleotide sequences of anti-TNFR1 dAbs
>DOM1h-574-178 (SEQ ID NO: 303) GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGGATACTGCTGATCGTAGA
TACTACGATCACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC
>DOM1h-574-179 (SEQ ID NO: 304) GAGGTGCAGCTGCTGGAGTCTGGGGGGGGGGCTCGCGGGGGGCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTTTCAAGTATTCGATGGGGTGGGT
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTAGA
TACTACGATGACGCGGTGAAGGGCCGGTTCACCATCACCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGTTGGGAGCCTTTTGTCTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

	TAB	LE .	5	
Anti-serum	albumin	dAb	(DOM7h)	fusions

(used in Rat studies):-
DOM7h-14/Exendin-4 fusion DMS number 7138
Amino acid sequence (SEQ ID NO: 305)
HGEGTFTSDLSKOMEEEAVRLFI EWLKNGGPSSGAPPPSGGGGGSGGGGSGGG

GSDIQMTQSPSSLSASVGDRVTITCRASQWIGSQLSWYQQKPGKAPKLLIMWRS

SLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQGAALPRTFGQGTKVEIKR

Nucleotide sequence (SEQ ID NO: 306) CATGGTGAAGGAACATTTACCAGTGACTTGTCAAAACAGATGGAAGAGGAG

 ${\tt GCAGTGCGGTTATTTATTGAGTGGCTTAAGAACGGAGGACCAAGTAGCGGG$

 ${\tt GCACCTCCGCCATCGGGTGGTGGAGGCGGTTCAGGCGGAGGTGGCAGCGGC}$

GGTGGCGGGTCGGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCAT

CTGTAGGAGACCGTGTCACCATCACTTGCCGGGCAAGTCAGTGGATTGGGT

CTCAGTTATCTTGGTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGA

 ${\tt TCATGTGGCGTTCCTCGTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAG}$

TGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGAT

 ${\tt TTTGCTACGTACTACTGTGCTCAGGGTGCGGCGTTGCCTAGGACGTTCGGCCAAGGGACCAA$

GGTGGAAATCAAACGG

DOM7h-14-10/Exendin-4 fusion DMS number 7139 Amino acid sequence (SEQ ID NO: 307) HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGGGGGGGGGGGGGGGG

GSDIQMTQSPSSLSASVGDRVTITCRASQWIGSQLSWYQQKPGKAPKLLIMWRS

SLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQGLRHPKTFGQGTKVEIKR

Anti-serum albumin dAb (DOM7h) fusions
Nucleotide sequence (SEQ ID NO: 308) CATGGTGAAGGAACATTTACCAGTGACTTGTCAAAACAGATGGAAGAGGAG
GCAGTGCGGTTATTTATTGAGTGGCTTAAGAACGGAGGACCAAGTAGCGGG
GCACCTCCGCCATCGGGTGGTGGAGGCGGTTCAGGCGGAGGTGGCAGCGGC
GGTGGCGGGTCGGACATCCAGATGACCCAGTCTCCATCCTCCTGTCTGCAT
CTGTAGGAGACCGTGTCACCATCACTTGCCGGGCAAGTCAGTGGATTGGGT
CTCAGTTATCTTGGTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGA
TCATGTGGCGTTCCTCGTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAG
TGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGAT
TTTGCTACGTACTACTGTGCTCAGGGTTTGAGGCATCCTAAGACGTTCGGCCAAGGGACC
AAGGTGGAAATCAAACGG
DOM7h-14-18/Exendin-4 fusion DMS number 7140 Amino acid sequence (SEQ ID NO: 309) HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGGGGGGGGGGGGGGG
GSDIQMTQSPSSLSASVGDRVTITCRASQWIGSQLSWYQQKPGKAPKLLIMWRS
SLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQGLMKPMTFGQGTKVEIKR
Nucleotide sequence (SEQ ID NO: 310) CATGGTGAAGGAACATTTACCAGTGACTTGTCAAAACAGATGGAAGAGGAG
GCAGTGCGGTTATTTATTGAGTGGCTTAAGAACGGAGGACCAAGTAGCGGG
GCACCTCCGCCATCGGGTGGTGGAGGCGGTTCAGGCGGAGGTGGCAGCGGC
GGTGGCGGGTCGGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCAT
CTGTAGGAGACCGTGTCACCATCACTTGCCGGGCAAGTCAGTGGATTGGGT
CTCAGTTATCTTGGTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGA
TCATGTGGCGTTCCTCGTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAG
TGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGAT
TTTGCTACGTACTACTGTGCTCAGGGTCTTATGAAGCCTATGACGTTCGGCCAAGGGACC
AAGGTGGAAATCAAACGG
DOM7h-14-19/Exendin-4 fusion DMS number 7141 Amino acid sequence (SEQ ID NO: 311) HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGGGGGGGGGGGGGGG
GSDIQMTQSPSSLSASVGDRVTISCRASQWIGSQLSWYQQKPGEAPKLLIMWRS
SLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQGAALPRTFGQGTKVEIKR
Nucleotide sequence (SEQ ID NO: 312) CATGGTGAAGGAACATTTACCAGTGACTTGTCAAAACAGATGGAAGAGAGAG
GCAGTGCGGTTATTTATTGAGTGGCTTAAGAACGGAGGACCAAGTAGCGGG
GCACCTCCGCCATCGGGTGGAGGCGGTTCAGGCGGAGGTGGCAGCGGC
GGTGGCGGGTCGGACATCCAGATGACCCAGTCTCCATCCTCCTGTCTGCAT
CTGTAGGAGACCGTGTCACCATCTCTTGCCGGGCAAGTCAGTGGATTGGGTC
TCAGTTATCTTGGTACCAGCAGAAACCAGGGGAAGCCCCTAAGCTCCTGAT
CATGTGGCGTTCCTCGTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAGT
GGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATT
TTGCTACGTACTACTGTGCTCAGGGTGCGGCGTTGCCTAGGACGTTCGGCCAAGGGACCAA
GGTGGAAATCAAACGG

Anti-serum albumin dAb (DOM7h) fusions

DOM7h-11/Exendin-4 fusion DMS number 7142 Amino acid sequence (SEQ ID NO: 313) HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGGGGGGGGGGGGGGGGG

 ${\tt GSDIQMTQSPSSLSASVGDRVTITCRASRPIGTTLSWYQQKPGKAPKLLIWFGSR}$

 $\label{eq:loss} LQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTKVEIKR$

Nucleotide sequence (SEQ ID NO: 314) CATGGTGAAGGAACATTTACCAGTGACTTGTCAAAACAGATGGAAGAGGAG

GCAGTGCGGTTATTTATTGAGTGGCTTAAGAACGGAGGACCAAGTAGCGGG

GCACCTCCGCCATCGGGTGGTGGAGGCGGTTCAGGCGGAGGTGGCAGCGGC

GGTGGCGGGTCGGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCAT

 ${\tt CTGTAGGAGACCGTGTCACCATCACTTGCCGGGCAAGTCGTCCGATTGGGA$

CGACGTTAAGTTGGTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGA

TCTGGTTTGGTTCCCGGTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAG

TGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGAT

 ${\tt TTTGCTACGTACTACTGTGCGCAGGCTGGGACGCATCCTACGACGTTCGGCCAAGGGACC}$

AAGGTGGAAATCAAACGG

GSDIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLILFGSR

 ${\tt LQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTKVEIKR}$

Nucleotide sequence (SEQ ID NO: 316) CATGGTGAAGGAACATTTACCAGTGACTTGTCAAAACAGATGGAAGAGGAG

GCAGTGCGGTTATTTATTGAGTGGCTTAAGAACGGAGGACCAAGTAGCGGG

GCACCTCCGCCATCGGGTGGTGGAGGCGGTTCAGGCGGAGGTGGCAGCGGC

GGTGGCGGGTCGGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCAT

CTGTAGGAGACCGTGTCACCATCACTTGCCGGGCAAGTCGTCCGATTGGGA

CGATGTTAAGTTGGTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGA

TCTTGTTTGGTTCCCGGTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAG

TGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGAT

TTTGCTACGTACTACTGTGCGCAGGCTGGGACGCATCCTACGACGTTCGGCCAAGGG

ACCAAGGTGGAAATCAAACGG

DOM7h-11-15/Exendin-4 fusion DMS number 7143 Amino acid sequence (SEQ ID NO: 317) HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGGGGGGGGGGGGGGGGGG

GSDIOMTOSPSSLSASVGDRVTITCRASRPIGTMLSWYOOKPGKAPKLLILAFSR

 ${\tt LQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTKVEIKR}$

Nucleotide sequence (SEQ ID NO: 318) CATGGTGAAGGAACATTTACCAGTGACTTGTCAAAACAGATGGAAGAGGAG

GCAGTGCGGTTATTTATTGAGTGGCTTAAGAACGGAGGACCAAGTAGCGGG

GCACCTCCGCCATCGGGTGGTGGAGGCGGTTCAGGCGGAGGTGGCAGCGGC

GGTGGCGGGTCGGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCAT

CTGTAGGAGACCGTGTCACCATCACTTGCCGGGCAAGTCGTCCGATTGGGA

Anti-serum albumin dAb (DOM7h) fusions

CGATGTTAAGTTGGTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGA

TCCTTGCTTTTTCCCGTTTGCAAAGTGGGGGTCCCATCACGTTTCAGTGGCAGT

GGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATT

TTGCTACGTACTACTGCGCGCAGGCTGGGACGCATCCTACGACGTTCGGCCAAGGGA

CCAAGGTGGAAATCAAACGG

DOM7h14-10/G4SC-NCE fusion Amino acid sequence (SEQ ID NO: 319) encoding DOM7h14-10/G4SC DIQMTQSPSSLSASVGDRVTITCRASQWIGSQLSWYQQKPGKAPKLLIMWRSSL

QSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQGLRHPKTFGQGTKVEIKRGGGGSC

The C-terminal cysteine can be linked to a new chemical entity (pharmaceutical chemical compound, NCE), eg using maleimide linkage. Nucleotide sequence (SEQ ID NO: 320) encoding DOM7h14-10/G4SC GACATCCAGATGACCCAGTCTCCATCCTCCTGTCTGCATCTGTAGGAGACC

GTGTCACCATCACTTGCCGGGCAAGTCAGTGGATTGGGTCTCAGTTATCTTG

GTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCATGTGGCGTTC

CTCGTTGCAAAGTGGGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGAC

 ${\tt AGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCTACGTAC$

 ${\tt TACTGTGCTCAGGGTTTGAGGCATCCTAAGACGTTCGGCCAAGGGACCAAGGTGGAAA}$

TCAAACGGGGTGGCGGAGGGGGTTCCTGT

DOM7h14-10/TVAAPSC fusion Amino acid sequence (SEQ ID NO: 321) DIQMTQSPSSLSASVGDRVTITCRASQWIGSQLSWYQQKPGKAPKLLIMWRSSL

 $\label{eq:construction} QSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQGLRHPKTFGQGTKVEIKRT$

VAAPSC

The C-terminal cysteine can be linked to a new chemical entity (pharmaceutical chemical compound, NCE), eg using maleimide linkage. Nucleotide sequence (SEQ ID NO: 322) GACATCCAGATGACCCAGTCTCCATCCTCCCTGCTGCATCTGTAGGAGACC

GTGTCACCATCACTTGCCGGGCAAGTCAGTGGATTGGGTCTCAGTTATCTTG

GTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCATGTGGCGTTC

CTCGTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGAC

AGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCTACGTAC

TACTGTGCTCAGGGTTTGAGGCATCCTAAGACGTTCGGCCAAGGGACCAAGGTGGAAA

TCAAACGGACCGTCGCTGCTCCATCTTGT

(used in mouse studies):-DOM7h-11/DOM1m-21-23 fusion DMS number 5515 Amino acid sequence (SEQ ID NO: 323) EVOLLESGGGLVOPGGSLRLSCAASGFTFNRYSMGWLROAPGKGLEWVSRIDS

YGRGTYYEDPVKGRFSISRDNSKNTLYLQMNSLRAEDTAVYYCAKISQFGSNA

FDYWGQGTQVTVSSASTSGPSDIQMTQSPSSLSASVGDRVTITCRASRPIGTTLS

WYQQKPGKAPKLLIWFGSRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHP

TTFGQGTKVEIKR

Amino acid plus nucleotide plus myc tag sequence (SEQ ID NO: 324) EVQLLESGGGLVQPGGSLRLSCAASGFTFNRYSMGWLRQAPGKGLEWVSRIDS

YGRGTYYEDPVKGRFSISRDNSKNTLYLQMNSLRAEDTAVYYCAKISQFGSNA

FDYWGQGTQVTVSSASTSGPSDIQMTQSPSSLSASVGDRVTITCRASRPIGTTLS

Anti-serum albumin dAb (DOM7h) fusions WYQQKPGKAPKLLIWFGSRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHP TTFGQGTKVEIKRAAAEQKLISEEDLN Nucleotide sequence (SEQ ID NO: 325) GAGGTGCAGCTGTTGGAGTCTGGGGGGGGGGGGGGTCC ${\tt CTGCGTCTCCTGTGCAGCCTCCGGATTCACCTTTAATAGGTATAGTATGG}$ GGTGGCTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACGGATTG ATTCTTATGGTCGTGGTACATACTACGAAGACCCCGTGAAGGGCCGGTTCA GCATCTCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCC TGCGTGCCGAGGACACCGCCGTATATTACTGTGCGAAAATTTCTCAGTTTGG GTCAAATGCGTTTGACTACTGGGGGTCAGGGAACCCAGGTCACCGTCTCGAG CGCTAGCACCAGTGGTCCATCGGACATCCAGATGACCCAGTCTCCATCCTCC CTGTCTGCATCTGTAGGAGACCGTGTCACCATCACTTGCCGGGCAAGTCGTC CGATTGGGACGACGTTAAGTTGGTACCAGCAGAAACCAGGGAAAGCCCCCTA AGCTCCTGATCTGGTTTGGTTCCCCGGTTGCAAAGTGGGGTCCCATCACGTTT CAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCA ACCTGAAGATTTTGCTACGTACTACTGTGCGCAGGCTGGGACGCATCCTACGACG TTCGGCCAAGGGACCAAGGTGGAAATCAAACGG Nucleotide plus myc tag sequence (SEQ ID NO: 326) GAGGTGCAGCTGTTGGAGTCTGGGGGGGGGGGGCTTGGTACAGCCTGGGGGGGTCC ${\tt CTGCGTCTCCTGTGCAGCCTCCGGATTCACCTTTAATAGGTATAGTATGG}$ GGTGGCTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACGGATTG ATTCTTATGGTCGTGGTACATACTACGAAGACCCCGTGAAGGGCCGGTTCA GCATCTCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCC TGCGTGCCGAGGACACCGCCGTATATTACTGTGCGAAAATTTCTCAGTTTGG GTCAAATGCGTTTGACTACTGGGGTCAGGGAACCCAGGTCACCGTCTCGAG CGCTAGCACCAGTGGTCCATCGGACATCCAGATGACCCAGTCTCCATCCTCC CTGTCTGCATCTGTAGGAGACCGTGTCACCATCACTTGCCGGGCAAGTCGTC CGATTGGGACGACGTTAAGTTGGTACCAGCAGAAACCAGGGAAAGCCCCCTA AGCTCCTGATCTGGTTTGGTTCCCCGGTTGCAAAGTGGGGTCCCATCACGTTT CAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCA ACCTGAAGATTTTGCTACGTACTACTGTGCGCAGGCTGGGACGCATCCTACG ACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGGGCGGCCGCAGAACAAAAA CTCATCTCAGAAGAGGATCTGAATTAA DOM7h-11-12/DOM1m-21-23 fusion DMS number 5516 Amino acid sequence (SEQ ID NO: 327) EVQLLESGGGLVQPGGSLRLSCAASGFTFNRYSMGWLRQAPGKGLEWVSRIDS

YGRGTYYEDPVKGRFSISRDNSKNTLYLQMNSLRAEDTAVYYCAKISQFGSNA

FDYWGQGTQVTVSSASTSGPSDIQMTQSPSSLSASVGDRVTITCRASRPIGTMLS

WYQQKPGKAPKLLILFGSRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCA QAGTHPTTFGQGTKVEIKR

Amino acid plus nucleotide plus myc tag sequence (SEQ ID NO: 328) EVQLLESGGGLVQPGGSLRLSCAASGFTFNRYSMGWLRQAPGKGLEWVSRIDS YGRGTYYEDPVKGRFSISRDNSKNTLYLQMNSLRAEDTAVYYCAKISQFGSNA FDYWGQGTQVTVSSASTSGPSDIQMTQSPSSLSASVGDRVTITCRASRPIGTMLS WYQQKPGKAPKLLILFGSRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCA QAGTHPTTFGQGTKVEI KRAAAEQKLI SEEDLN Nucleotide sequence (SEQ ID NO: 329) GAGGTGCAGCTGTTGGAGTCTGGGGGGGGGGGGCTTGGTACAGCCTGGGGGGGTCC CTGCGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTAATAGGTATAGTATGG GGTGGCTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACGGATTG ATTCTTATGGTCGTGGTACATACTACGAAGACCCCCGTGAAGGGCCGGTTCA GCATCTCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCC TGCGTGCCGAGGACACCGCCGTATATTACTGTGCGAAAATTTCTCAGTTTGG GTCAAATGCGTTTGACTACTGGGGTCAGGGAACCCAGGTCACCGTCTCGAG CGCTAGCACCAGTGGTCCATCGGACATCCAGATGACCCAGTCTCCATCCTCC CTGTCTGCATCTGTAGGAGACCGTGTCACCATCACTTGCCGGGCAAGTCGTC CGATTGGGACGATGTTAAGTTGGTACCAGCAGAAACCAGGGAAAGCCCCCTA AGCTCCTGATCTTGTTTGGTTCCCGGTTGCAAAGTGGGGTCCCATCACGTTT CAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCA ACCTGAAGATTTTGCTACGTACTACTGTGCGCAGGCTGGGACGCATCCTACG ACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGG Nucleotide plus myc tag sequence (SEQ ID NO: 330) GAGGTGCAGCTGTTGGAGTCTGGGGGGGGGGGGCTTGGTACAGCCTGGGGGGGTCC CTGCGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTAATAGGTATAGTATGG GGTGGCTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACGGATTG ${\tt ATTCTTATGGTCGTGGTACATACTACGAAGACCCCGTGAAGGGCCGGTTCA$ GCATCTCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCC TGCGTGCCGAGGACACCGCCGTATATTACTGTGCGAAAATTTCTCAGTTTGG GTCAAATGCGTTTGACTACTGGGGGTCAGGGAACCCAGGTCACCGTCTCGAG CGCTAGCACCAGTGGTCCATCGGACATCCAGATGACCCAGTCTCCATCCTCC CTGTCTGCATCTGTAGGAGACCGTGTCACCATCACTTGCCGGGCAAGTCGTC CGATTGGGACGATGTTAAGTTGGTACCAGCAGAAACCAGGGAAAGCCCCTA AGCTCCTGATCTTGTTTGGTTCCCGGTTGCAAAGTGGGGTCCCATCACGTTT

CAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCA ACCTGAAGATTTTGCTACGTACTACTGTGCGCAGGCTGGGACGCATCCTACG ACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGGGCGGCCGCAGAACA

AAAACTCATCTCAGAAGAGGATCTGAATTAA

DOM7h-11-15/DOM1m-21-23 fusion DMS number 5517 Amino acid sequence (SEQ ID NO: 331) EVQLLESGGGLVQPGGSLRLSCAASGFTFNRYSMGWLRQAPGKGLEWVSRIDS

 $\verb"YGRGTYYEDPVKGRFSISRDNSKNTLYLQMNSLRAEDTAVYYCAKISQFGSNA"$

FDYWGQGTQVTVSSASTSGPSDIQMTQSPSSLSASVGDRVTITCRASRPIGTMLS

TABLE 5-continued Anti-serum albumin dAb (DOM7h) fusions

WYQQKPGKAPKLLILAFSRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCA
QAGTHPTTFGQGTKVEIKR
Amino acid plus nucleotide plus myc tag sequence(SEQ ID NO: 332) EVQLLESGGGLVQPGGSLRLSCAASGFTFNRYSMGWLRQAPGKGLEWVSRIDS
YGRGTYYEDPVKGRFSISRDNSKNTLYLQMNSLRAEDTAVYYCAKISQFGSNA
FDYWGQGTQVTVSSASTSGPSDIQMTQSPSSLSASVGDRVTITCRASRPIGTMLS
WYQQKPGKAPKLLILAFSRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCA
QAGTHPTTFGQGTKVE1KRAAAEQKL1SEEDLN
Nucleotide sequence (SEQ ID NO: 333) GAGGTGCAGCTGTTGGAGTCTGGGGGGGGGGGCTTGGTACAGCCTGGGGGGGTCC
CTGCGTCTCCCGTGCAGCCTCCGGATTCACCTTTAATAGGTATAGTATGG
GGTGGCTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACGGATTG
ATTCTTATGGTCGTGGTACATACTACGAAGACCCCGTGAAGGGCCGGTTCA
GCATCTCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCC
TGCGTGCCGAGGACACCGCCGTATATTACTGTGCGAAAATTTCTCAGTTTGG
GTCAAATGCGTTTGACTACTGGGGTCAGGGAACCCAGGTCACCGTCTCGAG
CGCTAGCACCAGTGGTCCATCGGACATCCAGATGACCCAGTCTCCATCCTCC
CTGTCTGCATCTGTAGGAGACCGTGTCACCATCACTTGCCGGGCAAGTCGTC
CGATTGGGACGATGTTAAGTTGGTACCAGCAGAAACCAGGGAAAGCCCCTA
AGCTCCTGATCCTTGCTTTTTCCCGTTTGCAAAGTGGGGTCCCATCACGTTTC
AGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAA
CCTGAAGATTTTGCTACGTACTACTGCGCGCAGGCTGGGACGCATCCTACGA
CGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGG
Nucleotide plus myc tag sequence (SEQ ID NO: 334) GAGGTGCAGCTGTTGGAGTCTGGGGGGGGGGCTTGGTACAGCCTGGGGGGGTCC
CTGCGTCTCCCGTGCAGCCTCCGGATTCACCTTTAATAGGTATAGTATGG
GGTGGCTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACGGATTG
ATTCTTATGGTCGTGGTACATACTACGAAGACCCCGTGAAGGGCCGGTTCA
GCATCTCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCC
TGCGTGCCGAGGACACCGCCGTATATTACTGTGCGAAAATTTCTCAGTTTGG
GTCAAATGCGTTTGACTACTGGGGTCAGGGAACCCAGGTCACCGTCTCGAG
CGCTAGCACCAGTGGTCCATCGGACATCCAGATGACCCAGTCTCCATCCTCC
CTGTCTGCATCTGTAGGAGACCGTGTCACCATCACTTGCCGGGCAAGTCGTC
CGATTGGGACGATGTTAAGTTGGTACCAGCAGAAACCAGGGAAAGCCCCTA
AGCTCCTGATCCTTGCTTTTTCCCGTTTGCAAAGTGGGGTCCCATCACGTTTC
AGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAA
CCTGAAGATTTTGCTACGTACTACTGCGCGCAGGCTGGGACGCATCCTACGA
CGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGGGCGGCCGCAGAACAA
AAACTCATCTCAGAAGAGGATCTGAATTAA

Where a myc-tagged molecule is indicated in this table, this was the version used in PK studies in the examples. Where no myc-tagged sequences are given, the PK studies in the examples were not done with myc-tagged material, ie, the studies were done with the non-tagged constructs shown. 5

EXEMPLIFICATION

All numbering in the experimental section is according to Kabat (Kabat, E. A. National Institutes of Health (US) & 10 Columbia University. Sequences of proteins of immunological interst, edn 5 (US Dept. Of Health and Human Services Public Health Service, National Institues of Health, Bethesda, Md., 1991)).

Derivation of DOM7h-11 and DOM7h-14 variants is 15 described. DOM7h-14 variants are not according to the invention.

Example 1

Vk Affinity Maturation

Selections:

HSA (Human Serum Albumin) and RSA (Rat Serum Albumin) antigens were obtained from Sigma (essentially 25 fatty acid free, ~99% (agarose gel electrophoresis), lyophilized powder Cat. No. A3782 and A6414 respectively)

Biotinylated products of above two antigens were made by using EZ Link Sulfo-NHS-SS-Biotin (Pierce, Cat. No. 21331). Free biotin reagent was removed by passing the 30 samples twice through PD10 desalting column followed by overnight dialysis against 1000× excess volume of PBS at 4° C. Resulting product was tested by mass spec and 1-2 biotins per molecule were observed. 35

Affinity Maturation Libraries:

Both error-prone and CDR libraries were created using DOM7h-11 and DOM7h-14 parental dAbs (see WO2008/ 096158 for the sequences of DOM7h-11 and DOM7h-14). The CDR libraries were generated in the pDOM4 vector and the error prone libraries were generated in the pDOM33 40 tion: vector (to allow for selection with or without protease treatment). Vector pDOM4, is a derivative of the Fd phage vector in which the gene III signal peptide sequence is replaced with the yeast glycolipid anchored surface protein (GAS) signal peptide. It also contains a c-myc tag between 45 the leader sequence and gene III, which puts the gene III back in frame. This leader sequence functions well both in phage display vectors but also in other prokaryotic expression vectors and can be universally used. pDOM33 is a modified version of the pDOM4 vector where the c-myc tag 50 has been removed which renders the dAb-phage fusion resistant to the protease trypsin. This allows the use of trypsin within the phage selection to select for dAbs that are more protease stable (see WO2008149143).

For error-prone maturation libraries, plasmid DNA encod- 55 ing the dAb to be matured was amplified by PCR, using the GENEMORPH® II RANDOM MUTAGENESIS KIT (random, unique mutagenesis kit, Stratagene). The product was digested with SalI and Not I and used in a ligation reaction with cut phage vector pDOM33. 60

For the CDR libraries, PCR reactions were performed using degenerate oligonucleotides containing NNK or NNS codons to diversify the required positions in the dAb to be affinity matured. Assembly PCR was then used to generate a full length diversified insert. The insert was digested with 65 Sal I and Not I and used in a ligation reaction with pDOM4 for mutagenesis of multiple residues and pDOM5 for muta-

genesis of single residues. The pDOM5 vector is a pUC119based expression vector where protein expression is driven by the LacZ promoter. A GAS 1 leader sequence (see WO 2005/093074) ensures secretion of isolated, soluble dAbs into the periplasm and culture supernatant of E. coli. dAbs are cloned Sall/NotI in this vector, which appends a myc tag at the C-terminus of the dAb. This protocol using Sall and Not I results in inclusion of an ST amino acid sequence at the N-terminus.

The ligation produced by either method was then used to transform E. coli strain TB1 by electroporation and the transformed cells plated on 2×TY agar containing 15 µg/ml tetracycline, yielding library sizes of $>5 \times 10^7$ clones.

The error-prone libraries had the following average mutation rate and size: DOM7h-11 (2.5 mutations per dAb), size: 6.1×10⁸, DOM7h-14 (2.9 mutations per dAb), size: 5.4×10⁸.

Each CDR library has four amino acid diversity. Two libraries were generated for each of CDRs 1 and 3, and one library for CDR2. The positions diversified within each 20 library are as follows (amino acids based on VK dummy DPK9 sequence):

	Lib	Library size	
	DOM7h-11	DOM7h-14	
1-Q27, S28, S30, S31 (CDR1) 2-S30, S31, Y32, N34 (CDR1) 3-Y49, A50, A51, S53 (CDR2) 4-Q89, S91, Y92, S93 (CDR3) 5-Y92, Y93, T94, N96 (CDR3)	$\begin{array}{c} 8.8 \times 10^{7} \\ 4.6 \times 10^{8} \\ 3.9 \times 10^{8} \\ 1.8 \times 10^{8} \\ 4.0 \times 10^{8} \end{array}$	5.8×10^{7} 4.2×10^{8} 2.4×10^{8} 2.5×10^{8} 3.3×10^{8}	

Example 2

Selection Strategies

Three phage selection strategies were adopted for $V\kappa$ ALBUDAB™ (anti-serum albumin dAb) affinity matura-

1) Selections against HSA only:

- Three rounds of selection against HSA were carried out. The error prone libraries and each CDR library were selected as an individual pool in all rounds. The first round of selection was performed against HSA passively coated onto an immunotube at 1 mg/ml. Round 2 was performed against 100 nM HSA and round 3 against 10 nM (CDR selections) or 20 or 100 nM (Error prone selections) HSA, both as soluble selections followed by a fourth round of selection with the error prone libraries against 1.5 nM HSA as a soluble selection. The error prone libraries were eluted with 0.1M glycine pH 2.0 before neutralisation with 1M Tris pH 8.0 and the CDR libraries were eluted with 1 mg/ml trypsin before infection into log phase TG1 cells. The third round of each selection was subcloned into pDOM5 for screening. Soluble selections used biotinylated HSA.
- 2) Trypsin selections against HSA:
- In order to select dAbs with increased protease resistance compared to the parental clone and with potentially improved biophysical properties, trypsin was used in phage selections (see WO2008149143). Four rounds of selection were preformed against HSA. The first round of selection of error prone libraries was performed against passively coated HSA at 1 mg/ml without trypsin; the second round against passively coated HSA

at 1 mg/ml with 20 μ g/ml trypsin for 1 hour at 37° C.; the third round selection was performed by soluble selection using biotinylated HSA against 100 nM HSA with 20 μ g/ml or 100 μ g/ml trypsin for 1 hour at 37° C. The final round of selection was performed by soluble ⁵ selection using biotinylated HSA against 100 nM HSA with 100 μ g/ml trypsin overnight at 37° C.

- 3) Cross-over selections against HSA (round 1) and RSA (rounds 2-4):
- The first round selection was carried out against 1 mg/ml passively coated HSA or 1 μ M HSA (soluble selection), followed by a further three rounds of soluble selections against biotinylated RSA at concentrations of 1 μ M for round 1, 100 nm for round 2 and 20 nM, 10 nM or 1 nM for round 3.

Screening Strategy and Affinity Determination:

In each case after selection a pool of phage DNA from the appropriate round of selection is prepared using a QIAfilter 20 midiprep kit (Qiagen), the DNA is digested using the restriction enzymes Sal1 and Not1 and the enriched V genes are ligated into the corresponding sites in pDOM5 the soluble expression vector which expresses the dAb with a myc tag (see PCT/EP2008/067789). The ligated DNA is used to ²⁵ electro-transform E. coli HB 2151 cells which are then grown overnight on agar plates containing the antibiotic carbenicillin. The resulting colonies are individually assessed for antigen binding. In each case at least 96 clones were tested for binding to HSA, CSA (Cynomlgus monkey Serum Albumin), MSA (mouse serum albumin) and RSA by BIACORE™ (surface plasmon resonance). MSA antigen was obtained from Sigma (essentially fatty acid free, ~99% (agarose gel electrophoresis), lyophilized powder Cat. No. 34 A3559) and CSA was purified from Cynomolgus serum albumin using prometic blue resin (Amersham). Soluble dAb fragments were produced in bacterial culture in ONEX culture media (Novagen) overnight at 37° C. in 96 well plates. The culture supernatant containing soluble dAb was 40 centrifuged and analysed by BiaCore[™] for binding to high density HSA, CSA, MSA and RSA CM5 chips. Clones were found to bind to all these species of serum albumin by off-rate screening. The clones were sequenced revealing unique dAb sequences.

The minimum identity to parent (at the amino acid level) of the clones selected was 97.2% (DOM7h-11-3: 97.2%, DOM7h-11-12: 98.2%, DOM7h11-15: 96.3%, DOM7h-11-18: 98.2%, DOM7h-11-19: 97.2%)

The minimum identity to parent (at the amino acid level) of the clones selected was 96.3% (DOM7h-14-10: 96.3%, DOM7h-14-18: 96.3%, DOM7h-14-19: 98.2%, DOM7h-14-28: 99.1%, DOM7h-14-36: 97.2%)

Unique dAbs were expressed as bacterial supernatants in 2.5 L shake flasks in Onex media at 30° C. for 48 hrs at 250 rpm. dAbs were purified from the culture media by absorption to protein L agarose followed by elution with 10 mM glycine pH2.0. Binding to HSA, CSA, MSA and RSA by 60 BiaCoreTM was confirmed using purified protein at 3 concentrations 1 μ M, 500 nM and 50 nM. To determine the binding affinity (K_D) of the ALBUDABsTM to each serum albumin; purified dAbs were analysed by BiaCoreTM over albumin concentration range from 5000 nM to 39 nM (5000 65 nM, 2500 nM, 1250 nM, 625 nM, 312 nM, 156 nM, 78 nM, 39 nM).

120	
TABLE	6

		Affinity (Kr.)			
	ALBUDAB TM	to SA (nM)	Kd	Ka	
5		Pat			
	Kai				
	DOM7h-14	60	2.095E-01	4.00E+06	
	DOM7h-14-10	4	9.640E-03	4.57E+06	
	DOM7h-14-18	410	2.275E-01	5.60E+05	
	DOM7h-14-19	890	2.870E-01	3.20E+05	
10	DOM7h-14-28	45 (140)	7.0E-02	2.10E+06	
	DOM71 14 26	20 (6120)	(1.141e-1)	(8.3e5)	
	DOM/11-14-30	30 (0120)	(5.54e-2)	(0e3)	
	DOM7h-11	2100	(0.040-2) 1.00E=01	4 80E+04	
	DOM7h-11-3	10000 (88000)	(7.18e-1)	(8.11e3)	
1.5	DOM7h-11-12	200	5.22E-01	2.76E+06	
15	DOM7h-11-15	20	2.10E-02	1.10E+06	
	DOM7h-11-18	80 (29000)	6.0E-02	1.64E+06	
			(3.7e-1)	(1.3e4)	
	DOM7h-11-19	28 (17000)	9.1e-02	9.80E+05	
		C	(1.4c-1)	(8.1c3)	
20		Cyno			
	DOM7h-14	66	9.65E-02	1.50E+06	
	DOM7h-14-10	9	1.15E-02	1.60E+06	
	DOM7h-14-18	180	1.05E-01	6.30E+5	
	DOM7h-14-19	225	1.56E-01	7.00E+05	
25	DOM7h-14-28	66 (136)	1.3E-01	2.50E+06	
25	DOM 71 14 24	25 (7920)	(1.34e-1)	(9.8e5)	
	DOM/n-14-36	35 (7830)	1.9E-02	9.80E+06	
	DOM7h-11	1000	(1.1e-1) 6.82E-01	(1.4564) 8.00E±05	
	DOM7h-11-3	670 (200)	9.6E-02	2.90E+05	
	2011/11/11/0	0,00 (200)	(1.5e-1)	(7.26e5)	
30	DOM7h-11-12	≥6000	× /	× /	
	DOM7h-11-15	3	5.57E-03	5.80E+06	
	DOM7h-11-18	10000 (65000)	1.36	2.25E+05	
	DOM75-11-10	>10000 (375000)	(4.8e-1)	(7.3e3) (1.7e3)	
	DOM/II-11-19	210000 (375000) Mouse	(0.20-1)	(1.765)	
35					
55	DOM7h-14	12	4.82E-02	4.10E+06	
	DOM7h-14-10	30	3.41E-02	1.29E+06	
	DOM7h-14-18	65	9.24E-02	2.28E+06	
	DOM/fi-14-19 DOM7b 14-28	00 26 (31)	5.70E-02 3.4E 02	1.10E+00	
	DOIV1/11-14-28	20 (51)	(7.15e-2)	(2, 28e6)	
40	DOM7h-14-36	35 (33)	2.3E-02	8.70E+05	
			(7.06e-2)	(2.11e6)	
	DOM7h-11	5000	9.00E-01		
	DOM7h-11-3	≥10000 (36000)	(6.12e-1)	(1.67e4)	
	DOM7h-11-12	130	1.89E-01	1.53E+06	
45	DOM7h-11-15	10	9.40E-03	1.10E+06	
75	DOM/11-11-18	150 (1000)	(6.23e-2)	4.40E+03	
	DOM7h-11-19	100 (18000)	(0.23c-2) 3 7E-02	1 40E+06	
	Domin II IV	100 (10000)	(8.8e-2)	(4.9e3)	
		Human	· · · · ·	· · ·	
	DO1/71-14	22	4175.00	1.435.04	
50	DOM/n-14 DOM7h 14 10	33	4.17E-02	1.43E+06	
	DOM7h-14-18	280	3.39E-02	1.30E+05	
	DOM7h-14-19	70	5.25E-02	8.26E+05	
	DOM7h-14-28	30 (8260)	3.3E-02	1.24E+06	
		, , , , , , , , , , , , , , , , , , ,	(5.6e-2)	(6.78e3)	
55	DOM7h-14-36	28 (1260)	2.4E-02	1.23E+06	
	5 0 1 1 1 1		(6.7e-2)	(5.4e4)	
	DOM7h-11	2800	6.41E-01	7.00E+05	
	DOM/II-11-3	32 (130)	(2.35 = 2)	0.300+03	
	DOM7h-11-12	350	(2.550-2) 4.13E-01	1.26E+06	
	DOM7h-11-15	1	1.84E-03	2.00E+06	
60	DOM7h-11-18	36 (32000)	5.1E-02	3.40E+06	
			(2.7e-1)	(8.39e3)	
	DOM7h-11-19	65 (38000)	1.1E-01	1.80E+06	
			(2.09e-1)	(5.4e3)	

*: values in brackets were derived from a second, independent SPR experiment.

All DOM7h-14 derived variants are cross-reactive to mouse, rat, human and cyno serum albumin. DOM7h-14-10

has improved affinity to rat, cyno and human serum albumin compared to parent. DOM7h-14-28 has an improved affinity to RSA. DOM7h-14-36 has an improved affinity to RSA, CSA and MSA.

DOM7h-11-3 has improved affinity to CSA and HSA. ⁵ DOM7h-11-12 has improved affinity to RSA, MSA and HSA. DOM7h-11-15 has improved affinity to RSA, MSA, CSA and HSA. DOM7h-11-18 and DOM7h-11-19 have improved affinity to RSA, MSA and HSA.

Example 3

Origins of Key DOM7h-11 Lineage Clones

DOM7h-11-3: From affinity maturation performed against HSA using the CDR2 library (Y49, A50, A51, S53), ¹⁵ round 3 output 10 nM HSA

DOM7h-11-12: From affinity maturation performed against HSA using the error prone library, round 3 outputs (100 nM, HSA) with 100 ug/ml trypsin.

DOM7h-11-15: From cross-over selections performed against HSA as round 1 followed by additional 3 rounds of selections against RSA using the CDR2 library (Y49, A50, A51, S53) at round 3 selection with 1 nM of RSA.

DOM7h-11-18 From cross-over selections performed against HSA as round 1 followed by additional 3 rounds of selections against RSA using the error prone library, round 3 output at 20 nM of RSA

DOM7h-11-19 From cross-over selections performed against HSA as round 1 followed by additional 3 rounds of selections against RSA using the error prone library, round 3 output at 5 nM of RSA

TABLE 7

CDR se	equences (accord	ing to Kabat; ref	. as above)
	CDR		
ALBUDAB™	CDR1	CDR2	CDR3
DPK9 Vk dummy	SQSISSYLN	YAASSLQS	QQSYSTPNT
	(SEQ ID NO: 335) (SEQ ID NO: 336) (SEQ ID NO: 337)
DOM7h-11	SRPIGTTLS	WFGSRLQS	AQAGTHPTT
	(SEQ ID NO: 338) (SEQ ID NO: 339) (SEQ ID NO: 340)
DOM7h-11-12	SRPIGTMLS	LFGSRLQS	AQAGTHPTT
	(SEQ ID NO: 341) (SEQ ID NO: 342) (SEQ ID NO: 343)
DOM 7h-11-15	SRPIGTMLS	LAFSRLQS	AQAGTHPTT
	(SEQ ID NO: 344) (SEQ ID NO: 345) (SEQ ID NO: 346)
DOM 7h-11-18	SRPIGTMLS	WFGSRLQS	AQAGTHPTT
	(SEQ ID NO: 347) (SEQ ID NO: 348) (SEQ ID NO: 349)
DOM 7h-11-19	SRPIGTMLS	LFGSRLQS	AQTGTHPTT
	(SEQ ID NO: 350) (SEQ ID NO: 351) (SEQ ID NO: 352)
DOM 7h-11-3	SRPIGTTLS	LWFSRLQS	AQAGTHPTT
	(SEQ ID NO: 353) (SEQ ID NO: 354) (SEQ ID NO: 355)

Example 4

Origins of Key DOM7h-14 Lineage Clones

DOM7h-14-19: From affinity maturation performed against HSA using the error prone library, round 3 outputs (100 nM, HSA) with 100 ug/ml trypsin.

DOM7h-14-10, DOM7h-14-18, DOM7h-14-28, 50 DOM7h-14-36: From affinity maturation performed against HSA using CDR3 library (Y92, Y93, T94, N96), round 3 output.

TABLE	8
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CDR se	equences (accordi	nq to Kabat; ref.	as above)
		CDR	
ALBUDAB™	CDR1	CDR2	CDR3
DPK9 Vk dummy	SQSISSYLN	YAASSLQS	QQSYSTPNT
	(SEQ ID NO: 335)	(SEQ ID NO: 336)	(SEQ ID NO: 337)
DOM 7h-14	SQWIGSQLS	MWRSSLQS	AQGAALPRT
	(SEQ ID NO: 356)	(SEQ ID NO: 357)	(SEQ ID NO: 358)
DOM 7h-14-10	SQWIGSQLS	MWRSSLQS	AQGLRHPKT
	(SEQ ID NO: 359)	(SEQ ID NO: 360)	(SEQ ID NO: 361)

TABLE 8-continued

	CDR sequences (according to Kabat; ref. as above)							
	CDR							
ALBU	JDAB™	CDR1		CDR2		CDR3		
DOM	7h-14-18	SQWIGSQLS (SEQ ID NO:	362)	MWRSSLQS (SEQ ID NO:	363)	AQGLMKPMT (SEQ ID NO: 364)		
DOM	7h-14-19	SQWIGSQLS (SEQ ID NO:	365)	MWRSSLQS (SEQ ID NO:	366)	AQGAALPRT (SEQ ID NO: 367)		
DOM	7h-14-28	SQWIGSQLS (SEQ ID NO:	368)	MWRSSLQS (SEQ ID NO:	369)	AQGAALPKT (SEQ ID NO: 370)		
DOM	7h-14-36	SQWIGSQLS (SEQ ID NO:	371)	MWRSSLQS (SEQ ID NO:	372)	AQGFKKPRT (SEQ ID NO: 373)		

Example 5

Expression and Biophysical Characterisation

The routine bacterial expression level in 2.5 L shake flasks was determined following culture in Onex media at 30° C. for 48 hrs at 250 rpm. The biophysical characteristics were determined by SEC MALLS and DSC.

SEC MALLS (size exclusion chromatography with multiangle-LASER-light-scattering) is a non-invasive technique for the characterizing of macromolecules in solution. 30 Briefly, proteins (at concentration of 1 mg/mL in buffer Dulbecco's PBS at 0.5 ml/min are separated according to their hydrodynamic properties by size exclusion chromatography (column: TSK3000 from TOSOH Biosciences; S200 from Pharmacia). Following separation, the propensity of 35 the protein to scatter light is measured using a multi-angle-LASER-light-scattering (MALLS) detector. The intensity of the scattered light while protein passes through the detector is measured as a function of angle. This measurement taken together with the protein concentration determined using the 40 refractive index (RI) detector allows calculation of the molar mass using appropriate equations (integral part of the analysis software Astra v.5.3.4.12). DSC (Differential Scanning calorimetry): briefly, the protein is heated at a constant rate of 180° C./hrs (at 1 mg/mL in PBS) and a detectable heat 45 change associated with thermal denaturation measured. The transition midpoint $(_{app}T_m)$ is determined, which is described as the temperature where 50% of the protein is in its native conformation and the other 50% is denatured. Here, DSC determined the apparent transition midpoint 50 (appTm) as most of the proteins examined do not fully refold. The higher the Tm, the more stable the molecule. Unfolding curves were analysed by non-2-state equations. The software package used was $\operatorname{Origin}^{R}$ v7.0383.

TABLE 9

Biophysical parameters			
SEC MALLS	DSC Tm(° C.)	_	
М	60	60	
М	59		
М	58		
М	59		
М	58.3/60.2		
М	59.2		
М	66.9-72.2	65	
M (95%)*	66.6/70.5		
	Biophysic SEC MALLS M M M M M M M M M M M (95%)*	Biophysical parameters SEC MALLS DSC Tm(° C.) M 60 M 59 M 58 M 59 M 59 M 59 M 59 M 59 M 59.2 M 66.9-72.2 M (95%)* 66.6/70.5	

TABLE 9-continued

	Biophy	Biophysical parameters				
ALBUDAB TM	SEC MALLS	DSC Tm(° C.)				
DOM7h-11-12 DOM7h-11-15 DOM7h-11-18 DOM7h-11-19	M (<2% D) M (<5% D) M (98%) M	71.7 58.5-60.5 58.9/65.8 71.8/76.6				

*in one other trial, monomer was primarily seen by SEC MALLS, although lower than 95%

We observed expression levels for all clones in Table 9 in the range from 15 to 119 mg/L in $E \ coli$.

For DOM7h-14 and DOM7h-11 variants, favorable biophysical parameters (monomeric in solution as determined by SEC MALLs and appTm of $>55^{\circ}$ C. as determined by DSC) and expression levels were maintained during affinity maturation. Monomeric state is advantageous because it avoids dimerisation and the risk of products that may cross-link targets such as cell-surface receptors.

Example 6

Determination of Serum Half Life in Rat, Mouse and Cynomolgus Monkey

ALBUDABs[™] DOM7h-14-10, DOM7h-14-18, DOM7h-14-19, DOM7h-11, DOM7h11-12 and DOM7h-11-15 were cloned into the pDOM5 vector. For each ALBUDAB[™], 20-50 mg quantities were expressed in *E. coli* and purified from bacterial culture supernatant using protein L affinity resin and eluted with 100 mM glycine pH2. The proteins were concentrated to greater than 1 mg/ml, buffer exchanged into PBS and endotoxin depleted using Q spin columns (Vivascience). For Rat pharmacokinetic (PK) analysis, 55 ALBUDABs[™] were dosed as single i.v injections at 2.5 mg/kg using 3 rats per compound. Serum samples were taken at 0.16, 1, 4, 12, 24, 48, 72, 120, 168 hrs. Analysis of serum levels was by anti-myc ELISA as per the method described below.

For Mouse PK, DOM7h-11, DOM7h11-12 and DOM7h-11-15 were dosed as single i.v injections at 2.5 mg/kg per dose group of 3 subjects and serum samples taken at 10 mins; 1 h; 8 h; 24 h; 48 h; 72 h; 96 h. Analysis of serum levels was by anti-myc ELISA as per the method described below.

For Cynomolgus monkey PK DOM7h-14-10 and DOM7h-11-15 were dosed as single i.v injections at 2.5

mg/kg into 3 female Cynomolgus monkeys per dose group and serum samples taken at 0.083, 0.25, 0.5, 1, 2, 4, 8, 24, 48, 96, 144, 192, 288, 336, 504 hrs. Analysis of serum levels was by anti-myc ELISA as per the method described below. Anti-Myc ELISA Method

The ALBUDAB[™] concentration in serum was measured by anti-myc ELISA. Briefly, goat anti-myc polyclonal antibody (1:500; Abcam, catalogue number ab9132) was coated overnight onto Nunc 96-well Maxisorp plates and blocked with 5% BSA/PBS+1% tween. Serum samples were added at a range of dilutions alongside a standard at known concentrations. Bound myc-tagged ALBUDAB™ was then detected using a rabbit polyclonal anti-Vk (1:1000; in-house reagent, bleeds were pooled and protein A purified before 15 use) followed by an anti-rabbit IgG HRP antibody (1:10, 000; Sigma, catalogue number A2074). Plates were washed between each stage of the assay with 3×PBS+0.1% Tween20 followed by 3×PBS. TMB (SureBlue TMB 1-Component Microwell Peroxidase Substrate, KPL, catalogue number 20 52-00-00) was added after the last wash and was allowed to develop. This was stopped with 1M HCl and the signal was then measured using absorbance at 450 nm.

From the raw ELISA data, the concentration of unknown samples was established by interpolation against the stan-²⁵ dard curve taking into account dilution factors. The mean concentration result from each time point was determined from replicate values and entered into WinNonLin analysis package (eg version 5.1 (available from Pharsight Corp., Mountain View, Calif. 94040, USA). The data was fitted ³⁰ using a non-compartmental model, where PK parameters were estimated by the software to give terminal half-lives. Dosing information and time points were selected to reflect the terminal phase of each PK profile.

TABLE 10

	Si	ngle ALBU	DAB ™ PK				
	eters		40				
Species	AlbudAb	Albumin K _D (nM)	$\begin{array}{l} AUC \\ h \times \mu g/ml \end{array}$	CL ml/h/kg	t½ h	Vz ml/kg	-10
Rat	DOM7h-14*	60					
	DOM7h-14-10	4	2134.6	1.2	42.1	71.2	
	DOM7h-14-18	410	617.3	4.1	38.4	228.1	45
	DOM 7h-14-19	890	632.6	4.1	36.3	213.3	
	DOM 7h-11	2100	320.1	7.8	23.3	263.9	
	DOM 7h-11-12	200	398.7	6.4	35.5	321.2	
	DOM 7h-11-15	20	843.4	3.0	30.3	130.7	
mouse	DOM 7h-11	5000	304.7	8.2	18.3	216.8	
	DOM 7h-11-12	130	646.6	3.9	43.9	244.8	50
	DOM 7h-11-15	10	499.2	5.0	33.7	243.4	
Cyno	DOM 7h-14*	66			217.5		
	DOM 7h-14-10	9	6174.6	0.4	200.8	117.8	
	DOM 7h-11*	3300			135.1		
	DOM 7h-11-15	3	4195	0.6	198.1	170.3	

*Historical data

Pharmacokinetic parameters derived from rat, mouse and cynomolgus monkey studies were fitted using a non-compartmental model. Key: AUC: Area under the curve from dosing time extrapolated to infinity; CL: clearance; t1/2: is 60 the time during which the blood concentration is halved; Vz: volume of distribution based on the terminal phase.

DOM7h-11 12 and DOM7h-11-15 have an improved AUC and t1/2 in rat and mouse compared to parent. DOM7h-11-15 also has an improved AUC and t1/2 in cyno 65 compared to parent. This improvement in AUC/t1/2 correlates with an improved in vitro KD to serum albumin.

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Example 7

ALBUDAB™ IFN Fusions

Cloning and Expression

As well as single ALBUDABsTM, the affinity matured Vk ALBUDABsTM were linked to Interferon alpha 2b (IFN α 2b) to determine whether a useful PK of the ALBUDABTM was maintained as a fusion protein.

Interferon Alpha 2b Amino Acid Sequence:

	(SEQ	ID	NO:	374)
CDLPOTHSLGSRRTLMLLAOMRRISLFSCLKDRHD	FGFPO	EEF	GNOF	OKA
			~	
ETIPVLHEMIQQIFNLFSTKDSSAAWDETLLDKFY	TELYQ	QLN	DLEA	CVI

QGVGVTETPLMKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRS

FSLSTNLQESLRSKE

Interferon Alpha 2b Nucleotide Sequence:

(SEQ ID NO: 375)
 TGTGATCTGCCTCAAACCCACAGCCTGGGTAGCAGAGAGGACCTTGATGCT
 CCTGGCACAGATGAGGAGAATCTCTCTTTTCTCCTGCTTGAAGGACAGAC
 ATGACTTTGGATTTCCCCAGGAGGAGTTTGGCAACCAGTTCCAAAAGGCT
 GAAACCATCCCTGTCCTCCATGAGATGATCCAGCAGATCTTCAATCTCTT
 CAGCACAAAGGACTCATCTGCTGCTGGGATGAGAGCCCTGCTGTGAAA
 CAGGGGGTGGGGGGTGACAGAGACTCCCCTGATGAAGGAGGACTCCCATTCT
 GGCTGTGAGGAAATACTTCCAAAGGATCATCAGAGA
 GAAATACAGCCCTTGTGCCTGGGAGGTTGTCAGAGCAGAAATCATGAGA
 TCTTTTCTTTGTCAACAAACTTGCAAGAAAGTTTAAGAAGTAAGGAA

IFNa2b was linked to the ALBUDAB[™] via a TVAAPS (SEQ ID NO: 422) linker region (see WO2007085814). The constructs were cloned by SOE-PCR (single overlap extension according to the method of Horton et al. Gene, 77, p 61 (1989)). PCR amplification of the ALBUDAB[™] and IFN sequences were carried out separately using primers with a ~15 base pair overlap at the TVAAPS (SEQ ID NO: 422) linker region. The primers used are as follows:—

	IFN α 2b SOE fragment 5'	(CEO	тр	NO	276)
	GCCCGGATCCACCGGCTGTGATCTG	(SEQ	тD	NO:	370)
	IFN α 2b SOE fragment 3'	(CEO	TD	NO	277)
55	GGAGGATGGAGACTGGGTCATCTGGATGTC	(SEQ	тD	NO:	377)
	Vk SOE fragment 5'	(CEO	TD	NO	270)
	GACATCCAGATGACCCAGTCTCCATCCTCC	(SEQ	тр	NO:	378)
60	Vk SOE fragment 3' to also introduc	eam	yc	tag	

(SEQ ID NO: 379) GCGCAAGCTTTTATTAATTCAGATCCTCTTCTGAGATGAGTTTTTGTT

CTGCGGCCGCCCGTTTGATTTCCACCTTGGTCCC

The fragments were purified separately and subsequently assembled in a SOE (single overlap extension PCR extension) reaction using only the flanking primers.

IFN α 2b SOE fragment 5'

(SEQ ID NO: 380)

GCCCGGATCCACCGGCTGTGATCTG

Vk SOE fragment 3' to also introduce a myc tag

(SEQ ID NO: 381)

GCGCAAGCTTTTATTAATTCAGATCCTCTTCTGAGATGAGTTTTTGTTCT

GCGGCCGCCCGTTTGATTTCCACCTTGGTCCC

The assembled PCR product was digested using the restriction enzymes BamHI and HindIII and the gene ligated into the corresponding sites in the pDOM50, a mammalian expression vector which is a pTT5 derivative with an N-terminal V-J2-C mouse IgG secretory leader sequence to facilitate expression into the cell media.

Leader Sequence (Amino Acid):

METDTLLLWVLLLWVPGSTG

(SEQ ID NO: 382)

⁵ Leader Sequence (Nucleotide):

(SEQ ID NO: 383)

ATGGAGACCGACACCCTGCTGCTGTGGGTGCTGCTGCTGCTGGGTGCCCGG

10 ATCCACCGGGC

Plasmid DNA was prepared using QIAfilter megaprep (Qiagen). 1 µg DNA/ml was transfected with 293-Fectin into HEK293E cells and grown in serum free media. The protein is expressed in culture for 5 days and purified from culture supernatant using protein L affinity resin and eluted with 100 mM glycine pH2. The proteins were concentrated to greater than 1 mg/ml, buffer exchanged into PBS and endotoxin depleted using Q spin columns (Vivascience).

TABLE 11

Interferon alpha 2b-ALBUDAB™ sequences with and without
myc-tag (as amino acid- and nucleotide sequence)
The Interferon alpha 2b is N-terminal to the ALBUDAB [™] in
the following fusions.

DMS7321 CDLPQTHSLGSRRT TGCGACTTGCC CDLPQTHSLG TC (IFNα2b-LMLLAQMRRISLFS ACAGACACAT SRRTLMLLA AC DOM7h- CLKDRHDFGFPQE AGTTTGGGATC QMRRISLFSC AC 14) EFGNQFQKAETIPV AAGAAGAACA LKDRHDFGFP AF LHEMIQQIFNLFST TTGATGTTATT QEEFGNQFQ TT KDSSAAWDETLLD AGCACAAATG KAETIPVLHE AC KFYTELYQQLNDL CGTAGAATTC MIQQIFNLFS CC EACVIQGVGVTETP TTTGTCTCTT TKDSSAAWD TT LMKEDSILAVRKY GTCTAAAGGAC ETLLDKFYTE GT FQRITLYLKEKKYS CGTCACGACTT LYQQLNDLE CC SFSLSTNLQESLRS AGGAAGAGTT TETPLMKEDS CF KETVAAPSDIQMT GGAAACCAATT LAVRKYFQR TT QSPSSLSASVGDRV CCAAAAGGA ITLYLKEKKY AT TITCRASQWIGSQL GAAACTATTCC SPCAWEVVR G SWYQQKPGKAPKL TGTCTTGCAG AEIMRSFSLS TT LIMWRSSLQSGVPS AAATGATCCAG TNLQESLRSK CF RF5GSGSGTDFTLT CAAATATTCAG ETVAAPSDIQ TC ISSLQPEDFATYYC TTTGTTTTCTA MTQSPSSLSA TT AQGAALPRTFGQG CAAAGGACT SVGDRVTITC TT KVEIKR ATCAGCGCGCTT RASQWIGSQL AC AAAEQKLISEEDL GGAGAGACT SVQQKPGK GG N* (SEQ ID NO: 384) TCTGTTAGATA APKLLIMWR AF AATCTACACT SSLQSGVPS ACACGAGT TLTISLQPED TC GACACTGAAC TLTISSLQPED TC GACACTGAAC TLTISSLQPED TC GACTATATCA FSGSGSGTDF TC								
<pre>(IFNα2b-LMLLAQMRRISLFS ACAGACACAT SRRTLMLLA AC DOMTh- CLKDRHDFGFPQE ACTTGGGATC QMRRISLFSC AC 14) EFGNQFQKAETIPV AAGAAGAACA LKDRHDFGFP AC LHEMIQQIFNLFST TTGATGTTATT QEEFGNQFQ TT KDSSAAWDETLLD AGCACAAATG KAETIPVLHE AC KFYTELYQQLNDL CGTAGAATTC MIQQIFNLFS CC EACVIQGVGVTETP TTTGTCTCTT TKDSSAAWD TT LMKEDSILAVRKY GTCTAAAGGAC ETLLDKFYTE GT FQRITLYLKEKKYS CGTCACGACTT LYQQLNDLE CC PCAWEVVRAEIMR CGGATCCCTC ACVIQGVGV TC SF5LSTNLQESLRS AGGAAGAGTTT TETPLMKEDS CZ KETVAAPSDIQMT GGAAACCAATT ILAVRKYPQR TT QSPSSLSASVGDRV CCAAAAAGCA ITLYLKEKKY AT TITCRASQWIGSQL GAAACCAATT ILAVRKYPQR TT LIMWRSSLQSGVPS AAATGATCCS PCAWEVVR GC SWYQQKPGKAPKL TGTCTTGCACG AEIMRSFSLS TT LIMWRSSLQSGVPS AAATGATCCAG TNLQESLRSK CZ RFSGSGSGTDFTLT CAAATATTCAA ETVAAPSDIQ TC ISSLQPEDFATYYC TTTGTTTTCTA MTQSFSSLSA TT AQGAALPRTFGQG CAAAGGACT SWQQKPGK GC N★ (SEQ ID NO: 384) TCTGTAGAAA SWYQQKPGK GC AAACCAATA FLSLQSUPS AAATGCACA TLISSLQPED GAACCTATATCA FSGSGSGTDF AC ACAACTGAAC TLTISSLQPED TC GAACTATATCA FSGSGSGTDF AC ACAACTGAAC TLTISSLQPED TC GAACTATATCA FSGSGSGTDF AC ACAACTGAAC TLTISSLQPED TC GAACTATATCA APKLLIMWR AC AATTCTACAGGG GTKVEKK TT GAACTATATCA APKLLIMWR AC ACAACTGAAC TLTISSLQPED TC GATCTAGAGGG GTKVEKK TT AGGAGTGTAGG GTKVEKK TT AGGGTGTAGG GTKVEKK TT AGGGTGTAGG GTKVEKK TT AGGGTGTAGG GTKVEKK TT AGGTTACTGAAA (SEQ ID GC</pre>	GCGACTTGCC							
DOM7h- CLKDRHDFGFPQE AGTTTGGAGATC QMRRISLFSC AG 14) EFGNQFQKAETIPV AAGAAGAACA LKDRHDFGFP AG LHEMIQQIFNLFST TTGATGTTATT QEEFGNQFQ TT KDSSAAWDETLLD AGCACAAATG KAETIPVLHE AG KPYTELYQQLNDL CGTAGAATTC MIQQIFNLFS CG EACVIQQVGVTETP TTTGTTCTCTT TKDSSAAWD TT LMKEDSILAVRKY GTCTAAAGGAC ETLLDKFYTE GT PQRITLYLKEKKYS CGTCACGACTT LYQUNDLE CG PCAWEVVRAEIMR CGGAATCCCTC ACVIQGVGV TG SFSLSTNLQESLRS AGGAAGAGTTT TETPLMKEDS CA VESSLSASVGDRV CCAAAAAGCA ITLYLKEKKY AT QSPSSLSASVGDRV CCAAAAAGCA ITLYLKEKKY AT TITCRASQWIGSQL GAAACTATTCC SPCAWEVVR GG SWYQQKPGKAPKL TGTCTTGCACG AEIMRSFSLS TT LIMWRSSLQSGVPS AAATGATCCAG TNLQESLRSK CZ RFSGSGSGTDFTLT CAAAGGACT SVGDRVITC TT AQGAALPRTFGQG CAAAGGACT SVGDRVITIC TT AQGAALPRTFGQG CAAAGGACT SVQQKPGK GG N* (SEQ ID NO: 384) TCTGTAGAAAC SWYQQKPGK GG AAAEQKLISEEDL GGACTATATCA FSGSGSGTDF AC GAACTATATCA FSGSGSGTDF AC ACAACTGAAAC TLTISSLQPED TO GAACTATATCA FSGSGSGTDF AC ACAACTGAAAC TLTISSLQPED TO	CAGACACAT							
 14) EFGNQPQKAETIPV AAGAAGAACA LKDRHDFGFP AA LHEMIQQIFNLFST TTGATGTTATT QEEFGNQFQ TT KDSSAAMDETLLD AGCACAAAG KAETIPVLHE AC KFYTELYQQLNDL CGTAGAATTTC MIQQIFNLFS CC EACVIQGVGVTETP TTTGTTCTCTT TKDSSAAWD TT LMKEDSILAVRKY GTCTAAAGGAC ETLLDKFYTE GT FQRITLYLKEKKYS CGTCACGACTT LYQQLNDLE CC PCAWEVVRAEIMR CGGATCCCTC ACVIQGVGV TC SFSLSTNLQESLRS AGGAAGAGTTT TETPLMKEDS CA KETVAAPSDLQMT GGAAACCAATT ILAVRKYFQR TT QSPSSLSASVGDRV CCAAAAAGCA ITLYLKEKKY AT TITCRASQWIGSQL GAAACTATTCC SPCAWEVVR GG SWYQQRPGKAPKL TGTCTTGCACG AELMRSFSLS TT LIMWRSSLQSGVPS AAATGATCCAG TNLQESLRSK CA RFSGSGSGTDFTLT CAAAATGCAC SVGDRVTITC TT AQGAALPRTFGQG CAAAGGACT SVGDRVTITC TT TKVEIKR ATCAGCGCGCTT RASQWIGSQL AC AAAEQKLISEEDL GGAGAGACC SWQQVPGK GG N* (SEQ ID NO: 384) TCTGTTAGATA APKLLIMWR AA AATTCTACACT SSLQSGVPS AAATGAACCAS TLISSLQPED GAACTATATCA FSGSGSGTDF A GAACTATATCA FSGSGSGTDF A CAAAGGGG TKVEFKR TT GAACTATATCA FTSGSGSGTDF A GAACTATATCA FSGSGSGTDF A CAAACTGAAC TLTISSLQPED TC GATCTAGAGGG GTKVEFKR TT GAACTATATCA ALPRTFGQ CAAGGGG GTKVEFKR TT GAACTATATCA ALPKFR TC GAACTGAAG GTKVEFKR TT GAACTATATCA ALPKFR TC GAACTATATCA ALPKFR TC GAACTGAAG GTKVEFKR TT GAACTATATCA ALPKFR TC GAACTATATCA ALPKFRF TC AGGGTGTAGG GTKVEFKR TT GAACTATACAA (SEQ ID GC 	GTTTGGGATC							
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KDSSAAWDETLLDAGCACAAATGKAETIPULHEAGKFYTELYQQLNDLCGTAGAATTCMIQQIFNLFSCGEACVIQGVGVTETPTTTGTTCTCTTTKDSSAAWDTTLMKEDSILAVRKYGTCTAAAGGACETLLDKFYTEGTPQRITLYLKEKKYSCGTCACGACTTLYQQLNDLECGPCAWEVVRAEIMRCGGATCCCTCACVIQGVGVTGSFSLSTNLQESLRSAGGAAGAGTTTETPLMKEDSCGQSPSSLSASVGDRVCCAAAAAGCAITLVLKEKKYATTITCRASQWIGSQLGAAACCAATTSPALENSGGSWQQKPGKAPKLTGTCTTGCACGAEIMRSFSLSTTLIMMESSLQSGVPSAAATGATCCAGTNLQESLRSKCGRFSGSGSGTDFTLTCAAATATTCAAETVAAPSDIQTGAQGAALPRTFGQGCAAAGGACTSVGDRVTITCTTAQGAALPRTFGQGCAAAGGACTSWQQKPGKGGN*(SEQ ID NO: 384)TCTGTTAGAAAAPKLLIMWRAAAATCTACACTSSLQSGVDFFACAACTGAACTLISSLQPEDGACTATATCAFSGSGSGTDFFGAACTATATCAAATCTACACTSSLQSGVPFAAAGULISEEDLGGGATGAAACTTTGSTTAGAGGACAACTGAACTTTGCGTTATACAAAACTATATCAAATCTACACTSSLQSGVPFACAACTGAACTTTSLQENFGACTATATCAAATCTACAGGCTATTSLQEVPEDGACGTGTAGGGACVENTGACTATATCAAATCTAGAGGGGTKVEIKRTTGACGTGTAGGGTKVENKRGACGTTACGAGAGACTATATCAAATCTAGAGGGTKVENKRTTGACGTATAGGGGTKVENKRGACGTATAGGG	TGATGTTATT							
KFYTELYQQLNDLCGTAGAATTTC MIQQIPNLES CCEACVIQGVGVTETPTTTGTTCTCTT TKDSSAAWDTTLMKEDSILAVRKYGTCTAAAGGAC ETLLDKFYTE G'FQRITLYLKEKKYSCGTCACGACTT LYQQLNDLECCPCAWEVVRAEIMRCGGATCCCTC ACVIQGVGVTCSFSLSTNLQESLRSAGGAAGAGTTT TETPLMKEDS CZKETVAAPSDIQMTGGAAACCAATT ILAVRKYFQRTTQSPSSLSASVGDRVCCAAAAAGCA ITLVLKEKKYATTITCRASQWIGSQLGAAACTATTCC SPCAWEVVRGCSWYQQKPGKAPKLTGTCTTGCACG AEIMRSFSLSTTLIMMRSSLQSGVPSAAATGTTCAA ETVAAPSDIQTCISSLQPEDFATYYCTTAGTTTCTA MTQSPSSLSATTAQGAALPRTFGQGCAAAGGACTCSVGQRVTITCTTTKVEIKRATCAGCCGCTTRASWIGSQLAC AAATGCKLISEEDL GGGATGAAACSWQQKPGKGC N* (SEQ ID NO: 384)TCTGTTAGATA APKLLIMWRAAAAAACTGAACTLISSLQPED TCGAACTATATCA FSGSGSGTDFACACAACTGAACTLTSSLQPEDTCGAACTATATCA AESCGVPSRACACAACTGAACTLTSSLQPEDTCGACTATATCA ALPRTFQQACAGGGTGTAGGGTKVEIKRTTAGGTACTAGAGG GTKVEIKRTT	GCACAAATG							
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PCAMEVVRAEIMR CGGATCCCTC ACVUGVGV TC SFSLSTNLQESLRS AGGAAGAGTTT TETPLMKEDS CZ KETVAAPSDIQMT GGAAACCAATT ILAVRKYFQR TT QSPSSLSASVGDRV CCAAAAAGCA ITLVLKEKKY AT TITCRASQWIGSQL GAAACTATTCC SPCAWEVVR GC SWYQQKPGKAPKL TGTCTTGCACG AEIMRSFSLS TT LIMWRSSLQSGVPS AAATGATCCAG TNLQESLRSK CZ RFSGSGSGTDFTLT CAAATGATCCAG TNLQESLRSK CZ RFSGSGSGTDFTLT CAAATGATCCAG TNLQESLRSK CZ AQGAALPRTFGQG CAAAGGACTC SVGDRVTITC T TKVEIKR ATCAGCCGCTT RASQWIGSQL AC AAAEQKLISEEDL GGGATGAAAC SWYQQKPGK GC N* (SEQ ID NO: 384) TCTGTTAGATA APKLLIMW AZ AATTCTACACT SSLQSGVPS AT GAACTATATCA FSGSGSGTDF AC ACAACTGAAC TLTISSLQPED TC GATCTAGAGGC FATYYCAQG AC TTGCGTTATG GTRAGGG GTKVEIKR TC	TCTAAAGGA							
SFSLSTNLQESLRS AGGAAGACTT TETPLMKEDS C KETVAAPSDIQMT GGAAAACCAATT ILAVRKYFQR T QSPSSLSASVGDRV CCAAAAAGCA ITLVLKEKKY AT TITCRASQWIGSQL GAAACTATTCC SPCAWEVVR GC SWYQQKPGKAPKL TGTCTGCACG AEIMRSFSLS T LIMMRSSLQSGVPS AAATGATCCAG TNLQESLRSK CZ RFSGSGSGTDFTLT CAAATATTCAA ETVAAPSDIQ TC ISSLQPEDFATYYC TTTGTTTCTA MTQSPSSLSA T AQGAALPRTFGQG CAAAGGACTC SVGDRVTITC T TKVEIKR ATCAGCCGCTT RASQWIGSQL AC AAAEQKLISEEDL GGGATGAAAC SWYQQKPGK GC N* (SEQ ID NO: 384) TCTGTTAGATA APKLLIMWR AZ AATTCTACACT SSLQSGVPS A GAACTATATCA FSGSGSGTDF AC CAACTGAAC TLTISSLQPED TC GATCTAGAGGC FATYYCAQG AC TTGCGTTATG ALPRTFQQ GC AGGGTGTAGG GTKVEIKR T AGGTACTGAAA (SEQ ID GC	CGICACGACI							
SFSDSTRUCTSSTAT AGGAAGAGTT ILLIFLIMMEDS C KETVAAPSDIQMT GGAAACCAATT ILLIFLIMMEDS C QSPSSLSASVGDRV CCAAAAAGCA ITLYLKEKKY AT TITCRASQWIGSQL GAAACTATTCC SPCAWEVVR GC SWYQQKPGKAPKL TGTCTTGCACG AEIMRSFSLS TT LIMWRSSLQSGVPS AAATGATCCAG TNLQESLRSK CZ RFSGSGSGTDFTLT CAAATATTCAA ETVAAPSDIQ TC ISSLQPEDPATYYC TTTGTTTTTCTA MTQSPSSLSA TT AQGAALPRTFGQG CAAAGGACTC SVGDRVTITC TT KVEIKR ATCAGCGCGTT RASWIGSQL AC AAABQKLISEEDL GGGATGAAAC SWQQKPGK AC N* (SEQ ID NO: 384) TCTGTTAGAAT APKLLIMWR AT GAACTATATCA FSGSGSGTDF AC ACAACTGAAC TLTSLQPED TC GAACTATATCA FSGSGSGTDF AC ACAACTGAAC TLTSLQPED TC GAACTATATCA FSGSGSGSGTDF AC ACAACTGAAC TLTSLQPED TC GAACTATATCA FSGSGSGSGTDF AC ACAACTGAAC TLTSLQPED TC GAACTATATCAA SALQPED	ACCARCACT							
QSPSSLSASVGDRV CCAAAAGCA ITLVLKEKKY AI TITCRASQWIGSQL GAAACTATTCC SPCAWEVVR GC SWYQQKPGKAPKL TGTCTTGCACG AEIMRSFSLS TJ LIMWRSSLQSGVPS AAATGATCCAG TNLQESLRSK CZ RFSGSGSGTDFTLT CAAATATTCAA ETVAAPSDIQ TC ISSLQPEDFATYYC TTTGTTTTCTA MTQSPSSLSA TJ AQGAALPRTFGQG CAAAGGACTC SVGDRVTITC TJ TKVEIKR ATCAGCCGCTT RASQWIGSQL AC AAAEQKLISEEDL GGGATGAAAC SWYQQKPGK GC N* (SEQ ID NO: 384) TCTGTTAGATA APKLLIMWR AZ AATTCTACACT SSLQSGVPSR AJ GAACTATATCA FSGSGSGTDF AC ACAACTGAAC TLTISSLQPED TC GATCTAGAGGG FATYYCAQ AC TTGCGTTATC AALPRTFGQ GC AGGGTGTAGG GTKVEIKR TJ AGGTACTGAAA (SEQ ID GC	TCCAAACCA							
QSFSUSSION CGAAACTATTCC SPCAWEVVR GGAACTATTCC SPCAWEVVR GG TITCRASQWIGSQL GAAACTATTCC SPCAWEVVR GG GGAACTATTCC SPCAWEVVR GG LIMMRSSLQSGVPS AAATGATCCAG TNLQESLRSK CZ RFSGSGSGTDFTLT CAAATATTCAA ETVAAPSDIQ TG ISSLQPEDFATYYC TTTGTTTTCTA MTQSPSSLSA TT AQGAALPRTFGQG CAAAGGACTC SVGDRVTITC TT TKVEIKR ATCAGCCGCTT RASQWIGSQL AC AAAEQKLISEEDL GGGATGAAAC SWYQQKPGK GA N* (SEQ ID NO: 384) TCTGTTGTAGATA APKLLIMWR AA GAACTATATCA FSGSGSGTDF AC ACAACTGAAC TLTISSLQPED GGATCTAAGGC GAACTATATCA FSGSGSGTDF AC ACAACTGAAC TLTSSLQPED GGATCTAAGGGC GAGGTGTAGG GTKVEIKR T AGGGTGTAGG GKVEIKR T	TTCCAAAAC							
SWYQQKPGKAPKL TGTCTTGCACG AEINGFVIL SWYQQKPGKAPKL TGTCTTGCACG AEINGFVILS T LIMWRSSLQSGVPS AAATGATCCAG TNLQESLRSK CZ RFSGSGSGTDFTLT CAAATGATCCAG TNLQESLRSK CZ RFSGSGSGTDFTLT CAAATGATCCAG TNLQESLSSK CZ AQGAALPRTFGQG CAAAGGACTC SVGDRVTITC T TKVEIKR ATCCACCGCTT RASQWIGSQL AC AAAEQKLISEEDL GGGATGAAAC SWYQQKPGK GC N* (SEQ ID NO: 384) TCTGTTAGATA APKLLIMW AZ AATTCTACACT SSLQSGVPSR AT GAACTATATCA FSGSGSGTDF AC ACAACTGAAC TLTISSLQPED TC GATCTAGAGGC FATYYCAQG AC TTGCGTATTC AALPRTFG TC AGGGTGTAGG GTKVEIKR TT AGTTACTGAAA (SEQ ID GC	CAGAAACTA							
LIMMESSLQSGVPS AAATGATCCAG TMLQESLRSK CZ RFSGSGSGTDFTLT CAAATGATCCAG TMLQESLRSK CZ ISSLQPEDFATYYC TTTGTTTTCTA MTQSPSSLSA TJ AQGAALPRTFGQG CAAAGGACTC SVGDRVTITC TJ TKVEIKR ATCAGCCGCTT RASQWIGSQL AC AAAEQKLISEEDL GGGATGAAAC SWYQQKPGK GC N* (SEQ ID NO: 384) TCTGTTAGATA APKLLIMWR AZ AATTCTACACT SSLQSGVPSR AJ GAACTATATCA FSGSGSGTDF AC ACAACTGAAC TLTISSLQPED TC GATCTAGAGGC FATYYCAQG AC TTGCGTTATTC AALPRTFAQG GC AGGGTGTAGG GTKVEIKR TT AGTTACTGAAA (SEQ ID GC	TCCTGTCTTG							
RFSGSGSGTDFTLT CAAATATTCAA ETVAAPSDIQ TC ISSLQPEDFATYYC TTTGTTTTCTA MTQSPSSLSA TT AQGAALPRTFGQG CAAAGGACTC SVGDRVTITC TT TKVEIKR ATCAGCGCGTT RASQWIGSQL AC AAAEQKLISEEDL GGGATGAAAC SWYQQKPGK GZ N* (SEQ ID NO: 384) TCTGTTAGATA APKLLIMWR AA AATTCTACACT SSLQSGVPSR AT GAACTATATCA FSGSGSGTDF AC ACAACTGAAC TLTISSLQPED TC GATCTAGAGGC FATYYCAQG AC TTGCGTTATTC AALPRTFGQ GC AGGGTGTAGG GTKVEIKR TT AGTTACTGAAA (SEQ ID GC	ACGAAATGA							
ISSLQPEDPATYYC TTTGTTTTCTA MTQSPSSLSA TT AQGAALPRTFGQG CAAAGGACTC SVGDRVTITC TT TKVEIKR ATCAGCGCGTT RASQWIGSQL AC AAAEQKLISEEDL GGGATGAAAC SWYQQKPGK GC N* (SEQ ID NO: 384) TCTGTTAGATA APKLLIMWR AF GAACTATATCA FSGSGSGTDF AC ACAACTGAAC TLTISSLQPED TC GAACTATATCA FSGSGSGTDF AC ACAACTGAAC TLTISSLQPED TC GACTATAGAGGC FATYYCAQG AC TTGCGTTATTC AALPRTFGQ GC AGGGTGTAGG GTKVEIKR TT AGTTACTGAAA (SEQ ID GC	CCAGCAAATA							
AQGAALPRTFGQG CAAAGGACTC SVGDRVTITC TT TKVEIKR ATCAGCCGCTT RASQWIGSQL AC AAAEQKLISEEDL GGGATGAAAC SWYQQKPGK GG N* (SEQ ID NO: 384) TCTGTTAGATA APKLLIMWR AA AATCTACACT SSLGSGVPSR AT GAACTATATCA FSGSGSGTDF AC ACAACTGAAC TLTISSLQPED TC GATCTAGAGGC FATYYCAQG AC TTGCGTTATTC AALPRTFGQ GC AGGGTGTTAGG GTKVEIKR TT AGTTACTGAAA (SEQ ID GC	TCAATTTGTT							
TKVEIKR ATCAGCCGCTT RASQWIGSQL AC AAAEQKLISEEDL GGGATGAAAC SWYQQKPGK GC N* (SEQ ID NO: 384) TCTGTTAGATA APKLLIMWR AA AATTCTACACT SSLQSGVPSR AT GAACTATATCA FSGSGSGTDF AC ACAACTGAAC TLTISSLQPED TC GATCTAGAGGC FATYYCAQG AC TTGCGTTATTC AALPRTFQC GC AGGGTGTTAGG GTKVEIKR TT AGTTACTGAAA (SEQ ID GC	TCTACAAAGG							
AAAEQKLISEEDL GGGATGAAAC SWYQQKPGK GC N* (SEQ ID NO: 384) TCTGTTAGATA APKLLIMWR AA AATTCTACACT SSLQSGVPSR AT GAACTATATCA FSGSGSGTPF AC ACAACTGAAC TLTISSLQPED TC GATCTAGAGGC FATYYCAQG AC TTGCGTTATTC AALPRTFGQ GC AGGGTGTAGG GTKVEIKR TT AGTTACTGAAA (SEQ ID GC	CTCATCAGCC							
N* (SEQ ID NO: 384) TCTGTTAGATA APKLLIMWR AA AATTCTACACT SSLQSGVPSR AT GAACTATATCA FSGSGSGTDF AC ACAACTGAAC TLTISSLQPED TC GATCTAGAGGC FATYYCAQG AC TTGCGTTATTC AALPRTFGQ GC AGGGTGTAGG GTKVEIKR TT AGTTACTGAAA (SEQ ID GC	CTTGGGATGA							
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GAACTATATCA FSGSGSGTDF AG ACAACTGAAC TLTISSLOPED T GATCTAGAGGC FATYYCAQG AG TTGCGTTATTC AALPRTFGQ GG AGGGTGTAGG GTKVEIKR TT AGTTACTGAAA (SEQ ID GG	TAAATTCTAC							
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AGTTACTGAAA (SEQ ID GO	TCAGGGTGTA							
	GAGTTACTGA							
CTCCCCTAATG NO: 386) AA	ACTCCCCTAA							
AAAGAAGATT TO	GAAAGAAGA							
CAATTCTAGCC TI	TCAATTCTAG							
GTTAGAAAATA CO	CGTTAGAAA							
CTTTCAGCGTA AT	TACTTTCAGC							
TCACATTGTAT GI	TATCACATTG							
TTAAAGGAAA TA	ATTTAAAGGA							
AGAAATACTCC AF	AAGAAATAC							
CCATGTGCATG TO	CCCCATGTGC							
GGAGGTGGTTA AT	TGGGAGGTG							
GAGCAGAAAT GJ	TTAGAGCAG							
TATGAGGTCCT AA	AATTATGAG							
TCTCTCTTTCT GI	TCCTTCTCTC							
ACGAATTTGCA T	TTCTACGAAT							
AGAATUTTTGA TI	TGCAAGAATC							
GATUTAAGGA TI	TIGAGATCTA							
AACCGTCGCTG AC	GGAAACCGT							
	GUIGUIUUAT							
ATUUAGATGAU C'I	IGACATCCAG							
	aa + myc		nt + 1	myc	aa 1	no tag	nt no	tag
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			CCAGT	CTCCAT			ATGAC	CCAGTC
			CCTCC	CTGTCT			TCCAT	CCTCCC
			AGACC	GTGTCA			GTAGG	AGACC
			CCATC.	ACTTGC			GTGTC	ACCATC
			CGGGC.	AAGTC			ACTTG	CCGGGC
			AGTGG.	ATTGGG			AAGTC	AGTGG
			TUTCA	ACCAGC			ATTGG GTTAT	GTCTCA
			AGAAA	CCAGG			ACCAG	CAGAA
			GAAAG	CCCCTA			ACCAG	GGAAA
			AGCTC	CTGATC			GCCCC	TAAGCT
			CTCGT	TGCAAA			GGCGT	TCATGT
			GTGGG	GTCCCA			TTGCA	AAGTGG
			TCACG	TTTCAG			GGTCC	CATCAC
			TGGCA	GTGGAT			GTTTC	AGTGGC
			TTCAC	TCTCAC			GACAG	ATCIGG
			CATCA	GCAGTC			CTCTC	ACCATC
			TGCAA	CCTGAA			AGCAG	TCTGCA
			GATTT	TGCTAC			ACCTG	AAGATT
			CTCAG	GGTGCG			TACTG	TGCTCA
			GCGTT	GCCTAG			GGGTG	CGGCG
			GACGT	TCGGCC			TTGCC	TAGGAC
			AAGGG	ACCAA			GTTCG	GCCAAG
			AAACG	GGCGG			GGAAA	TCAAA
			CCGCA	GAACA			CGG (SEQ ID
			AAAAC	TCATC			NO: 3	87)
			ATCTG	AGAGG AATTA				
			A (SE	Q ID				
			NO: 3	85)				
DMS732	CDLPQTHSLGSRRT		TGCGA	CTTGCC	CDLI	POTHSLG	TGCGA	CTTGCC
(IFNa2b-	LMLLAQMRRISLFS		ACAGA	CACAT	SRR	FLMLLA	ACAGA	CACAT
DOM7h-	CLKDRHDFGFPQE		AGTTT	GGGATC	QMRI	RISLFSC	AGTTT	GGGATC
14-10)	LHEMIOOIENLEST		TTGAT	GAACA GTTATT	OFFI	RHDFGFP	TTGAT	GAACA GTTATT
	KDSSAAWDETLLD		AGCAC	AAATG	KAE	CIPVLHE	AGCAC	AAATG
	KFYTELYQQLNDL		CGTAG	AATTTC	MIQ	QIFNLFS	CGTAG	AATTTC
	EACVIQGVGVTETP		TTTGT	TCTCTT	TKDS	SSAAWD	TTTGT	TCTCTT
	FORTTLYLKEKKYS		CGTCA	CGACTT	LYO	JUNDLE	CCGTC	AAGGA ACGACT
	PCAWEVVRAEIMR		CGGAT	TCCCTC	ACV:	EQGVGV	TCGGA	TTCCCT
	SFSLSTNLQESLRS		AGGAA	GAGTTT	TETI	PLMKEDS	CAGGA	AGAGT
	KETVAAPSDIQMT		GGAAA	CCAATT	ILA	/RKYFQR	TTGGA	AACCA
	TITCRASOWIGSOL		GAAAC	TATTCC	SPCA	AWEVVR	GCAGA	AACTA
	SWYQQKPGKAPKL		TGTCT	TGCACG	AEIN	MRSFSLS	TTCCT	GTCTTG
	LIMWRSSLQSGVPS		AAATG	ATCCAG	TNL	QESLRSK	CACGA	AATGA
	RFSGSGSGSGTDFTLT		CAAAT.	ATTCAA	ETVA	AAPSDIQ	TCCAG	CAAATA
	AOGLRHPKTFGOG		CAAAG	GACTC	SVGI	DRVTITC	TTCTA	CAAAGG
	TKVEIKR		ATCAG	CCGCTT	RAS	QWIGSQL	ACTCA	TCAGCC
	AAAEQKLISEEDL		GGGAT	GAAAC	SWY	QKPGK	GCTTG	GGATGA
	N* (SEQ ID NO:	388)	AATTC	TAGATA	SSL	PCGADGB	AACTC	TGTTAG TTCTAC
			GAACT.	ATATCA	FSG	GSGTDF	ACTGA	ACTATA
			ACAAC	TGAAC	TLT	ISSLQPEI	TCAAC	AACTGA
			GATCT.	AGAGGC	FATY	YYCAQG	ACGAT	CTAGA
			AGGGT	GTAGG	GTK	/EIKR	TTCAG	GGTGTA
			AGTTA	CTGAAA	(SEG	Q ID	GGAGT	TACTGA
			CTCCC	CTAATG	NO :	390)	AACTC	CCCTAA
			AAAGA	AGATT			TGAAA	GAAGA
			GTTAG	AAAATA			CCGTT	AGAAA
			CTTTC.	AGCGTA			ATACT	TTCAGC
			TCACA	TTGTAT			GTATC	ACATTG
			TTAAA	GGAAA			TATT	AAAGGA

	aa + myc	nt + myc	aa no tag	nt no tag
		AGAAATACTCC		AAAGAAATAC TCCCCATGTGC
		GGAGGTGGTTA		ATGGGAGGTG
		GAGCAGAAAT		GTTAGAGCAG
		TATGAGGTCCT		AAATTATGAG
		ACCAATTTCC		GTCCTTCTCTC
		AGAATCTTTGA		TTGCAAGAATC
		GATCTAAGGA		TTTGAGATCTA
		AACCGTCGCTG		AGGAAACCGT
		CTCCATCTGAC		CGCTGCTCCAT
		CCAGTCTCCAT		ATGACCCAGTC
		CCTCCCTGTCT		TCCATCCTCCC
		GCATCTGTAGG		TGTCTGCATCT
		AGACCGTGTCA		GTAGGAGACC
		CCATCACTTGC		GTGTCACCATC
		AGTGGATTGGG		ACTIGCCGGGC
		TCTCAGTTATC		ATTGGGTCTCA
		TTGGTACCAGC		GTTATCTTGGT
		AGAAACCAGG		ACCAGCAGAA
		GAAAGCCCCTA		ACCAGGGAAA
		AGCTCCTGATC		CCTGATCATGT
		CTCGTTGCAAA		GGCGTTCCTCG
		GTGGGGTCCCA		TTGCAAAGTGG
		TCACGTTTCAG		GGTCCCATCAC
		TGGCAGTGGAT		GTTTCAGTGGC
		TTCACTCTCAC		GACAGATCIGG
		CATCAGCAGTC		CTCTCACCATC
		TGCAACCTGAA		AGCAGTCTGCA
		GATTTTGCTAC		ACCTGAAGATT
		GTACTACTGTG		TTGCTACGTAC
		AGGCATCCTAA		GGGTTTGAGGC
		GACGTTCGGCC		ATCCTAAGACG
		AAGGGACCAA		TTCGGCCAAGG
		GGTGGAAATC		GACCAAGGTG
		AAACGGGCGG		GAAATCAAAC
		AAAACTCATC		NO: 391)
		TCAGAAGAGG		10. 001)
		ATCTGAATTA		
		A (SEQ ID NO: 389)		
DMS7303	CDLPOTHCLCCPPT	TGCGACTTGCC	CDLPOTUCIC	TGCGACTTCCC
(IFNa2b-	LMLLAQMRRISLFS	ACAGACACAT	SRRTLMLLA	ACAGACACAT
DOM7h-	CLKDRHDFGFPQE	AGTTTGGGATC	QMRRISLFSC	AGTTTGGGATC
14-18)	EFGNQFQKAETIPV	AAGAAGAACA	LKDRHDFGFP	AAGAAGAACA
	LHEMIQQIFNLFST	AGCACAAATG	QEEFGNQFQ	ACCACAAATC
	KFYTELYOOLNDL	CGTAGAATTTC	MIOOIFNLFS	CGTAGAATTTC
	EACVIQGVGVTETP	TTTGTTCTCTT	TKDSSAAWD	TTTGTTCTCTT
	LMKEDSILAVRKY	GTCTAAAGGAC	ETLLDKFYTE	GTCTAAAGGA
	FQRITLYLKEKKYS	CGTCACGACTT	LYQQLNDLE	CCGTCACGACT
	PCAWEVVKAEIMR SESLSTNLOESLPS	AGGAATTCCCTC	ACVIQGVGV TETPI.MKEDC	CAGGAATTCCCT
	KETVAAPSDIOMT	GGAAACCAATT	ILAVRKYFOR	TTGGAAACCA
	QSPSSLSASVGDRV	CCAAAAAGCA	ITLYLKEKKY	ATTCCAAAAA
	TITCRASQWIGSQL	GAAACTATTCC	SPCAWEVVR	GCAGAAACTA
	SWYQQKPGKAPKL	TGTCTTGCACG	AEIMRSFSLS	TTCCTGTCTTG
	LIMWRSSLQSGVPS RESCSCSCTDETLT	AAATGATCCAG	TNLQESLRSK	CACGAAATGA TCCAGCAAATA
	ISSLOPEDFATYYC	TTTGTTTTCTA	MTOSPSSLSA	TTCAATTTGTT
	AQGLMKPMTFGQ	CAAAGGACTC	SVGDRVTITC	TTCTACAAAGG
	GTKVEIKR AAAEQ	ATCAGCCGCTT	RASQWIGSQL	ACTCATCAGCC
	KLISEEDLN* (SEQ	GGGATGAAAC	SWYQQKPGK	GCTTGGGATGA
	TD NO: 392)	AATTCTACATA	SSI OCANDED	AACICIGITAG
		GAACTATATCA	FSGSGSGTDF	ACTGAACTATA

aa + myc	nt + myc	aa no tag	nt no tag
	ACAACTGAAC GATCTAGAGGC	TLTISSLQPED FATYYCAQG	TCAACAACTGA ACGATCTAGA
	TTGCGTTATTC	LMKPMTFGQ	GGCTTGCGTTA
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	GTTAGAAAATA		CCGTTAGAAA
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	TTADAGGADA		TATTTAAAGGA
	AGAAATACTCC		AAAGAAATAC
	CCATGTGCATG		TCCCCATGTGC
	GGAGGTGGTTA		ATGGGAGGTG
	GAGCAGAAAT		GTTAGAGCAG
	TATGAGGICCI		GTCCTTCTCTC
	ACGAATTTGCA		TTTCTACGAAT
	AGAATCTTTGA		TTGCAAGAATC
	GATCTAAGGA		TTTGAGATCTA
	AACCGTCGCTG		AGGAAACCGT
	ATCCAGATGAC		CTGACATCCAG
	CCAGTCTCCAT		ATGACCCAGTC
	CCTCCCTGTCT		TCCATCCTCCC
	GCATCTGTAGG		TGTCTGCATCT
	CCATCACTTCC		GTAGGAGACC
	CGGGCAAGTC		ACTTGCCGGGC
	AGTGGATTGGG		AAGTCAGTGG
	TCTCAGTTATC		ATTGGGTCTCA
	TTGGTACCAGC		GTTATCTTGGT
	GAAAGCCCCTA		ACCAGGGAAA
	AGCTCCTGATC		GCCCCTAAGCT
	ATGTGGCGTTC		CCTGATCATGT
	CTCGTTGCAAA		GGCGTTCCTCG
	TCACGTTTCAG		GGTCCCATCAC
	TGGCAGTGGAT		GTTTCAGTGGC
	CTGGGACAGAT		AGTGGATCTGG
	TTCACTCTCAC		GACAGATTTCA
	TGCAACCTGAA		ACCACTCACCATC
	GATTTTGCTAC		ACCTGAAGATT
	GTACTACTGTG		TTGCTACGTAC
	CTCAGGGTCTT		TACTGTGCTCA
	ATGAAGCCTAT		ACCCTATGACG
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	AAACGGGCCGG		GAAATCAAAC
	AAAACTCATC		GG (SEQ ID NO· 395)
	TCAGAAGAGG		10. 333,
	ATCTGAATTA		
	A (SEQ ID		
	TNO: 393)		
DMS7324 CDLPQTHSLGSRRT	TGCGACTTGCC	CDLPQTHSLG	TGCGACTTGCC
(IFNa2b-LMLLAQMRRISLFS	ACAGACACAT	SRRTLMLLA	ACAGACACAT
DOM/h- CLKDRHDFGFPQE	AGTTTGGGATC	QMRRISLFSC	AGTTTGGGATC
LHEMIOOIFNLFST	TTGATGTTATT	QEEFGNOFO	TTGATGTTATT
KDSSAAWDETLLD	AGCACAAATG	KAETIPVLHE	AGCACAAATG
KFYTELYQQLNDL	CGTAGAATTTC	MIQQIFNLFS	CGTAGAATTTC
EACVIQGVGVTETP	TTTGTTCTCTT	TKDSSAAWD	TTTGTTCTCTT GTCTAAACCA
FQRITLYLKEKKYS	CGTCACGACTT	LYQQLNDLE	CCGTCACGACT
PCAWEVVRAEIMR	CGGATTCCCTC	ACVIQGVGV	TCGGATTCCCT
SFSLSTNLQESLRS	AGGAAGAGTTT	TETPLMKEDS	CAGGAAGAGT
KETVAAPSDIQMT	GGAAACCAATT	ILAVRKYFQR	TTGGAAACCA

aa + myc		nt +	myc	aa r	no	tag	nt	no	ta	g
aa + myc QSPSSLSASVGDRV TISCRASQWIGSQL SWYQQKPGEAPKL LIMWRSSLQSGVPS RFSGSGGGTDFTLT ISSLQPEDFATYYC AQGAALPRTFGQG TKVEIKR AAAEQKLISEEDL N* (SEQ ID NO:	396)	nt + CCAAA GAAAC TGTCI AAATG CAAAT TTTGI CAAAG GGGAI TCTGI AATCC GAACI ACACC	myc AAGCA TATTCC TGCACG AATCCAG ATTCAA TTTCTA GACCC CCGCTT GAAAC TACACT ATACACT	aa r SPCA AEIN TNL(ETVA MTQS SVGI RAS(SVGI RAS(SVGI SSL(FSGS TLTT	NO YLK AWE QES QES DRV QWI QQK LLI QSG SGS SSS	tag EKKY VVR FSLS LRSK SDIQ SLSA TISC GSQL PGE MWR VPSR GTDF LQPED	nt ATT GCA TTC CAC TTC TTC ACT ACT ACT TCA	no CCCA AGAJ CCCC CCA CCA CCA CCA CCA CCA CCA CCA	ta AAA STC AAT CAA TTT CAA SGA CTC ACT	g AA TA TA GA ATA GGT AGG GGC TGA TAG TAG TAC ATA TGA
		TTGCG AGGGT AGTTA CTCCC AAAGA CAATT	TTATTC GTAGG CTGAAA CTGAAA CTAATG AGATT	AALI GTKV (SE) NO:	PRT VEI Q I 39	FGQ KR D 8)	GGC TTC GGZ AAC TGZ	CTTC CAGC AGT CTCC AAAC	GCG GT CCC GAA	TTA GTA TGA TAA .GA
		GTTAG CTTTC TCACA TTAAA AGAAA	AAAATA AGCGTA ATTGTAT AGGAAA ATACTCC				CCC ATZ GTZ TAT AAZ	ACT ACT ATC ATC ATC ATC ACT		AA AGC TTG GGA AC
		GGAGCA GAGCA TATGA TCTCT ACGAA	GGTCCT CTTTCT CTTTCCA				ATC GTT AAF GTC TTT	GGI FAGI ATTI CCTI CCTI	AGG AGC ATG CT ACG	AG AG CTC AAT
		GATCI AACCO CTCCA ATCCA CCAGI	AAGGA TCGCTG TCTGAC GATGAC CTCCAT				TTT AGC CGC CTC ATC	GAG GAA GAA GAC GAC GAC	SAT ACC CTC ATC CA	CTA GT CAT CAG GTC
		GCATC AGACC CCATC CGGGC AGTGG TCTCA	TGTAGG GTGTCA TCTTGC AAGTC ATTGGG AGTTATC				TGT GTZ GTC TCT AAC	CTC AGG2 GTC2 GTC2 GTC2 GTC2	GA AGA ACC CCG AGT	TCT CC ATC GGC GG
		TTGGT AGAAA GGAAG AGCTC ATGTG CTCGT	ACCAGC CCAGG CCCCTA CCTGATC GCGTTC TGCAAA				GTT ACC ACC GCC GCC GGC	CAG CAG CAG CAG CAG CGT	CTT CAG GGG TAA TCA	GGT AA AA .GCT .TGT .TCG
		GTGGG TCACG TGGCA CTGGG TTCAC	GTCCCA TTTCAG GTGGAT ACAGAT TCTCAC				TTC GG7 GT7 AG7 GAC	CAP CCC TCP GGP CAGP	AG CAT AGT ATC ATC	TGG CAC GGC TGG TCA
		TGCAA GATTI GTACI CTCAG GCGTI	CCTGAA TGCTAC ACTGTG GGTGCG GCCTAG				AGO ACO TTO TAO GGO	CAG CTG CTG CTG CTG CTG	CT AG ACG CGC	GCA ATT TAC TCA CG
		GACGI AAGGG GGTGG AAACG CCGCA	TCGGCC ACCAA AAATC GGCGG GAACA				TTC GTT GGZ GGZ CGC		TAG GCC AAG TCA SEQ	GAC AAG GT AA ID
		AAAAC TCAGA ATCTG A (SE NO: 3	AGAGG AAATTA Q ID				: 01	2 ک :	19)	

	aa + myc	nt + myc	aa no tag	nt no tag
DMS7325	CDLPOTHSLGSRRT	TGCGACTTGCC	CDLPOTHSLG	TGCGACTTGCC
(IFNa2b-	LMLLAQMRRISLFS	ACAGACACAT	SRRTLMLLA	ACAGACACAT
DOM7h-	CLKDRHDFGFPQE	AGTTTGGGATC	QMRRISLFSC	AGTTTGGGATC
11)	EFGNQFQKAETIPV	AAGAAGAACA	LKDRHDFGFP	AAGAAGAACA
	LHEMIQQIFNLFST	TTGATGTTATT	QEEFGNQFQ	TTGATGTTATT
	KDSSAAWDETLLD	AGCACAAATG	KAETIPVLHE	AGCACAAATG
	EACVIOGVGVTETP	TTTGTTCTCTT	TKDSSAAWD	TTTGTTCTCTT
	LMKEDSILAVRKY	GTCTAAAGGAC	ETLLDKFYTE	GTCTAAAGGA
	FQRITLYLKEKKYS	CGTCACGACTT	LYQQLNDLE	CCGTCACGACT
	PCAWEVVRAEIMR	CGGATTCCCTC	ACVIQGVGV	TCGGATTCCCT
	SFSLSTNLQESLRS	AGGAAGAGTTT	TETPLMKEDS	CAGGAAGAGT
	OSPSSI.SASVGDRV	CCAAAACCAATT	ITTI'AAKKULAĞK	ATTCCAAAA
	TITCRASRPIGTTLS	GAAACTATTCC	SPCAWEVVR	GCAGAAACTA
	WYQQKPGKAPKLL	TGTCTTGCACG	AEIMRSFSLS	TTCCTGTCTTG
	IWFGSRLQSGVPSR	AAATGATCCAG	TNLQESLRSK	CACGAAATGA
	FSGSGSGTDFTLTIS	CAAATATTCAA	ETVAAPSDIQ	TCCAGCAAATA
	SLQPEDFATYYCA	TTTGTTTTCTA	MTQSPSSLSA	TTCAATTTGTT
	KAEIKB ÖVGIULLILGÕGI	ATCAGCCGCTT	RASEPIGTTL	ACTCATCAGCC
	AAAEQKLISEEDL	GGGATGAAAC	SWYQQKPGK	GCTTGGGATGA
	N* (SEQ ID NO: 400)	TCTGTTAGATA	APKLLIWFGS	AACTCTGTTAG
		AATTCTACACT	RLQSGVPSRF	ATAAATTCTAC
		GAACTATATCA	SGSGSGTDFT	ACTGAACTATA
		ACAACTGAAC	LIISSLQPEDF	ACGATCTACA
		TTGCGTTATTC	THPTTFGOGT	GGCTTGCGTTA
		AGGGTGTAGG	KVEIKR (SEQ	TTCAGGGTGTA
		AGTTACTGAAA	ID NO: 402)	GGAGTTACTGA
		CTCCCCTAATG		AACTCCCCTAA
		AAAGAAGATT		TGAAAGAAGA
		GTTAGAAAATA		CCGTTAGAAA
		CTTTCAGCGTA		ATACTTTCAGC
		TCACATTGTAT		GTATCACATTG
		TTAAAGGAAA		TATTTAAAGGA
		AGAAATACTCC		AAAGAAATAC
		GGAGGTGGTTA		ATGGGAGGTG
		GAGCAGAAAT		GTTAGAGCAG
		TATGAGGTCCT		AAATTATGAG
		TCTCTCTTTCT		GTCCTTCTCTC
		ACGAATTTGCA		TTTCTACGAAT
		GATCTAAGGA		TTGCAAGAATC
		AACCGTCGCTG		AGGAAACCGT
		CTCCATCTGAC		CGCTGCTCCAT
		ATCCAGATGAC		CTGACATCCAG
		CCAGTCTCCAT		ATGACCCAGTC
		CCTCCCTGTCT		TCCATCCTCCC
		AGACCGTGTCA		GTAGGAGACC
		CCATCACTTGC		GTGTCACCATC
		CGGGCAAGTC		ACTTGCCGGGC
		GTCCGATTGGG		AAGTCGTCCGA
		ACGACGTTAAG		TTGGGACGAC
		AGAAACCAGG		ACCAGCAGAA
		GAAAGCCCCTA		ACCAGGGAAA
		AGCTCCTGATC		GCCCCTAAGCT
		TGGTTTGGTTC		CCTGATCTGGT
		CCGGTTGCAAA		TTGGTTCCCGG
		GTGGGGTCCCA		TTGCAAAGTGG GGTCCCATCAC
		TGGCAGTGGAT		GTTTCAGTGGC
		CTGGGACAGAT		AGTGGATCTGG
		TTCACTCTCAC		GACAGATTTCA
		CATCAGCAGTC		CTCTCACCATC
		TGCAACCTGAA		AGCAGTCTGCA
		GTACTACTO		TTGCTACCTAC
		CGCAGGCTGG		TACTGTGCGCA
				1101010000A

	aa + myc		nt ·	+ myc	aa	no t	ag	nt no tag
			GACC CGAC AGG CAAC GCCC AAAC GCCC AAAC GAT AA NO :	GCATCCTA CGTTCGGC GGGACCA IGGAAAT ACGGGCG GCAGAAC AACTCAT AGAAGAG CTGAATT (SEQ ID 401)				GGCTGGGACG CATCCTACGAC GTTCGGCCAAG GGACCAAGGT GGAAATCAAA CGG (SEQ ID NO: 403)
DMS7326 (IFNa2b- DOM7h- 11-12)	CDLPQTHSLGSRRT LMLLAQMRRISLFS CLKDRHDFGFPQE EFGNQFQKAETIPV LHEMIQQIFNLFST KDSSAAWDETLLD KFYTELYQQLNDL EACVIQGVGVTETP LMKEDSILAVRKY FQRITLYLKEKKYS PCAWEVVRAEIMR SFSLSTNLQESLRS KETVAAPSDIQMT QSPSSLSASVGDV TITCRASRPIGTML SWYQQKPGKAPKL LILFGSRLQSGVPS RFSGSGSGTDFTLT ISSLQPEDFATYYC AQAGTHPTTFQG TKVEIKR AAAEQKLISEEDL N* (SEQ ID NO:	404)	TGCC ACAA AGT AAGA AGC CGTT CGGG GGC GGC GGA GGA TGT CCAA ATT CCAA ATT CCAA CAA ATT CCAA CAA	GACTTGCC GACACAT TTGGGATC AAGAACA AAGAACA AAGAACA AGTATATT ACAAATG AGAATTTC GTTCTCTT TTAAAGGAC CACGACTT AATTCCCTC AAGAGATT AACAATT CACCAATT AGACCAATT AGACCAATT AGACCAAT AGCACCT GTGATCCAG ATTTTCTA AGCACCT CTATACACT GTGATAGAC GTGATCAGA GTAGAAC GTTAGACC GTTATTCA CCTATATCA ACTGAAC CTAGAGGC GTTATTC GTGATAGA CCTAATGTAT AAGGAAA CCCTAATG GAGGACT CAGCACATG GGTGGTA CAGCACTTGC GGTGGTA CATTGTCA GGTGGCAT GGCAGTG CCTGTTCCAT CCTGTCAT CCTGTCAG GTCCTGTC CCTGTCCAT CCCGGTCA CCCGGCCCA CCCGGTCA CCCGGCCCA CCCGGTCA CCCGGCCCA CCCGGTCA CCCGGCCCA CCCCGGTCA CCCCGGTCA CCCGGTCA CCCGGCCCA CCCCGGTCA CCCGGCCCA CCCGGCCCA CCCGGCCCA CCCCCAG CCCCGG CCCCCAC CCCCCAC CCCCCAC CCCCCCA CCCCCCA CCCCCC	CDI SRFF LACATEL SPORT SALATEL SPORT SALATEL SALAT	PQTH RILMI RILMI RILMI PRHOP PSGN(2TIP\ PSGN(2TIP\ PSGN(2QINI PLMI PSGN(2QINI PLMI PSGN(2QSS1 2QSS2 2SPSS 2SP	HSLG LLA LFSC CGFP FQ FQ VLHE LLFS AWD YTTE EXKY V/R SLSA FGS SCRF TDFT CGC CGTML GCC STML GCC CGTML GCC CGTML GCC CGTML CGC CGTML CGC CGTML CGC CGC CGC CGC CGC CGC CGC CGC CGC CG	TGCGACTTGCC ACAGACACAT AGTTGGGATC AGAGAAGACA TTGATGTTTGGGATC GTAGAAATG GTAGAAATG GTAGAAATG GTCTAAAGGA CCGTCACGACT TGGAAACCA TTGGAAACCA ATTCCACACAC GCAGAAACA TTCCAGTGTCTG CAGGAAACTA TTCACTGTCTG CAGGAAACTA TTCACTGTCTG CAGGAAACA CCAGCAAATA TCCAGCGTCAG CATGGACTAG CCTTGGGATGA ACTCTGTAG CAGATTAG ACTCTGTAG CCGTTAGACTAC CGTTGGGATGA CCAGCACACTG CGTAGGACATGA CCAGCACACTG CGTAGGAGAG CGTTAGAGAGA CCGTTAGAACA TTCAATTCTAG GGCTTCCCCTAA CGATCTACAC CGTTAGACACTG CGTTAGAACA CCGTAGAACA CCGTAGACACTG CTTGCACACTG CTTGCACACTG CGTAGGAGGTG GTATCACATCG CCGTAGACAC CCGTAGCACATG CCGTAGCACATG CCGTAGCACATG CCGTAGCACATG CCGTAGCACATG CTTGCCAGAC CCGTCCCCT CTGCCCCCA CTGCCCCCA CTGCCCCCC CTGCCCCCC CGTGCCCCA CGCTGCCCCA CGCTGCCCCA CGCTGCCCCA CGCTGCCCCA CGCTGCCCCA CGCTGCCCCA CGCTGCCCCA CGCTGCCCCA CGCGCGCCCA CGCGCGCCCA CGCGCGCCCA CGCGGCACA CCCCCAAGCC CGTGCCCCA CGCGCGCCCA CGCGCGCCCA CGCGCGCCCA CCGCCGAC CCCCCAAGCC CGCTGCCCCA CCGCCGAC CCCCCAAGCC CCCCCACGCC CCCTCCCC CGCCGCCCCA CCCCCACGCC CCCCCACGCC CCCCCCCC

	aa + myc		nt + m	iyc	aa no t	ag	nt no	tag
			TTGTTT GTGGGG TCACGT TGGCAG TTCACT CATCAG TGCAAC GACTAT GTACTA CGCAGG GACGCA CGACGT CAAGGG GCCACGA GACGCA CCAAGGG GCCACA GACCTG GACCCA CCACGA GACCTG GACCCA CCACGA GACCTG GACCCA CCACGA	GGTTC GCAAA TTCCAG TTCAG TTGAT CCAGAT CCAGAT CCAGAT CCAGAC CCA CCA			CTGAT TGGTT TGCAA GGTCC GTTTCC AGTGG GACAG CACCTG GGCTG GGCTG GGACC GGAAA CGG (NO: 4	CTTGTT AGTGG CATCAC AGTGGC ATTTGG ATTTCA ACCATC TCTGCA AAGATT ACGTAC TGCGCA GGACG TACGAC GGCAAG AAGGT TCCAA SEQ ID 07)
DMS7327 (IFNα2b- DOM7h- 11-15)	CDLPQTHSLGSRRT LMLLAQMRRISLFS CLKDRHDFGFPQE EFGNQFQKAETIPV LHEMIQQIFNLFST KDSSAAWDETLLD KFYTELYQQLNDL EACVIQGVGVTETP LMKEDSILAVRKY FQRITLYLKEKKYS PCAWEVVRAEIMR SFSLSTNLQESLRS KETVAAPSDIQMT QSPSSLSASVGDRV TITCRASRPIGTML SWYQQKPGKAPKL LILAFSRLQSGVPS RFSGSGSGTDFTLT ISSLQPEDFATYYC AQAGTHPTTFGQG TKVEIKR AAAEQKLISEEDL N★ (SEQ ID NO:	408)	TGCGAC ACAGAC AGTATTG AGCACA CGTAGA CGTAGA CGTCAC CGGACA CGTCAC CGGACA CGTCAC CGGACA CGACAT ACCCA CCAATA TTTGTT CAAAGG CCAATA TTTGTT CAAAGG TCTGTT AAATGA GGATGT AGGATGT ACCAC GTTAGA CACTT CAAAG CGACTA CAATTC TTAGAG GTTAGA CTTCCA AGAATC GAGCAT CCCAT AGAACC CCCAT	TTGCC ACAT IGAATC AACA ITTATT AATG AATG AATG AATG AATG ITTATT CCTCT AGGAC ITATT CCCTC GACTT CCATT AGCA ITCCA ITATCC ITATCA	CDLPQTH SRRTLMI QMRRISI LKDRHDI QEEFGM, KAETIPV MIQQIFT TKDSSAJ ETLLDKI SPCAWEY ITLYLKI SPCAWEY ILAVRKS SVGQKU RASRPIC SVGQRU APKLLII RLQSGVI SGSGSC LTISSLQ THPTTFC KVEIKR ID NO:	ASLG JLA LIAS GFP GGFP JPQ VILHE ULFS AWD YYTE DIE CEUS GEUS GEUS GEUS GEUS GEUS GEUS GEUS G	TGCGA ACAGA AGATA AGGAT TTGAT GCCTA CCGTAG TTTGT GCCTA CCGGC TTCGGA ATTCCT CACGA TTCCA TTCCA TCCAG TTCCA TCCAG ACTCC ACATA ACTCC ACGAT GCCTT TCCAG ACTCC TCAGA TCCAG GCTTG AACTC TCCAG GGCTT TCCAG GGCTT TCCAG GGCTT TCCAG GGCTT TCCAG CAGAA TCCAG CGCTG AACTC TCCAG CTGAA TCCAG CTGAA TCCAG CTGAA TCCAG CTGAA TCCAG CTGAC CTGGC CTGAC CTGAG CTGAG CTGAC	CTTGCC CACAT GGATCA GGATCA GTTATT AAATG AATTC TCTCTT AAGGA ACGACT TTCCCT AGAGT AAGGA ACCA AACAA AACTA AACCA AACCA AACCA AACCA AACCA AACCA CCAATA GTCTGC CAAATA CCAATG CCAATA GTCTGC CAAATA CCAATG CCAATA GTCTGC GGATGA CCAATG GGATGA CCAACA CCAACA CCAACA CCAACA CCAACA CCAACA CCAACA CCACAC AACGA CCACAC AACGA CCCTAA AACGA CCCTAA AAGGA CCCTAC AAGGA CCCTAC ACGATC ACGATC ACGATC ACGATC ACGATC ACGATC ACGATC ACGATC ACGATC CCCTAA

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TABLE 11-continued

Interferon alpha 2b-ALBUDAB[™] sequences with and without myc-tag (as amino acid- and nucleotide sequence) The Interferon alpha 2b is N-terminal to the ALBUDAB^M in the following fusions.

aa + myc	nt + myc aa no tag	nt no tag
	CCAGTCTCCAT	ATGACCCAGTC
	CCTCCCTGTCT	TCCATCCTCCC
	GCATCTGTAGG	TGTCTGCATCT
	AGACCGTGTCA	GTAGGAGACC
	CCATCACTTGC	GTGTCACCATC
	CGGGCAAGTC	ACTTGCCGGGC
	GTCCGATTGGG	AAGTCGTCCGA
	ACGATGTTAAG	TTGGGACGATG
	TTGGTACCAGC	TTAAGTTGGTA
	AGAAACCAGG	CCAGCAGAAA
	GAAAGCCCCTA	CCAGGGAAAG
	AGCTCCTGATC	CCCCTAAGCTC
	CTTGCTTTTTC	CTGATCCTTGC
	CCGTTTGCAAA	TTTTTCCCGTT
	GTGGGGTCCCA	TGCAAAGTGG
	TCACGTTTCAG	GGTCCCATCAC
	TGGCAGTGGAT	GTTTCAGTGGC
	CTGGGACAGAT	AGTGGATCTGG
	TTCACTCTCAC	GACAGATTTCA
	CATCAGCAGTC	CTCTCACCATC
	TGCAACCTGAA	AGCAGTCTGCA
	GATTTTGCTAC	ACCTGAAGATT
	GTACTACTGCG	TTGCTACGTAC
	CGCAGGCTGG	TACTGCGCGCA
	GACGCATCCTA	GGCTGGGACG
	CGACGTTCGGC	CATCCTACGAC
	CAAGGGACCA	GTTCGGCCAAG
	AGGTGGAAAT	GGACCAAGGT
	CAAACGG GCG	GGAAATCAAA
	GCCGCAGAAC	CGG (SEQ ID
	AAAAACTCAT	NO: 411)
	CTCAGAAGAG	
	GATCTGAATT	
	AA (SEQ ID	
	NO: 409)	

The amino acid and nucleotide sequences highlighted in bold represents the cloning site and MYC tag. $\ast represents$ the stop codon at the end of the gene.

Affinity Determination and Biophysical Characterisation:

To determine the binding affinity (K_D) of the ALBU-DABTM-IFNa2b fusion proteins to each serum albumin; purified fusion proteins were analysed by BiaCore™ over albumin (immobilised by primary-amine coupling onto 4: CM5 chips; BiaCoreTM) using fusion protein concentrations from 5000 nM to 39 nM (5000 nM, 2500 nM, 1250 nM, 625 nM, 312 nM, 156 nM, 78 nM, 39 nM) in HBS-EP BiaCore™ buffer.

TABLE 12

	Affinity to SA								
ALBUDAB™	Fusion	Affinity to SA (nM)	Kd	Ka	5				
		Rat			_				
DOM7h-14	IFNa2b	350	4.500E-02	1.28E+05					
DOM7h-14-10	IFNa2b	16	4.970E-03	5.90E+05					
DOM7h-14-18	IFNa2b	780	2.127E-01	5.80E+05					
DOM7h-14-19	IFNa2b	1900	1.206E-01	7.96E+04	6				
DOM7h-11	IFNa2b	6000	7.500E-01	nd					
DOM7h-11-12	IFNa2b	1700	3.100E-01	1.30E+05					
DOM7h-11-15	IFNa2b	200	1.660E-02	1.50E+05					
		Cyno			-				
DOM7h-14	IFNa2b	60	1.32E-02	5.0E+05	6				
DOM7h-14-10	IFNa2b	19	7.05E-03	4.50E+05					

			Affinity to SA		
5	ALBUDAB™	Fusion	Affinity to SA (nM)	Kd	Ka
	DOM7h-14-18	IFNa2b	no binding	no binding	no binding
	DOM7h-14-19	IFNa2b	520	8.47E-02	2.73E+05
	DOM7h-11	IFNa2b	3300	3.59E-01	1.20E+05
	DOM7h-11-12	IFNa2b	630	3.45E-01	7.00E+05
0	DOM7h-11-15	IFNa2b	15	4.86E-03	3.60E+05
Č			Mouse		
	DOM7h-14	IFNa2b	240	3.21E-02	1.50E+06
	DOM7h-14-10	IFNa2b	60	3.45E-02	6.86E+05
	DOM7h-14-18	IFNa2b	180	1.50E-01	9.84E+05
5	DOM7h-14-19	IFNa2b	49 0	4.03E-02	1.19E+05
	DOM7h-11	IFNa2b	6000	1.55E-01	nd
	DOM7h-11-12	IFNa2b	150	9.49E-02	6.30E+05
	DOM7h-11-15	IFNa2b	28	6.69E-03	2.80E+05
			Human		
0	DOM7h-14	IFNa2b	244	2.21E-02	9.89E+04
	DOM7h-14-10	IFNa2b	32	6.58E-03	3.48E+05
	DOM7h-14-18	IFNa2b	470	2.75E-01	6.15E+05
	DOM7h-14-19	IFNa2b	350	4.19E-02	1.55E+05
	DOM7h-11	IFNa2b	670	2.02E-01	7.00E+05
	DOM7h-11-12	IFNa2b	500	1.66E-01	3.90E+05
5	DOM7h-11-15	IFNa2b	10	1.87E-03	3.50E+05

TABLE 12-continued

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When IFNα2b is linked to the ALBUDAB[™] variants, in all cases the affinity of ALBUDABTM binding to serum albumin is reduced. DOM7h-14-10 and DOM7-11-15 retain improved binding affinity to serum albumin across species compared to parent. DOM7h-11-12 also shows improved 5 binding affinity to serum albumin across species compared to parent.

TABLE 13

Biophysical Characterisation							
		_	Biophysical	parameters			
ALBUDAB™	Fusion	DMS number	SEC MALLS	DSC Tm(° C.)			
DOM7h-14	IFNa2b	DMS7321	M/D	58-65			
DOM7h-14-10	IFNa2b	DMS7322	M/D	55-65			
DOM7h-14-18	IFNa2b	DMS7323	M/D	55-65			
DOM7h-14-19	IFNa2b	DMS7324	M/D	59-66			

mg quantities in HEK293 cells and purified from culture supernatant using protein L affinity resin and eluted with 100 mM glycine pH2. The proteins were concentrated to greater than 1 mg/ml, buffer exchanged into Dulbecco's PBS and endotoxin depleted using Q spin columns (Vivascience).

For Rat PK, IFN-ALBUDABs[™] were dosed as single i.v injections at 2.0 mg/kg using 3 rats per compound. Serum samples were taken at 0.16, 1, 4, 8, 24, 48, 72, 120, 168 hrs. Analysis of serum levels was by EASY ELISA according to manufacturers instructions (GE Healthcare, catalogue number RPN5960).

For Mouse PK, DMS7322 (IFN2b-DOM7h-14-10) DMS7325 (IFN2b-DOM7h-11), DMS7326 (IFN2b-15 DOM7h-11-12), DMS7327 (IFN2b-DOM7h-11-15) all with myc tags were dosed as single i.v injections at 2.0 mg/kg per dose group of 3 subjects and serum samples taken at 10 mins; 1 h; 8 h; 24 h; 48 h; 72 h; 96 h. Analysis of serum levels was by EASY ELISA according to manufacturers instructions (GE Healthcare, catalogue number RPN5960).

TABLE 14

					PK paramete	ers	
Species	ALBUDAB TM	Fusion	Albumin K_D (nM)	AUC h × ug/ml	CL ml/h/kg	t½ h	Vz ml/kg
Rat	7h-14	IFNa2b	350	832.1	2.4	27	94.5
	7h-14-10	IFNa2b	16	1380.7	1.5	35.8	75.2
	7h-14-18	IFNa2b	780	691.2	2.9	22.4	93.7
	7h-14-19	IFNa2b	1900	969.4	2.2	25	78.7
	7h-11	IFNa2b	6000	327.9	6.5	11	101.9
	7h-11-12	IFNa2b	1700	747.1	2.8	25.8	104.7
	7h-11-15	IFNa2b	200	1118.7	1.8	39.5	103.6
nouse	7h-14	IFNa2b	240	761.2	2.6	30.4	115.3
	7h-14-10	IFNa2b	60	750.5	2.7	30.9	118.6
	7h-11	IFNa2b	6000	493.9	4.0	8.8	51.2
	7h-11-12	IFNa2b	150	439.6	4.5	21.5	140.9
	7h-11-15	$\text{IFN}\alpha 2b$	28	971.8	2.1	33.6	99.6

TABLE 13-continued

	Biophy	sical Character	risation		-
		-	Biophysical	parameters	- ,
ALBUDAB™	Fusion	DMS number	SEC MALLS	DSC Tm(° C.)	4
DOM7h-11 DOM7h-11-12 DOM7h-11-15	IFNα2b IFNα2b IFNα2b	DMS7325 DMS7326 DMS7327	M/D M/D M/D	65.8-66.2 67-67.3 56.3-66.2	5

Biophysical Characterisation was carried out by SEC MALLS and DSC as described above for the single ALBUDABsTM.

M/D indicates a monomer/dimer equilibrium as detected by SEC MALLS

range of 17.5 to 54 mg/L in HEK293.

For IFNa2b-DOM7h-14 and IFNa2b-DOM7h-11 variants, favorable biophysical parameters and expression levels were maintained during affinity maturation. PK Determination for ALBUDAB[™]-IFNα2b Fusions

ALBUDABs™ IFNa2b fusions DMS7321 (IFNa2b-DOM7h-14) DMS7322 (IFNa2b-DOM7h-14-10) DMS7323 (IFNa2b-DOM7h-14-18), DMS7324 (IFNa2b-DOM7h-14-19), DMS7325 (IFNα2b-DOM7h-11), 65 DMS7326 (IFNa2b-DOM7h-11-12), DMS7327 (IFNa2b-DOM7h-11-15) were expressed with the myc tag at 20-50

40

60

Pharmacokinetic parameters derived from rat and mouse studies were fitted using a non-compartmental model. Key: AUC: Area under the curve from dosing time extrapolated to infinity; CL: clearance; t1/2: is the time during which the blood concentration is halved; Vz: volume of distribution based on the terminal phase.

IFNα2b—ALBUDABs[™] were tested in rat and mouse. For all IFNa2b-DOM7h-11 variant fusion proteins in both rat and mouse, t1/2 is improved compared to parent. The improvement in t1/2 correlates with the improved in vitro K_D to serum albumin. For IFN α 2b-DOM7h-14-10 variants, the improvement in in vitro K_D to serum albumin also correlated to an improvement in t1/2 in rat.

All IFNα2b-ALBUDAB[™] fusion proteins exhibit a 5 to We observed expression for all clones in Tabale 13 in the 55 10-fold decrease in the binding to RSA compared to the single ALBUDABTM. This effect is more pronounced (i.e. 10-fold) for the DOM7h-14 series than the DOM7h-11 series (only 5-fold decrease).

Example 8

Further ALBUDAB[™] Fusions with Proteins, Peptides and NCEs

Various ALBUDABs[™] fused to other chemical entities namely domain antibodies (dAbs), peptides and NCEs were tested. The results are shown in table 15.

TABLE	15
-------	----

				PK parameters					
Species	ALBUDAB TM	Fusion	Albumin K _D (nM)	AUC h × ug/ml	CL ml/h/kg	t½ h	Vz ml/kg		
Rat	DOM7h-14	Exendin-4	2400	18	57.1	11	901.9		
	DOM7h-14-10 DOM7h-14-18	Exendin-4 Exendin-4	16000	43.0 16.9	23.1 75.7	22.1 9.4	1002.5		
	DOM7h-14-19	Exendin-4	17000	31.4	32.5	11.9	556.7		
	DOM7h-11	Exendin-4	24000	6.1	168	7.1	1684.1		
	DOM7h-11-12	Exendin-4	1400	24.2	59.9	13	1068.7		
	DOM7h-11-15	Exendin-4	130	36.3	27.6	19.3	765.7		
	DOM7h14-10	NCE-GGGGSC	62						
	DOM7h14-10	NCE-TVAAPSC	35						
Human	DOM7h-14	NCE	204						
mouse	DOM7h-11	DOM1m-21-23		234	10.7	4.7	72.5		
	DOM7h-11-12	DOM1m-21-23		755	3.3	18	86.2		
	DOM7h-11-15	DOM1m-21-23		1008	2.5	17.4	62.4		

Key: DOM1m-21-23 is an anti-TNFR1 dAb, Exendin-4 is a peptide (a GLP-1 agonist) of 39 amino acids length. NCE, NCE-GGGGSC and NCE-TVAAPSC are described below.

Previously we have described the use of genetic fusions with an albumin-binding dAb (ALBUDAB[™]) to extend the PK half-life of anti-TNFR1 dAbs in vivo (see, eg, WO04003019, WO2006038027, WO2008149148). Reference is made to the protocols in these PCT applications. In 25 the table above, DOM1m-21-23 is an anti-mouse TNFR1 dAb.

To produce genetic fusions of exendin-4 or with DOM7h-14 (or other ALBUDABTM) which binds serum albumin, the exendin-4-linker-ALBUDABTM sequence was cloned into 30 the pTT-5 vector (obtainable from CNRC, Canada). In each case the exendin-4 was at the 5' end of the construct and the dAb at the 3' end. The linker was a (G₄S)₃ linker. Endotoxinfree DNA was prepared in E. coli using alkaline lysis (using the endotoxin-free plasmid Giga kit, obtainable from Qiagen CA) and used to transfect HEK293E cells (obtainable from CNRC, Canada). Transfection was into 250 ml/flask of HEK293E cells at 1.75×10⁶ cells/ml using 333u1 of 293fectin (Invotrogen) and 250 ug of DNA per flask and expression $_{40}$ was at 30° C. for 5 days. The supernatant was harvested by centrifugation and purification was by affinity purification on protein L. Protein was batch bound to the resin, packed on a column and washed with 10 column volumes of PBS. Protein was eluted with 50 ml of 0.1M glycine pH2 and 45 neatralised with Tris pH8. Protein of the expected size was identified on an SDS-PAGE gel. NCE ALBUDAB[™] Fusions:

A new chemical entity (NCE) ALBUDABTM fusion was tested. The NCE, a small molecule ADAMTS-4 inhibitor 50 was synthesised with a PEG linker (PEG 4 linker (ie 4 PEG molecules before the maleimide) and a maleimide group for conjugation to the ALBUDAB[™]. Conjugation of the NCE to the ALBUDAB[™] is via an engineered cystine residue at 55 amino acid position R108C, or following a 5 amino acid (GGGGSC) or 6 amino acid (TVAAPSC (SEQ ID NO: 419)) spacer engineered at the end of the ALBUDAB[™]. Briefly, the ALBUDAB™ was reduced with TCEP (Pierce, Catalogue Number 77720), desalted using a PD10 column (GE 60 healthcare) into 25 mM Bis-Tris, 5 mM EDTA, 10% (v/v) glycerol pH6.5. A 5 fold molar excess of maleimide activated NCE was added in DMSO not to exceed 10% (V/V) final concentration. The reaction was incubated over night at 65 room temperature and dialysed extensively into 20 mM Tris pH7.4





Sequences:

DOM7h-14 R108C:

(SEQ ID NO: 412) DIQMTQSPSSLSASVGDRVTITCRASQWIGSQLSWYQQKPGKAPKLLIM WRSSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQGLRHPKTFG QGTKVEIKC

Nucleotide:

(SEQ ID NO: 413) GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGA CCGTGTCACCATCACTTGCCGGGCAAGTCAGTGGATTGGGTCTCAGTTAT CTTGGTACCAGCAGAAAACCAGGGGAAAGCCCCTAAGCTCCTGATCATGTG GCGTTCCTCGTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAGTGGAA CTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTT GCTACGTACTACTGTGCTCAGGGTTTGAGGCATCCTAAGACGTTCGGCCA AGGGACCAAGGTGGAAATCAAATGC

See table 5 for the sequences of DOM7h-14-10/TVAAPSC and DOM7h-14-10/GGGGSC (ie, DOM7h-14-10/G4SC).

NCE-ALBUDABsTM DOM7h-14-10 GGGGSC(SEQ ID NO: 62) and DOM7h14-10 TVAAPSC, exhibit a 5 to 10 fold decrease in in vitro affinity (K_D) to RSA as determined by BiaCoreTM when fused to the chemical entity. PK data are not available for these molecules yet.

dAb-ALBUDAB™ fusion: the 2 DOM7h-11 ALBUD-ABsTM with the highest affinity to RSA experience a 2-fold decrease in affinity to RSA as on BiaCore[™] when fused to a therapeutic domain antibody (DOM1m-21-23) compared to the unfused ALBUDAB[™] The DOM7h-11 clone shows 5 a micromolar K_D when fused (2.8 uM) as well as when unfused (~5 uM).

Exendin 4-ALBUDABTM fusion: the effect of fusing the ALBUDABs[™] to a peptide on the binding ability to RSA is about 10-fold, apart from DOM7h-14-10, which only shows 10 a 4-fold decrease in binding. The effect, however, is more pronounced for the DOM7h-14 series (except DOM7h-14-10) than it appears to be for the DOM7h-11 series.

For all the above data, the T1/2 of the fusion increased with improved affinity to the species' SA.

We generally classify ALBUDAB[™]-therapeutics as being therapeutically amenable (for treatment and/or prophylaxis of diseases, conditions or indications) when the ALBUDABTM-drug fusions show an affinity range (K_D) of from 0.1 nM to 10 mM for serum albumin binding. 20

We define the therapeutic ranges of ALBUDABs[™] and ALBUDAB[™] fusions (Protein-ALBUDABs[™] for example IFNα2b-DOM7h-14-10; Peptide—ALBUDABs[™] for example Exendin-4-DOM7h-14-10; dAb-ALBUDABs™ for example DOM1m21-23-DOM7h11-15; NCE-ALBU- 25 AGGGACCAAGGTGGAAATCAAACGG DAB[™] for example ADAMTS-4-DOM7h-14-10) as follows: Affinity (K_D) ranges that are useful for therapy of chronic or acute conditions, diseases or indictions are shown. Also shown are affinity ranges marked as "intermediate". ALBUDABs[™] and fusions in this range have utility 30 for chronic or acute diseases, conditions or indications. In this way, the affinity of the ALBUDABTM or fusion for serum albumin can be tailored or chosen according to the disease, condition or indication to be addressed. As described above, the invention provides ALBUDABsTM 35 with affinities that allow for each ALBUDABTM to be categorised as "high affinity", "medium affinity" or "low affinity", thus enabling the skilled person to select the appropriate ALBUDAB[™] of the invention according to the 40 therapy at hand. See FIG. 2.

Example 9

DOM7h-11-15^{S12P} Sequences

Amino Acid Sequence of DOM7h-11-15 S12P

(SEO ID NO: 414) DIQMTQSPSSLPASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLILA

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 422 <210> SEQ ID NO 1 <211> LENGTH: 108 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEOUENCE: 1 Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly 1 5 10 15

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FSRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQ

GTKVEIKR

An aspect of the invention provides a nucleic acid comprising the nucleotide sequence of DOM7h-11-15^{S12P} or a nucleotide sequence that is at least 80% identical to said selected sequence. DOM7h-11-15^{S12P} was produced using the following nucleic acid sequence (the underlined C denotes the change (versus the nucleic acid encoding DOM7h-11-15) leading to a proline at position 12):-

(SEQ ID NO: 415) GACATCCAGATGACCCAGTCTCCATCCTCCCTGCCTGCATCTGTAGGAGA CCGTGTCACCATCACTTGCCGGGCAAGTCGTCCGATTGGGACGATGTTAA GTTGGTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCCTTGCT ${\tt TTTTCCCGTTTGCAAAGTGGGGGTCCCATCACGTTTCAGTGGCAGTGGATC}$ ${\tt TGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTG$ CTACGTACTACTGCGCGCAGGCTGGGACGCATCCTACGACGTTCGGCCA

DOM7h-11-15^{S12P} was constructed by using DOM7h-11-15 as a template in a PCR where a primer was used to introduce the S12P mutation. The primer sequence is:-

(SEQ ID NO: 416) GCAACAGCGTCGACGGACATCCAGATGACCCAGTCTCCATCCTCCCTGCC

TGCATCTGTAGG.

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An alternative aspect of the invention provides a nucleic acid comprising the nucleotide sequence of SEQ ID NO: 415 or a nucleotide sequence that is at least 80% identical to said selected sequence. In one embodiment, DOM7h-11- 15^{S12P} is encoded by, and expressed from, a vector that contains a linker region and a C-terminal sequence encoding a protein or peptide drug or a single variable domain or other antibody fragment to make the in-line protein fusion product. The linker, in one embodiment, comprises the amino acid sequence TVA, eg, TVAAPS (SEQ ID NO: 422). Other aspects of the invention are a vector comprising the nucleic acid; and an isolated host cell comprising the vector. The invention also provides a method of treating or preventing a disease or disorder in a patient, comprising administering at least one dose of DOM7h-11-15^{S12P} to said patient.

<210> SEQ ID NO 2 <211> LENGTH: 108 <212> TYPE: PRT

<220> FEATURE:

<400> SEQUENCE: 2

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Arg Pro Ile Gly Thr Met Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Leu Phe Gly Ser Arg Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Ala Gln Ala Gly Thr His Pro Thr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg <213> ORGANISM: Artificial Sequence <223> OTHER INFORMATION: Derived from a Human Germline sequence. Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Arg Pro Ile Gly Thr Met Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Leu Ala Phe Ser Arg Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Ala Gln Ala Gly Thr His Pro Thr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg

<210> SEQ ID NO 3 <211> LENGTH: 108 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEQUENCE: 3 Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Arg Pro Ile Gly Thr Met Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Trp Phe Gly Ser Arg Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr His Cys Ala Gln Ala Gly Thr His Pro Thr

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg

<210> SEQ ID NO 4 <211> LENGTH: 108 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEQUENCE: 4 Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly 10 Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Arg Pro Ile Gly Thr Met 20 25 Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile 35 40 Leu Phe Gly Ser Arg Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly 50 55 60 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro65707580 Glu Asp Phe Ala Thr Tyr Tyr Cys Ala Gln Thr Gly Thr His Pro Thr 85 90 95 Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg 100 105 <210> SEO ID NO 5 <211> LENGTH: 108 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEOUENCE: 5 Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly 5 10 1 15 Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Arg Pro Ile Gly Thr Thr 20 25 30 Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile 40 35 45 Leu Trp Asn Ser Arg Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly 50 55 60 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro 65 70 75 80 Glu Asp Phe Ala Thr Tyr Tyr Cys Ala Gln Ala Gly Thr His Pro Thr 85 90 Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg 100 105 <210> SEQ ID NO 6 <211> LENGTH: 324 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEQUENCE: 6 qacatecaqa tqacecaqte tecatectee etqtetqeat etqtaqqaqa eeqtqteace atcacttgcc gggcaagtcg tccgattggg acgatgttaa gttggtacca gcagaaacca gggaaagccc ctaagctcct gatcttgttt ggttcccggt tgcaaagtgg ggtcccatca

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cgtttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct	240
gaagattttg ctacgtacta ctgtgcgcag gctgggacgc atcctacgac gttcggccaa	300
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gggaaagccc ctaagctcct gatccttgct ttttcccgtt tgcaaagtgg ggtcccatca	180
cgtttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct	240
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gggaaagccc caaagctcct gatctggttt ggttcccggt tgcaaagtgg ggtcccatca	180
cgtttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct	240
gaagattttg ctacgtacca ctgtgcgcag gcggggacgc atcctacgac gttcggccaa	300
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atcacttgcc gggcaagtcg tccgattggg acgatgttaa gttggtacca gcagaaacca	120
gggaaagccc ctaagctcct gatcttgttt ggttcccggt tgcaaagtgg ggtcccatca	180
cgtttcagtg gcagtggatc tgggacggat ttcactctca ccatcagcag tctgcaacct	240
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<223> OTHER INFORMATION: Derived from a Human Germline sequence.								
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gggaaagccc ctaagctcct gatcctttgg aattcccgtt tgcaaagtgg ggtcccatca	180							
cgtttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct	240							
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gggaccaagg tggaaatcaa acgg	324							
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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Gln Tyr 20 25 30								
Arg Met His Trp Val Arg Gln Ala Pro Gly Lys Ser Leu Glu Trp Val 35 40 45								
Ser Ser Ile Asp Thr Arg Gly Ser Ser Thr Tyr Tyr Ala Asp Pro Val 50 55 60								
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr 65 70 75 80								
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys 85 90 95								
Ala Lys Ala Val Thr Met Phe Ser Pro Phe Phe Asp Tyr Trp Gly Gln 100 105 110								
Gly Thr Leu Val Thr Val Ser Ser 115 120								
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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ala Asp Tyr 20 25 30								
Gly Met Arg Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val 35 40 45								
Ser Ser Ile Thr Arg Thr Gly Arg Val Thr Tyr Tyr Ala Asp Ser Val 50 55 60								
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr 65 70 75 80								
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys 85 90 95								
Ala Lys Trp Arg Asn Arg His Gly Glu Tyr Leu Ala Asp Phe Asp Tyr								

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Arg Met	: His 35	Trp	Val	Arg	Gln	Ala 40	Pro	Gly	Lys	Gly	Leu 45	Glu	Trp	Val
Ser Ser 50	: Ile	Asp	Ser	Asn	Gly 55	Ser	Ser	Thr	Tyr	Tyr 60	Ala	Asp	Ser	Val
Lys Gly 65	⁄ Arg	Phe	Thr	Ile 70	Ser	Arg	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80
Leu Glr	n Met	Asn	Ser 85	Leu	Arg	Ala	Glu	Asp 90	Thr	Ala	Val	Tyr	Tyr 95	Суа
Ala Lys	a Yab	Arg 100	Thr	Glu	Arg	Ser	Pro 105	Val	Phe	Asp	Tyr	Trp 110	Gly	Gln
Gly Thr	Leu 115	Val	Thr	Val	Ser	Ser 120								
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Lys Gly 65	⁄ Arg	Phe	Thr	Ile 70	Ser	Arg	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80
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<223> OTHER INFORMATION: Derived from a Human Germline sequence
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Ser Gln Ile Ser Asn Thr Gly Gly His Thr Tyr Tyr Ala Asp Ser Val 50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr 65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys 85 90 95
Ala Lys Tyr Thr Gly His Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly 100 105 110
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<400> SEQUENCE: 16
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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr 20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val 35 40 45
Ser Gln Ile Ser Asn Thr Gly Gly His Thr Tyr Tyr Ala Asp Ser Val 50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr 65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys 85 90 95
Ala Lys Tyr Thr Gly Arg Trp Glu Pro Tyr Asp Tyr Trp Gly Gln Gly 100 105 110
Thr Leu Val Thr Val Ser Ser 115
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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr 20 25 30

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Ser Gln Ile Ser Asn Thr Gly Gly His Thr Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Lys Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser <210> SEQ ID NO 18 <211> LENGTH: 119 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEQUENCE: 18 Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Gln Ile Ser Asn Thr Gly Gly His Thr Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser <210> SEQ ID NO 19 <211> LENGTH: 119 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEQUENCE: 19 Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Pro Glu Trp Val Ser Gln Ile Ser Asn Thr Gly Gly His Thr Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

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Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly 100 105 110 Thr Leu Val Thr Val Ser Ser 115 <210> SEQ ID NO 20 <211> LENGTH: 119 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEQUENCE: 20 Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly 5 10 1 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr 20 25 30 Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val 35 40 45 Ser Gln Ile Ser Asn Thr Gly Gly His Thr Tyr Tyr Ala Asp Ser Val 50 55 60 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr 65 70 75 80 Met Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys 85 90 95 Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly 100 105 110 Thr Leu Val Thr Val Ser Ser 115 <210> SEQ ID NO 21 <211> LENGTH: 119 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEQUENCE: 21 Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly 5 10 1 15 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Gly Lys Tyr 20 25 Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Asp Leu Glu Trp Val 35 40 Ser Gln Ile Ser Asn Thr Gly Gly His Thr Tyr Tyr Ala Asp Ser Val 55 60 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr 65 70 75 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys 85 90 95 Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly 100 105 110 Thr Leu Val Thr Val Ser Ser 115 <210> SEQ ID NO 22 <211> LENGTH: 119

<212> TYPE: PRT
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Ser	Leu	Arg	Leu 20	Ser	Суз	Ala	Ala	Ser 25	Gly	Phe	Thr	Phe	Val 30	Lys	Tyr
Ser	Met	Gly 35	Trp	Val	Arg	Gln	Ala 40	Pro	Gly	Lys	Gly	Leu 45	Glu	Trp	Val
Ser	Gln 50	Ile	Ser	Asn	Thr	Gly 55	Gly	His	Thr	Tyr	Tyr 60	Ala	Asp	Ser	Val
Lys 65	Gly	Arg	Phe	Thr	Ile 70	Ser	Arg	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80
Leu	Gln	Met	Asn	Ser 85	Leu	Arg	Ala	Glu	Asp 90	Thr	Ala	Val	Tyr	Tyr 95	Суз
Ala	Lys	Tyr	Thr 100	Gly	Arg	Trp	Glu	Pro 105	Phe	Asp	His	Trp	Gly 110	Gln	Gly
Thr	Leu	Val 115	Thr	Val	Ser	Ser									
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Ser	Leu	Arg	Leu 20	Ser	Сүв	Ala	Ala	Ser 25	Gly	Phe	Thr	Phe	Val 30	Lys	Tyr
Ser	Met	Gly 35	Trp	Val	Arg	Gln	Ala 40	Pro	Gly	Lys	Gly	Leu 45	Glu	Trp	Val
Ser	Gln 50	Ile	Ser	Asn	Thr	Gly 55	Asp	His	Thr	Tyr	Tyr 60	Ala	Asp	Ser	Val
Lys 65	Gly	Arg	Phe	Thr	Ile 70	Ser	Arg	Asp	Asn	Ser 75	LÀa	Asn	Thr	Leu	Tyr 80
Leu	Gln	Met	Asn	Ser 85	Leu	Arg	Ala	Glu	Asp 90	Thr	Ala	Val	Tyr	Tyr 95	Суз
Ala	Lys	Tyr	Thr 100	Gly	Arg	Trp	Glu	Pro 105	Phe	Asp	Tyr	Trp	Gly 110	Gln	Gly
Thr	Leu	Val 115	Thr	Val	Ser	Ser									
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<400)> SE	EQUEN	ICE :	24											
Glu 1	Val	Gln	Leu	Leu 5	Glu	Ser	Gly	Gly	Gly 10	Leu	Val	Gln	Pro	Gly 15	Gly
Ser	Leu	Arg	Leu 20	Ser	Cya	Ala	Ala	Ser 25	Gly	Phe	Thr	Phe	Val 30	Lys	Tyr

Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp

Ser Gln Ile Ser Asn Thr Gly Asp Arg Thr Tyr Tyr Ala Asp Ser

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr

Val			
Val			
Tyr 80			
Суз			
a]			

Ala Lys Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser <210> SEQ ID NO 25 <211> LENGTH: 119 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEOUENCE: 25 Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Gln Ile Ser Asn Thr Gly Asp Arg Thr Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser <210> SEQ ID NO 26 <211> LENGTH: 119 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEQUENCE: 26 Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Gln Ile Ser Asn Thr Gly Asp His Thr Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly 100 105 110 Thr Leu Val Thr Val Ser Ser 115 <210> SEQ ID NO 27 <211> LENGTH: 119 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEQUENCE: 27 Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly 1 5 10 15 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr 20 25 30 Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Pro Glu Trp Val 35 40 45 Ser Gln Ile Ser Asn Thr Gly Asp Arg Thr Tyr Tyr Ala Asp Ser Val 55 50 60 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr 65 70 75 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys 85 90 Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly 100 105 110 Thr Leu Val Thr Val Ser Ser 115 <210> SEQ ID NO 28 <211> LENGTH: 119 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEQUENCE: 28 Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly 5 10 1 15 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr $\ensuremath{\mathsf{Phe}}$ Val Lys Tyr 20 25 Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Pro Glu Trp Val 35 40 Ser Gln Ile Ser Asn Thr Gly Asp His Thr Tyr Tyr Ala Asp Ser Val 55 60 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr 65 70 75 Leu Gl
n Met As
n Ser Leu Arg Ala Glu Asp \mbox{Thr} Ala Val
 \mbox{Tyr} Tyr Cys 85 90 Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly 105 100 110 Thr Leu Val Thr Val Ser Ser 115 <210> SEQ ID NO 29

<211> LENGTH: 119 <212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEQUENCE: 29 Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly 1 5 10 15 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Gly Lys Tyr 25 20 30 Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Asp Leu Glu Trp Val 40 35 Ser Gln Ile Ser Asn Thr Gly Asp Arg Thr Tyr Tyr Ala Asp Ser Val 55 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr 75 65 70 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys 85 90 Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly 100 105 110 Thr Leu Val Thr Val Ser Ser 115 <210> SEQ ID NO 30 <211> LENGTH: 119 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEQUENCE: 30 Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly 1 5 10 15 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Gly Lys Tyr 20 25 30 Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Asp Leu Glu Trp Val 35 40 45 Ser Gln Ile Ser Asn Thr Gly Asp His Thr Tyr Tyr Ala Asp Ser Val 55 50 60 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr 75 65 70 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys 85 90 Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly 100 105 110 Thr Leu Val Thr Val Ser Ser 115 <210> SEQ ID NO 31 <211> LENGTH: 119 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEQUENCE: 31 Glu Val Gl
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n $\mbox{Pro Gly Gly}$ Gly 1 5 10 15 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr 20 25 30

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Ser	Met	Gly 35	Trp	Val	Arg	Gln	Ala 40	Pro	Gly	Lys	Gly	Leu 45	Glu	Trp	Val
Ser	Gln 50	Ile	Ser	Asn	Thr	Gly 55	Asp	Arg	Thr	Tyr	Tyr 60	Ala	Asp	Ser	Val
Lys 65	Gly	Arg	Phe	Thr	Ile 70	Ser	Arg	Asp	Asn	Ser 75	Гла	Asn	Thr	Leu	Tyr 80
Leu	Gln	Met	Asn	Ser 85	Leu	Arg	Ala	Glu	Asp 90	Thr	Ala	Val	Tyr	Tyr 95	Суз
Ala	Ile	Tyr	Thr 100	Gly	Arg	Trp	Glu	Pro 105	Phe	Val	Tyr	Trp	Gly 110	Gln	Gly
Thr	Leu	Val 115	Thr	Val	Ser	Ser									
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Ser	Leu	Arg	Leu 20	Ser	Сув	Ala	Ala	Ser 25	Gly	Phe	Thr	Phe	Val 30	Гла	Tyr
Ser	Met	Gly 35	Trp	Val	Arg	Gln	Ala 40	Pro	Gly	Lys	Gly	Leu 45	Glu	Trp	Val
Ser	Gln 50	Ile	Ser	Asn	Thr	Gly 55	Asp	Arg	Thr	Tyr	Tyr 60	Ala	Asp	Ser	Val
Lys 65	Gly	Arg	Phe	Thr	Ile 70	Ser	Arg	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80
Leu	Gln	Met	Asn	Ser 85	Leu	Arg	Ala	Glu	Asp 90	Thr	Ala	Val	Tyr	Tyr 95	Сүз
Ala	Ile	Tyr	Thr 100	Gly	Arg	Trp	Glu	Pro 105	Phe	Glu	Tyr	Trp	Gly 110	Gln	Gly
Thr	Leu	Val 115	Thr	Val	Ser	Ser									
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Ser	Leu	Arg	Leu 20	Ser	Сүз	Ala	Ala	Ser 25	Gly	Phe	Thr	Phe	Val 30	Lys	Tyr
Ser	Met	Gly 35	Trp	Val	Arg	Gln	Ala 40	Pro	Gly	Lys	Gly	Leu 45	Glu	Trp	Val
Ser	Gln 50	Ile	Ser	Asn	Thr	Gly 55	Asp	Arg	Thr	Tyr	Tyr 60	Ala	Asp	Ser	Val
Lys 65	Gly	Arg	Phe	Thr	Ile 70	Ser	Arg	Asp	Asn	Ser 75	ГЛа	Asn	Thr	Leu	Tyr 80
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys

1	7	7

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	85				90					95	
Ala Ile Tyr Th 10	r Gly 2 0	Arg Tr	р Lуз	Pro 105	Phe	Glu	Tyr	Trp	Gly 110	Gln	Gly
Thr Leu Val Th 115	r Val S	Ser Se	r								
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Ser Leu Arg Le 20	u Ser (Cys Al	a Ala	Ser 25	Gly	Phe	Thr	Phe	Val 30	Lys	Tyr
Ser Met Gly Tr 35	p Val 2	Arg Gl	n Ala 40	Pro	Gly	Lys	Gly	Leu 45	Glu	Trp	Val
Ser Gln Ile Se 50	r Asn '	Thr Gl 55	y Asp	Arg	Thr	Tyr	Tyr 60	Ala	Asp	Ser	Val
Lys Gly Arg Ph 65	e Thr :	Ile Se 70	r Arg	Asp	Asn	Ser 75	ГЛа	Asn	Thr	Leu	Tyr 80
Leu Gln Met As	n Ser 1 85	Leu Ar	g Ala	Glu	Asp 90	Thr	Ala	Val	Tyr	Tyr 95	Cys
Ala Ile Tyr Th 10	r Gly 2 0	Arg Tr	p Val	Pro 105	Phe	Glu	Tyr	Trp	Gly 110	Gln	Gly
Thr Leu Val Th 115	r Val S	Ser Se	r								
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Glu Val Gln Le 1	u Leu (5	Glu Se	r Gly	Gly	Gly 10	Leu	Val	Gln	Pro	Gly 15	Gly
Ser Leu Arg Le 20	u Ser (Cys Al	a Ala	Ser 25	Gly	Phe	Thr	Phe	Val 30	ГЛа	Tyr
Ser Met Gly Tr 35	p Val A	Arg Gl	n Ala 40	Pro	Gly	Lys	Gly	Leu 45	Glu	Trp	Val
Ser Gln Ile Se 50	r Asn '	Thr Gl 55	у Азр	Arg	Thr	Tyr	Tyr 60	Ala	Asp	Ser	Val
Lys Gly Arg Ph 65	e Thr : ,	Ile Se 70	r Arg	Asp	Asn	Ser 75	ГЛа	Asn	Thr	Leu	Tyr 80
Leu Gln Met As	n Ser 1 85	Leu Ar	g Ala	Glu	Asp 90	Thr	Ala	Val	Tyr	Tyr 95	Суз
Ala Ile Tyr Th 10	r Gly 2 0	Arg Tr	p Arg	Pro 105	Phe	Glu	Tyr	Trp	Gly 110	Gln	Gly
Thr Leu Val Th 115	r Val S	Ser Se	r								

<210> SEQ ID NO 36 <211> LENGTH: 119

<212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEQUENCE: 36 Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly 5 10 15 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr 25 20 30 Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val 35 40 Ser Gln Ile Ala Asn Thr Gly Asp Arg Arg Tyr Tyr Ala Asp Ser Val 50 55 60 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr 65 75 70 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ala Tyr Tyr Cys 85 90 95 Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly 100 105 110 Thr Leu Val Thr Val Ser Ser 115 <210> SEO ID NO 37 <211> LENGTH: 119 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEQUENCE: 37 Glu Val Gl
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n Pro Gly Gly 1 5 10 15 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr 20 25 30 Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val 35 40 45 Ser Gln Ile Ser Asn Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val 55 50 60 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr 70 75 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys 85 90 Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asn Tyr Trp Gly Gln Gly 100 105 110 Thr Leu Val Thr Val Ser Ser 115 <210> SEQ ID NO 38 <211> LENGTH: 119 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEQUENCE: 38 Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly 5 10 15 1 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr

		20					25					30			
Ser Me	et Gly 35	Trp	Val	Arg	Gln	Ala 40	Pro	Gly	Lys	Gly	Leu 45	Glu	Trp	Val	
Ser Gl 50	ln Ile)	Ser	Asn	Thr	Gly 55	Asp	Arg	Thr	Tyr	Tyr 60	Ala	Asp	Ser	Val	
Lys G] 65	ly Arg	Phe	Thr	Ile 70	Ser	Arg	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80	
Leu Gl	ln Met	Asn	Ser 85	Leu	Arg	Ala	Glu	Asp 90	Thr	Ala	Val	Tyr	Tyr 95	Cys	:
Ala Il	le Tyr	Thr 100	Gly	Arg	Trp	Ala	Pro 105	Phe	Glu	Tyr	Trp	Gly 110	Gln	Gly	,
Thr Le	eu Val 115	Thr	Val	Ser	Ser										
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<400>	SEQUE	NCE:	39												
Glu Va 1	al Gln	Leu	Leu 5	Glu	Ser	Gly	Gly	Gly 10	Leu	Val	Gln	Pro	Gly 15	Gly	•
Ser Le	eu Arg	Leu 20	Ser	Сув	Ala	Ala	Ser 25	Gly	Phe	Thr	Phe	Val 30	Lys	Tyr	
Ser Me	et Gly 35	Trp	Val	Arg	Gln	Ala 40	Pro	Gly	Lys	Gly	Leu 45	Glu	Trp	Val	
Ser Gl 50	ln Ile)	Ser	Asn	Thr	Gly 55	Asp	Arg	Thr	Tyr	Tyr 60	Ala	Asp	Ser	Val	
Lys G] 65	ly Arg	Phe	Thr	Ile 70	Ser	Arg	Asp	Asn	Ser 75	Lys	Asn	Ser	Leu	Tyr 80	
Leu Gl	ln Met	Asn	Ser 85	Leu	Arg	Ala	Glu	Asp 90	Thr	Ala	Val	Tyr	Tyr 95	Суз	I
Ala Il	le Tyr	Thr 100	Gly	Arg	Trp	Val	Pro 105	Phe	Asp	Asn	Trp	Gly 110	Gln	Gly	
Thr Le	eu Val 115	Thr	Val	Ser	Ser										
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Glu Va	al Gln	Leu	Leu	Glu	Ser	Glv	Glv	Glv	Leu	Val	Gln	Pro	Glv	Glv	,
1		- 4	5			-1	-1	10					15	-4	
Ser Le	eu Arg	Leu 20	Ser	Сүз	Ala	Ala	Ser 25	Gly	Phe	Thr	Phe	Ile 30	Thr	Tyr	
Ser Me	et Gly 35	Trp	Val	Arg	Gln	Ala 40	Pro	Gly	Lys	Gly	Leu 45	Glu	Trp	Val	
Ser Gl 50	ln Ile)	Ser	Asn	Thr	Gly 55	Asp	Arg	Thr	Tyr	Tyr 60	Ala	Aab	Ser	Val	
Lys Gl 65	ly Arg	Phe	Thr	Ile 70	Ser	Arg	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80	

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Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys 85 90 95 Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Gln Tyr Trp Gly Gln Gly 100 105 110 Thr Leu Val Thr Val Ser Ser 115 <210> SEQ ID NO 41 <211> LENGTH: 119 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEQUENCE: 41 Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly 1 5 10 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Gly Lys Tyr 20 25 30 20 30 Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val 40 35 45 Ser Gln Ile Ser Asn Thr Gly Asp Arg Thr Tyr Tyr Ala Asp Ser Val 50 55 60 Lys Gly \mbox{Arg} Phe Thr Ile Ser \mbox{Arg} As
p Asn Ser Lys Asn Thr Leu Tyr 65 70 75 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys 85 90 95 Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly 100 105 110 Thr Leu Val Thr Val Ser Ser 115 <210> SEQ ID NO 42 <211> LENGTH: 119 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEQUENCE: 42 Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly 1 5 10 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Phe Lys Tyr 20 25 30 Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val 40 35 45 Ser Gln Ile Ser Asn Thr Gly Asp Arg Thr Tyr Tyr Ala Asp Ser Val 55 60 50 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr 65 70 75 80 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys 85 90 95 Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly 100 105 110 Thr Leu Val Thr Val Ser Ser 115

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Ser Met Gl 35	y Trp	Val	Arg	Gln	Ala 40	Pro	Gly	Lys	Gly	Leu 45	Glu	Trp	Val
Ser Gln Il 50	e Ser	Asn	Thr	Gly 55	Asp	Arg	Thr	Tyr	Tyr 60	Ala	Asp	Ser	Val
Lys Gly Ar 65	g Phe	Thr	Ile 70	Ser	Arg	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80
Leu Gln Me	t Asn	Ser 85	Leu	Arg	Ala	Glu	Asp 90	Thr	Ala	Val	Tyr	Tyr 95	Сүз
Ala Ile Ty	r Thr 100	Gly	Arg	Trp	Glu	Pro 105	Phe	Lys	Tyr	Trp	Gly 110	Gln	Gly
Thr Leu Va 11	l Thr 5	Val	Ser	Ser									
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1 Ser Leu Ar	a Levi	5 Ser	Cve	∠ا⊳	- 21 -	Ser	10 ⁻	Phe	Thr	Phe	Ser	15 Lvg	- Tvr
den Mei Al	20 20	Det	CYD	AT d	nid	25	CTY	1.116			30	шу 3 m-	- Y -
Ser Met Gl 35	y Trp	Val	Arg	Gln	Ala 40	Pro	Gly	Lys	Gly	Leu 45	Glu	Trp	Val
Ser Gln Il 50	e Ser	Asn	Thr	Gly 55	Glu	Arg	Arg	Tyr	Tyr 60	Ala	Asp	Ser	Val
Lys Gly Ar 65	g Phe	Thr	Ile 70	Ser	Arg	Asp	Asn	Pro 75	ГÀа	Asn	Thr	Leu	Tyr 80
Leu Gln Me	t Asn	Ser 85	Leu	Arg	Ala	Glu	Asp 90	Thr	Ala	Val	Tyr	Tyr 95	Суз
Ala Ile Ty	r Thr 100	Gly	Arg	Trp	Glu	Pro 105	Phe	Glu	Tyr	Trp	Gly 110	Gln	Gly
Thr Leu Va 11	l Thr 5	Val	Ser	Ser									
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Ser Met Gl 35	y Trp	Val	Arg	Gln	Ala 40	Pro	Gly	Lys	Gly	Leu 45	Glu	Trp	Val
Ser Gln Il 50	e Ser	Asn	Thr	Gly 55	Asp	Arg	Thr	Tyr	Tyr 60	Ala	Asp	Ser	Val
Lys Gly Ar 65	g Phe	Thr	Ile 70	Ser	Arg	Asp	Asn	Ser 75	ГÀа	Asn	Thr	Leu	Tyr 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys 85 90 95 Ala Ile Tyr Thr Gly Arg Trp Glu Pro Tyr Glu Tyr Trp Gly Gln Gly 100 105 110 Thr Leu Val Thr Val Thr Ser 115 <210> SEQ ID NO 48 <211> LENGTH: 119 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEQUENCE: 48 Glu Val Gl
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n Met As
n Ser Leu Arg Ala Glu Asp
 Thr Ala Val Tyr Tyr Cys $% \left({{\left({{{\left({{{\left({{{}}} \right)} \right)}} \right)}} \right)} \right)$ 85 90 95 Ala Ile Tyr Thr Gly Arg Trp Lys Pro Phe Glu Tyr Trp Gly Gln Gly 100 105 110 Thr Leu Val Thr Val Ser Ser

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200

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	1	Lev	2~~	Lev	5	C17~	<u>م</u> ام	- ماھ	- 5	10	Dhe	ጥኩም	Dha	V-1	15 Luc	- Tur~
	Jer	nea	чт.д	20	ser	сув	лта	та	25 	GTÀ	File	. IIF	-116	30	- тув	тут
	Ser	Met	Gly 35	Trp	Val	Arg	Gln	Ala 40	Pro	Gly	Lys	Gly	Leu 45	Glu	Trp	Val
	Ser	Gln 50	Ile	Ser	Aap	Thr	Gly 55	Asp	Arg	Arg	Tyr	Tyr 60	Asp	Asp	Ser	Val
	Lуз 65	Gly	Arg	Phe	Thr	Ile 70	Ser	Arg	Asp	Asn	Ser 75	ГЛа	Asn	Thr	Leu	Tyr 80
	Leu	Gln	Met	Asn	Ser 85	Leu	Arg	Ala	Glu	Asp 90	Thr	Ala	Val	Tyr	Tyr 95	Суз
	Ala	Ile	Tyr	Thr 100	Gly	Arg	Trp	Val	Pro 105	Phe	Glu	Tyr	Trp	Gly 110	Gln	Gly
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Ser	Met	Gly 35	Trp	Val	Arg	Gln	Ala 40	Pro	Gly	Lys	Gly	Leu 45	Glu	Trp	Val
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Ala	Ile	Tyr	Thr	85 Gly	Arg	Trp	Arg	Pro	Phe	Glu	Tyr	Trp	Gly	Gln	Glγ
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Ala	Ile	Tyr	Thr	Gly	Arg	Trp	Ala	Pro	Phe	Glu	Tyr	Trp	Gly	Gln	Gly
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		112													
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~ 404	0 < CI	- UPK	лсь. тир,	60	TTON	. ре	r T A G	а II(Jui di	Hum	an G	GI III.	me :	seque	nee.
Glu	Val	Gln	Leu	us Leu	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly
1 Ser	Leu	Ara	Leu	5 Ser	Cvs	Ala	Ala	Ser	10 Glv	Phe	Thr	Phe	Leu	15 Lvs	Phe
			20		-			25					30	_,5	
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Ser	Gln 50	Ile	Ala	Asn	Thr	Gly 55	Asp	Arg	Arg	Tyr	Tyr 60	Ala	Asp	Ser	Val

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr 70 75 80 65 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys 85 90 Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly 100 105 Thr Leu Val Thr Val Ser Ser 115 <210> SEQ ID NO 69 <211> LENGTH: 119 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEQUENCE: 69 Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly 5 10 1 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Leu Lys Tyr 25 20 30 Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val 35 40 45 Ser Gln Ile Ser Asn Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val 50 55 60 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr 65 70 75 80 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys 85 90 95 Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly 100 105 110 Thr Leu Val Thr Val Ser Ser 115 <210> SEQ ID NO 70 <211> LENGTH: 119 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEQUENCE: 70 Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly 10 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Phe Lys Tyr 25 20 30 Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val 35 40 Ser Gln Ile Ser Asp Thr Gly Asp Arg Arg Tyr Tyr Asp Asp Ser Val 50 55 60 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr 65 70 75 80 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys 85 90 Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly 100 105 110

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p \mbox{Asn} Ser Lys Asn Thr Leu Tyr 65 70 75 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys 85 90 95 Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly 100 105 Thr Leu Val Thr Val Ser Ser 115 <210> SEQ ID NO 82 <211> LENGTH: 119 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEQUENCE: 82 Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly 10 5 15 1 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr 20 25 30 Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Pro Glu Trp Val 35 40 45

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	Ala	Ile	Tyr	Thr 100	Gly	Arg	Trp	Glu	Pro 105	Phe	Asp	Tyr	Trp	Gly 110	Gln	Gly
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Leu	Gln	Met	Asn	Ser 85	Leu	Arg	Ala	Glu	Asp 90	Thr	Ala	Val	Tyr	Tyr 95	Суз
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Ser Met Gly Trp 35	Val Arg	g Gln Ala 40	Pro Gly	Lys	Gly L 4	eu Glu 5	Trp	Val
Ser Gln Ile Ser 50	Asp Thr	Ala Asp 55	Arg Arg	Tyr	Tyr A 60	la His.	Ser	Val
Lys Gly Arg Phe 65	Thr Ile 70	e Ser Arg	Asp Asn	Ser 75	Lys A	sn Thr.	Leu	Tyr 80
Leu Gln Met Asn	Ser Leu 85	ı Arg Ala	Glu Asp 90	Thr	Ala V	al Tyr	Tyr 95	Суз
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Ser Met Gly Trp 35	Val Arg	g Gln Ala 40	Pro Gly	Lys	Gly L 4	eu Glu 5	Trp	Val
Ser Gln Ile Ser 50	Asp Thr	Ala Asp 55	Arg Arg	Tyr	Tyr A 60	sp His.	Ser	Val
Lys Gly Arg Phe 65	Thr Ile 70	e Ser Arg	Asp Asn	Ser 75	Lys A	sn Thr.	Leu	Tyr 80
Leu Gln Met Asn	Ser Leu 85	ı Arg Ala	Glu Asp 90	Thr	Ala V	al Tyr	Tyr 95	Суз
Ala Ile Tyr Thr 100	Gly Arg	g Trp Ala	Pro Phe 105	Glu	Tyr T	rp Gly 110	Gln	Gly
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Ser Met Gly Trp	Val Arg	g Gln Ala	Pro Gly	Lys	Gly L	eu Glu	Trp	Val

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	35					40					45			
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Lys Gly 65	y Arg	Phe	Thr	Ile 70	Ser	Arg	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80
Leu Gli	n Met	Asn	Ser 85	Leu	Arg	Ala	Glu	Asp 90	Thr	Ala	Val	Tyr	Tyr 95	Суз
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Lys Gly 65	y Arg	Phe	Thr	Ile 70	Ser	Arg	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80
Leu Gli	n Met	Asn	Ser 85	Leu	Arg	Ala	Glu	Asp 90	Thr	Ala	Val	Tyr	Tyr 95	Суз
Ala Lei	u Tyr	Thr 100	Gly	Arg	Trp	Val	Ser 105	Phe	Glu	Tyr	Trp	Gly 110	Gln	Gly
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Ser Gli 50	n Ile	Ser	Asn	Thr	Ala 55	Asp	Arg	Thr	Tyr	Tyr 60	Ala	His	Ser	Val
Lys Gly 65	y Arg	Phe	Thr	Ile 70	Ser	Arg	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80
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Ala	Ile	Tyr	Thr	Gly	Arg	Trp	Glu	Pro	Phe	Val	Tyr	Trp	Gly	Gln	Gly
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Ser	Gln 50	Ile	Ser	Asp	Thr	Ala 55	Asp	Arg	Thr	Tyr	Tyr 60	Ala	His	Ser	Val
Lys 65	Gly	Arg	Phe	Thr	Ile 70	Ser	Arg	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80
Leu	Gln	Met	Asn	Ser 85	Leu	Arg	Ala	Glu	Asp 90	Thr	Ala	Val	Tyr	Tyr 95	Суз
Ala	Ile	Tyr	Thr 100	Gly	Arg	Trp	Gly	Pro 105	Phe	Val	Tyr	Trp	Gly 110	Gln	Gly
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Ser	Leu	Arg	Leu 20	Ser	Суз	Ala	Ala	Ser 25	Gly	Phe	Thr	Phe	Val 30	Lys	Tyr
Ser	Met	Gly 35	Trp	Val	Arg	Gln	Ala 40	Pro	Gly	Lys	Gly	Leu 45	Glu	Trp	Val
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Lys 65	Gly	Arg	Phe	Thr	Ile 70	Ser	Arg	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80
Leu	Gln	Met	Asn	Ser 85	Leu	Arg	Ala	Glu	Asp 90	Thr	Ala	Val	Tyr	Tyr 95	Сүз
Ala	Ile	Tyr	Thr 100	Gly	Arg	Trp	Val	Pro 105	Phe	Ala	Tyr	Trp	Gly 110	Gln	Gly
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Ser	Met	Gly 35	Trp	Val	Arg	Gln	Ala 40	Pro	Gly	Lys	Gly	Leu 45	Glu	Trp	Val
Ser	Gln 50	Ile	Ser	Asp	Thr	Ala 55	Asp	Arg	Thr	Tyr	Tyr 60	Ala	His	Ser	Val
Lys 65	Gly	Arg	Phe	Thr	Ile 70	Ser	Arg	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80

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n Met As
n Ser Leu Arg Ala Glu Asp
 Thr Ala Val Tyr Tyr Cys $% \left({{\left({{{\left({{{\left({{{}}} \right)} \right)}} \right)}} \right)} \right)$ 85 90 95 Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly 100 105 110 Thr Leu Val Thr Val Ser Ser

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<210> SEQ ID NO 129 <211> LENGTH: 119 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEQUENCE: 129 Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly 5 10 1 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr 25 20 Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val 40 Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val 55 60 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr 70 75 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys 85 90 95 85 Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Gln Tyr Trp Gly Gln Gly 100 105 110 Thr Leu Val Thr Val Ser Ser 115 <210> SEQ ID NO 130 <211> LENGTH: 119 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEQUENCE: 130 Glu Val Gl
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167	
207	

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Ser	Met	Gly 35	Trp	Val	Arg	Gln	Ala 40	Pro	Gly	Lys	Gly	Leu 45	Glu	Trp	Val
Ser	Gln 50	Ile	Ser	Asp	Thr	Ala 55	Asp	Arg	Thr	Tyr	Tyr 60	Ser	His	Ser	Val
Lуз 65	Gly	Arg	Phe	Thr	Ile 70	Ser	Arg	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80
Leu	Gln	Met	Asn	Ser 85	Leu	Arg	Ala	Glu	Asp 90	Thr	Ala	Val	Tyr	Tyr 95	Cys
Ala	Ile	Tyr	Thr 100	Gly	Arg	Trp	Val	Pro 105	Phe	Glu	Tyr	Trp	Gly 110	Gln	Gly
Thr	Leu	Val 115	Thr	Val	Ser	Ser									
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Glu 1	Val	Gln	Leu	Leu 5	Glu	Ser	Gly	Gly	Gly 10	Leu	Val	Gln	Pro	Gly 15	Gly
Ser	Leu	Arg	Leu 20	Ser	Сув	Ala	Ala	Ser 25	Gly	Phe	Thr	Phe	Phe 30	Lys	Tyr
Ser	Met	Gly 35	Trp	Val	Arg	Gln	Ala 40	Pro	Gly	Lys	Gly	Leu 45	Glu	Trp	Val
Ser	Gln 50	Ile	Ser	Aap	Thr	Ala 55	Asp	Arg	Thr	Tyr	Tyr 60	Ser	His	Ser	Val
Lys 65	Gly	Arg	Phe	Thr	Ile 70	Ser	Arg	Asp	Asn	Ser 75	ГЛа	Asn	Thr	Leu	Tyr 80
Leu	Gln	Met	Asn	Ser 85	Leu	Arg	Ala	Glu	Asp 90	Thr	Ala	Val	Tyr	Tyr 95	Суз
Ala	Ile	Tyr	Thr 100	Gly	Arg	Trp	Val	Pro 105	Phe	Glu	Tyr	Trp	Gly 110	Gln	Gly
Thr	Leu	Val 115	Thr	Val	Ser	Ser									
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- Ser	Leu	Arg	Leu 20	Ser	СЛа	Ala	Ala	Ser 25	Gly	Phe	Thr	Phe	Phe 30	Lys	Tyr
Ser	Met	Gly 35	Trp	Val	Arg	Gln	Ala 40	Pro	Gly	Lys	Gly	Leu 45	Glu	Trp	Val
Ser	Gln 50	Ile	Ser	Asp	Thr	Ala 55	Asp	Arg	Thr	Tyr	Tyr 60	Thr	His	Ser	Val
	2.5					55									

Lys 65	Gly	Arg	Phe	Thr	Ile 70	Ser	Arg	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80
Leu	Gln	Met	Asn	Ser 85	Leu	Arg	Ala	Glu	Asp 90	Thr	Ala	Val	Tyr	Tyr 95	Сув
Ala	Ile	Tyr	Thr	Gly	Arg	Trp	Val	Pro	Phe	Glu	Tyr	Trp	Gly	Gln	Gly
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		115													
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<223	> 01 > SH	iher Souei	INFO	141	LION	: De:	rıved	a iro	om a	Huma	an G	ermi	ine s	seque	ence.
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Ser	Leu	Arg	Leu	Ser	Суа	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Leu	Lys	Tyr
Ser	Met	Gly	∠u Trp	Val	Arg	Gln	Ala	∠5 Pro	Gly	Lys	Gly	Leu	30 Glu	Trp	Val
Ser	Gln	35 Ile	Ser	Asp	Thr	Ala	40 Asp	Arg	Thr	Tyr	Tyr	45 Thr	His	Ser	Val
Lare	50 Glv	۵ra	Dhe	- Thr	TIA	55 Ser	- Arc	Acr	Age	Cer	60 Larc	Age	Thr	Lev	ጥነም
ыуы 65	сту	πy	File	1111	70	Ser	Ar y	чар	-	75 	цув		1111		80 80
Leu	Gln	Met	Asn	Ser 85	Leu	Arg	Ala	Glu	Asp 90	Thr	Ala	Val	Tyr	Tyr 95	Суз
Ala	Ile	Tyr	Thr 100	Gly	Arg	Trp	Val	Pro 105	Phe	Glu	Tyr	Trp	Gly 110	Gln	Gly
Thr	Leu	Val 115	Thr	Val	Ser	Ser									
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<223	> 01	THER	INF	DRMA	TION	: De:	rive	d fro	om a	Huma	an G	erml:	ine s	eque	ence.
<400 Glu	> SH Val	Gln	Leu	142 Leu	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly
1	T.c	7	Lov	5	0	م ٦ <i>ح</i>	- - ר ה	e e e	10	Dhr	The	Dhe	Dh a	15	
əer	ьeu	Arg	ьец 20	ьer	суз	АІА	АІА	ser 25	сту	rne	Thr	rne	₽ne 30	гда	ıyr
Ser	Met	Gly 35	Trp	Val	Arg	Gln	Ala 40	Pro	Gly	Lys	Gly	Leu 45	Glu	Trp	Val
Ser	Gln 50	Ile	Ser	Asp	Thr	Ala 55	Asp	Arg	Thr	Tyr	Tyr 60	Ala	His	Ser	Val
Lys 65	Gly	Arg	Phe	Thr	Ile 70	Ser	Arg	Asp	Asn	Ser 75	ГЛа	Asn	Thr	Leu	Tyr 80
Leu	Gln	Met	Asn	Ser 85	Leu	Arg	Ala	Glu	Asp 90	Thr	Ala	Val	Tyr	Tyr 95	Суа
Ala	Ile	Tyr	Thr	Gly	Arg	Trp	Ala	Pro	Phe	Glu	Tyr	Trp	Gly	Gln	Gly
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Ser	Met	Gly 35	Trp	Val	Arg	Gln	Ala 40	Pro	Gly	Lys	Gly	Leu 45	Glu	Trp	Val
Ser	Gln 50	Ile	Ala	Asp	Thr	Ala 55	Asp	Arg	Thr	Tyr	Tyr 60	Ala	His	Ser	Val
Lys 65	Gly	Arg	Phe	Thr	Ile 70	Ser	Arg	Asp	Asn	Ser 75	ГЛа	Asn	Thr	Leu	Tyr 80
Leu	Gln	Met	Asn	Ser 85	Leu	Arg	Ala	Glu	Asp 90	Thr	Ala	Val	Tyr	Tyr 95	Суз
Ala	Ile	Tyr	Thr 100	Gly	Arg	Trp	Val	Pro 105	Phe	Glu	Tyr	Trp	Gly 110	Gln	Gly
Thr	Leu	Val 115	Thr	Val	Ser	Ser									
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Glu 1	Val	Gln	Leu	Leu 5	Glu	Ser	Gly	Gly	Gly 10	Leu	Val	Gln	Pro	Gly 15	Gly
Ser	Leu	Arg	Leu 20	Ser	Сүз	Ala	Ala	Ser 25	Gly	Phe	Thr	Phe	Phe 30	Lys	Tyr
Ser	Met	Gly 35	Trp	Val	Arg	Gln	Ala 40	Pro	Gly	Lys	Gly	Leu 45	Glu	Trp	Val
Ser	Gln 50	Ile	Ser	Asp	Thr	Ala 55	Asp	Arg	Thr	Tyr	Tyr 60	Ala	His	Ala	Val
Lys 65	Gly	Arg	Phe	Thr	Ile 70	Ser	Arg	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80
Leu	Gln	Met	Asn	Ser 85	Leu	Arg	Ala	Glu	Asp 90	Thr	Ala	Val	Tyr	Tyr 95	Cys
Ala	Ile	Tyr	Thr 100	Gly	Arg	Trp	Val	Pro 105	Phe	Glu	Tyr	Trp	Gly 110	Gln	Gly
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Ser	Met	Gly 35	Trp	Val	Arg	Gln	Ala 40	Pro	Gly	Lys	Gly	Leu 45	Glu	Trp	Val
Ser	Gln 50	Ile	Ala	Asp	Thr	Ala 55	Asp	Arg	Thr	Tyr	Tyr 60	Asp	His	Ser	Val

275

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr 70 75 80 65 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys 85 90 Ala Ile Tyr Thr Gly Arg Trp Val Pro Phe Glu Tyr Trp Gly Gln Gly 100 105 Thr Leu Val Thr Val Ser Ser 115 <210> SEQ ID NO 148 <211> LENGTH: 119 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEQUENCE: 148 Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly 5 10 1 15 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr 25 20 30 Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val 35 40 45 Ser Gln Ile Ala Asp Thr Ala Asp Arg Thr Tyr Tyr Asp His Ala Val 50 55 60 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr 65 70 75 80 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys 90 85 95 Ala Ile Tyr Thr Gly Arg Trp Val Pro Phe Glu Tyr Trp Gly Gln Gly 100 105 110 Thr Leu Val Thr Val Ser Ser 115 <210> SEQ ID NO 149 <211> LENGTH: 119 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEQUENCE: 149 Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly 10 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr 25 20 30 Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val 35 40 Ser Gln Ile Ala Asp Thr Ala Asp Arg Arg Tyr Tyr Ala His Ser Val 50 55 60 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr 75 65 70 80 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys 85 90 Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly 100 105 110

Thr Leu Val Thr Val Ser Ser

115

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Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser <210> SEQ ID NO 155 <211> LENGTH: 119 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEQUENCE: 155 Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Phe Lys Tyr Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Gln Ile Ser Asp Thr Ala Asp Arg Arg Tyr Tyr Asp Asp Ala Val Lys Gly Arg Phe Thr Ile Thr Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser <210> SEQ ID NO 156 <211> LENGTH: 119 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEQUENCE: 156 Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Ala His Ala Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Ile Tyr Thr Gly Arg Trp Val Pro Phe Glu Tyr Trp Gly Gln Gly

Thr Leu Val Thr Val Ser Ser 115

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ccagggaagg gtctagagtg ggtctcatcg attgattcta atggttctag tacatactac	180					
gcagacteeg tgaagggeeg gtteaceate teeegegaea atteeaagaa eaegetgtat	240					
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gaaagatcgt	300					
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ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtggtca tacatactac	180					
gcagacteeg tgaagggeeg gtteaceate teeegegaea atteeaagaa eaegetgtat	240					
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gaaatatacg	300					
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ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtggtca tacatactac	180					
gcagacteeg tgaagggeeg gtteaceate teeegegaea atteeaagaa eaegetgtat	240					
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gaaatatacg	300					
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teetgtgeag ceteeggatt cacettgtt aagtattega tggggtgggt eegeeagget 120 ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtggtca tacatactac 180 gcagacteeg tgaagggeeg gtteaceate teeegegaca atteeaagaa caegetgtat 240 ctgcaaatga acageetgeg tgeegaggae acegeggtat attactgtge gatatataeg 300 ggtcgttggg agccttttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357 <210> SEQ ID NO 167 <211> LENGTH: 357 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEOUENCE: 167 gaggtgcage tgttggagte tgggggggge ttggtacage etgggggggte cetgegtete 60 tcctqtqcaq cctccqqatt cacctttqtt aaqtattcqa tqqqatqqqt ccqccaqqct 120 ccagggaaag gtccagagtg ggtctcacag atttcgaata cgggtggtca tacatactac 180 gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240 ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300 ggtcgttggg agccttttga ctactggggt cagggaaccc tggtcacagt ctcgagc 357 <210> SEO ID NO 168 <211> LENGTH: 357 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEQUENCE: 168 gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctggggggtc cctgcgtctc 60 teetgtgeag ceteeggatt cacetttgtt aagtattega tggggtgggt eegeeagget 120 ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtggtca tacatactac 180 gcagactccg tgaagggccg gttcaccata tcccgcgaca attccaagaa cacgctgtat 240 atgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300 ggtcgttggg agccttttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357 <210> SEQ ID NO 169 <211> LENGTH: 357 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEQUENCE: 169 qaqqtqcaqc tqttqqaqtc tqqqqqaqqc ttqqtacaqc ctqqqqqqtc cctqcqtctc 60 teetgtgeag eeteeggatt eacetttggt aagtattega tggggtgggt eegeeagget 120 ccagggaagg atctagagtg ggtctcacag atttcgaata cgggtggtca tacatactac 180 gcagacteeg tgaagggeeg gtteaceate teeegegaea atteeaagaa eaegetgtat 240 ctgcaaatga acageetgeg tgeegaggae acegeggtat attaetgtge gatatataeg 300 357 qqtcqttqqq aqccttttqa ctactqqqqt caqqqaaccc tqqtcaccqt ctcqaqc

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ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtggtca tacatactac 1	80						
gcagacteeg tgaagggeeg gtteaceate teeegegaea atteeaagaa caegetgtat 2	40						
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ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatca tacatactac 1	80						
gcagacteeg tgaagggeeg gtteaceate teeegegaea atteeaagaa eaegetgtat 2	40						
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gaaatatacg 3	00						
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ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatcg tacatactac 1	80						
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gcagacteeg tgaagggeeg gtteaceate teeegegaea atteeaagaa eaegetgtat	240
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gcagacteeg tgaagggeeg gtteaceate teeegegaea atteeaagaa eaegetgtat	240
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gcagacteeg tgaagggeeg gtteaceate teeegegaea atteeaagaa eaegetgtat	240
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ccagggaagg gtctagagtg ggtctcacag atttcgaata ctgctgatcg tacatactac	180	
gcacactoog tgaagggoog gttoaccato tooogogaca attocaagaa caogotgtat	240	
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ccagggaagg gtctagagtg ggtctcacag atttcgaata ctgctgatcg tacatactac	180	
gcacacteeg tgaagggeeg gtteaceate teeegegaca atteeaagaa caegetgtat	240	
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ccagggaagg gtctagagtg ggtctcacag atttcgaata ctgctgatcg tacatactac	180	
gcacactoog tgaagggoog gttoaccato tooogogaca attocaagaa caogotgtat	240	
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg	300	
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ccagggaagg gtctagagtg ggtctcacag atttcggata cgggtgatcg tagatactac	180
gatgactetg tgaagggeeg gtteaceate teeegegaea atteeaagaa eaegetgtat	240
ctgcaaatga acageetgeg tgeegaggae acegeggtat attaetgtge gatatataeg	300
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teetgtgeag eeteeggatt eaetttgtt aagtattega tggggtgggt eegeeaggee	120
ccagggaagg gtctagagtg ggtctcacag atttcggata cgggtgatcg tagatactac	180
gatgactetg tgaagggeeg gtteaceate teeegegaea atteeagaa eaegetgtat	240
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ccagggaagg gtctagagtg ggtctcacag atttcggata cgggtgatcg tagatactac	180
gatgactetg tgaagggeeg gtteaceate teeegegaea atteeaagaa eaegetgtat	240
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teetgtgeag eeteeggatt eacetttgtt aagtattega tggggtgggt eegeeagget	120

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314

ccagggaagg gtctagagtg ggtctcacag atttcggata cgggtgatcg tagatactac	180		
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teetgtgeag eeteeggatt eacetttgtt aagtattega tggggtgggt eegeeagget	120		
ccagggaagg gtctagagtg ggtctcacag atttcggata cgggtgatcg tagatactac	180		
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ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatcg tagatactac	180		
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teetgtgeag eeteeggatt eacetttgtt aagtattega tggggtgggt eegeeagget	120		
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gcagacgcgg tgaaggggcg gttcaccatc tcccgcgaca attccaagaa	cacgctgtat 240
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ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatcg	tagatactac 180
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ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatcg	tagatactac 180
gcagacgcgg tgaagggggg gttcaccatc tcccgcgaca attccaagaa	cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc	gatatatacg 300
ggtcggtggg cgccttttga gtactggggt cagggaaccc tggtcaccgt	ctcgagc 357
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ccagggaagg gtctagagtg ggtctcacag attgcgaata cgggtgatcg	tagatactac 180
gcagactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa	cacgctgtat 240

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ctgesaatga acagectogog tgeogaggae acogogget attactgtge gatatataog 300 ggteggtggg egeentitga gtactggggt caggggaece tggteacegt etcegaec 357 -220 SRO ID NO 217 -221 KANNEN: 357 -222 OTHE: DINA -223 OTHE: DUMOWATION: Derived from a Human Germline Bequence. -400 SEQURIC: 217 gaggtgeage tgtoggatge tggggagge tggtacage etggggggt oggeagggg 100 ccagggaagg geetatggg etcacage atteggata digggtgggg oggeagggg 100 ccagggaagg geetatgg geetacage atteggata digggtgggg oggeaggg 120 ccagggaagg geetatgg geetacage atteggata digggtgggg oggeaggg 120 ccagggaagg geetatgg geetacage atteggata atteggat gatatatag 100 ggteggtggg geettitg agattegggt caggggae acogogget attactgtg gatatatag 100 ggteggtggg geettitg gatatgggg cagggae acogogget attactgtg gatatatag 100 ggteggtggg geettitg gatatgggg cagggae acogogget attactgtg gatatatag 100 ggteggtggg geettitg gatatgggg cagggae acogogget attactgtg gatatatag 100 ggteggtggg geettitg gatatgggg tgggaege tgggaege tggaege etcegage 120 ccagggaagg geetatggagt tgggggggg tgggaege tgggaege tgggaege 120 ccagggaagg getaggggg tggggggg tgggaggg tgggaege tgggaege 120 ccagggaagg getaggggg tggggggg tggggggg tgggaege tgggaege 120 ccagggaagg getaggggg tggggggg tggggggg tgggaege 120 ccagggaagg getaggggt gggggggg tgggaggg tgggaggg tgggagg 120 ccagggaagg getagggg tggggggg tgggaggae tgggaagg tgggaggg t gaggagg 120 ccagggaagg getaggggg tggcgaggae taggaacac tggggaege tggaaatata 180 gatgaettg baagggeog gtscacagg tacacate tcocggaa attactggg tggatagg 120 ccagggaagg getagggg tggcgaggae acggggaa attactggg gatagatata 180 gatgaettg baagggeog gtscacag attacggg acoctggggae cotggage 120 ccagggaagg getagggg tgggggg tgggaag acggggaa attactgg gatagaag 120 ccagggaagg getaggggg ggetagggg tgggaag acggggaa attactgg gatagaag 120 ccagggaagg getagggg gggggg tgggagg tgggaag acggggaa attactgg gatagaag 120 ccagggaagg getaggggg gggggg tgggagg tgggaagg tgggaggg tgggaagg tgggaagg 120 ccagggaagg getaggggg ggggg tgggaagg tgggaagg tgggaagg tgggaagg 120 ccagggaagg getaggggg gggggg tgggaaggaaggaggaaggaaggaggg tgggaaggagg 120		
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<pre>clos SEQ ID NO 217 clis LEMATH: 357 clis CHEANTH: 357 clis CH</pre>	ggtcggtggg cgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc	357
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ccagggaaag gtccagagtg ggtctcacag atttcggacg gcggtcagag gacatactac 180
gcagacteeg tgaagggeeg gtteaceate teeegggaea atteeaagaa eaegetgtat 240
ctgcaaatga acageetgeg tgeegaggae acegeggtat attaetgtge gatatataeg 300
ggtcgttggg agccttttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357
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gcagacteeg tgaagggeeg gtteaceate teeegegaca atteeaagaa caegetgtat 240
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coordinate decodered attaces attaces are the second attaces and the second attaces att
coaggyaagy yuulaagy yuulaalay autugyaby yyyytabyby yabatablad 180
ctocaatoa acagootoo tocogogaca accoogotat attactor ostatataco
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ccagggaaag gtccagagtg ggtctcacag atttcggaca agggtacgcg cacatactac 180
gcagacteeg tgaagggeeg gtteaceate teeegegaca atteeaagaa caegetgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
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<213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEQUENCE: 231 gaggtgcagc tgttggagtc tggggggggc ttggtacagc ctggggggtc cctgcgtctc 60 teetgtgeag eeteeggatt eacetttgtt aagtattega tgggatgggt eegeeagget 120 ccagggaaag gtccagagtg ggtctcacag atttcggaga ccggtcgcag gacatactac 180 gcagacteeg tgaagggeeg gtteaceate teeegegaea atteeaagaa eaegetgtat 240 ctgcaaatga acageetgeg tgeegaggae acegeggtat attaetgtge gatatataeg 300 ggtcgttggg agccttttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357 <210> SEQ ID NO 232 <211> LENGTH: 357 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEQUENCE: 232 60 gaggtgcagc tgttggagtc tggggggggc ttggtacagc ctggggggtc cctgcgtctc tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120 ccagggaagg gtctagagtg ggtctcacag attaacaata cgggttcgac cacatactac 180 gcagacteeg tgaagggeeg gtteaceate teeegegaea atteeaagaa eaegetgtat 240 ctgcaaatga acageetgeg tgeegaggae acegeggtat attactgtge gatatataeg 300 ggtcgttggg agccttttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357 <210> SEQ ID NO 233 <211> LENGTH: 357 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEOUENCE: 233 gaggtgcagc tgttggagtc tggggggggc ttggtacagc ctgggggggtc cctgcgtctc 60 teetgtgeag eeteeggatt eacetttgtt aagtattega tggggtgggt eegeeagget 120 ccagggaagg gtccagagtg ggtctcacag atttcgaata ctgctgatcg tacatactac 180 gcacactoog tgaagggoog gttoaccato tooogogaca attocaagaa caogotgtat 240 ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatact 300 gggcgttggg tgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357 <210> SEQ ID NO 234 <211> LENGTH: 357 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEQUENCE: 234 gaggtgcagc tgttggagtc tggggggggc ttggtacagc ctgggggggtc cctgcgtctc 60 tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120 ccagggaagg gtccagagtg ggtctcacag atttcgaata ctgctgatcg tacatactac 180 gcacacteeg tgaagggeeg gtteaceate teeegegaea atteeaagaa eaegetgtat 240

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Э	4	1

ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg	300
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ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac	180
gcacacteeg tgaagggeeg gtteaceate teeegegaea atteeaagaa eaegetgtat	240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatact	300
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ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac	180
gcacacteeg tgaagggeeg gtteaceate teeegegaca atteeaagaa eaegetgtat	240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg	300
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ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac	180
gatgactetg tgaagggeeg gtteaceate teeeggaca atteeaagaa eaegetgtat	240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg	300
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<220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence.

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acacactcog tgaagggoog gttcaccato tooogogaca attocaagaa caogotgtat	240
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ccagggaagg gtctagagtg ggtctcacag atttcgaata ctgctgatcg cagatactac	180
gcacactoog tgaagggoog gttoaccato tooogogaca attooaagaa caogotgtat	240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg	300
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ccagggaagg gtctagagtg ggtctcacag attttgaata ctgctgatcg tacatactac	180
gatcactoog tgaagggoog gttoaccato tooogogaca attooaagaa caogotgtat	240
ctgcaaatga acageetgeg tgeegaggae acegeggtat attaetgtge gatatataeg	300
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ccaqqqaaqq gtctaqaqtq gqtctcacaq atttcqaata ctgctgatcg tacatagtag	180
dateacted taaagged attaceate tecograde attecaages cacetotet	240
charapatas angagatang tanggagana angagatat attatatan attitit	300
eryeaaalya acayeeryey ryeegaggae acegeggtat attactgtge gatatataeg	300
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<210> SEQ ID NO 242 <211> LENGTH: 357 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEQUENCE: 242 gaggtgcagc tgttggagtc tggggggggc ttggtacagc ctggggggtc cctgcgtctc 60 tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120 ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tagatactac 180 gcacacteeg tgaagggeeg gtteaceate teeegegaea atteeaagaa eaegetgtat 240 ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300 ggtcggtggg cgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357 <210> SEQ ID NO 243 <211> LENGTH: 357 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEOUENCE: 243 60 gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggggtc cctgcgtctc tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120 ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tagatactac 180 gatcactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240 ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300 ggtcggtggg cgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357 <210> SEQ ID NO 244 <211> LENGTH: 357 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEQUENCE: 244 gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggggtc cctgcgtctc 60 tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120 ccagggaagg gtctagagtg ggtctcacag atttcgaata ctgctgatcg tacatactac 180 gcacacteeg tgaagggeeg gtteaceate teeegegaea atteeaagaa eaegetgtat 240 ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc ggtatatact 300 357 gggcgttggg tgtcttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc <210> SEQ ID NO 245 <211> LENGTH: 357 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence.

<400> SEQUENCE: 245

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- 4	- 4	- •
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334

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gcacacteeg tgaagggeeg gtteaceate teeegegaea atteeaagaa eaegetgtat	240
ctgcaaatga acageetgeg tgeegaggae acegeggtat attaetgtge getatataet	300
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ccagggaagg gtctagagtg ggtctcacag atttcgaata ctgctgatcg tacatactac	180
gcacacteeg tgaagggeeg gtttaceate teeegegaca atteeaagaa caegetgtat	240
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ccagggaagg gtctagagtg ggtctcacag atttcgaata ctgctgatcg tacatactac	180
gcacacteeg tgaagggeeg gtteaceate teeegegaea atteeaagaa eaegetgtat	240
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ccagggaagg gtctagagtg ggtctcacag attgcgaata ctgctgatcg tagatactac	180
gcacacteeg tgaagggeeg gtteaceate teeegegaea atteeaagaa eaegetgtat	240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg	300
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<210> SEQ ID NO 249 <211> LENGTH: 357

<212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence.	
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ccagggaagg gtctagagtg ggtctcacag atttcgaata ctgctgatcg tagatactac	180
gcagacgcgg tgaaggggcg gttcaccatc tcccgcgaca attccaagaa cacgctgtat	240
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ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggcgatcg tagatactac	180
gcacacgcgg tgaaggggcg gttcaccatc tcccgcgaca attccaagaa cacgctgtat	240
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ccagggaagg gtctagagtg ggtctcacag attgcgaata ctgctgatcg tagatactac	180
gcagacgcgg tgaaggggcg gttcaccatc tcccgcgaca attccaagaa cacgctgtat	240
ctgcaaatga acageetgeg tgeegaggae acegeggtat attaetgtge gatatataeg	300
ggtcgttggg agccttttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc	357
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teetgtgeag eeteeggatt eacetttgtt aagtattega tggggtgggt eegeeagget	120
ccagggaagg gtctagagtg ggtctcacag attgcgaata cgggtgatcg tagatactac	180

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gcacacgcgg tgaagggggg gttcaccatc tcccgcgaca attccaagaa cacgctgtat	240
ctgcaaatga acageetgeg tgeegaggae acegeggtat attaetgtge gatatataeg	300
ggtcgttggg agccttttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc	357
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gcacacgegg tgaagggggg gttcaccate teeegggaca atteeaagaa caegetgtat	240
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gcacacgcgg tgaagggggg gttcaccatc teeegggaca atteeaagaa caegetgtat	240
ctgcaaatga acageetgeg tgeegaggae acegeggtat attaetgtge gatatataeg	300
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ccagggaagg gtctagagtg ggtctcacag attgtgaata cgggtgatcg tagatactac	180
gcagacgcgg tgaagggggg gttcaccatc tcccgcgaca attccaagaa cacgctgtat	240
ctgcaaatga acageetgeg tgeegaggae acegeggtat attaetgtge gatatataeg	300
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<223> OTHER INFORMATION: Derived from a Human Germline sequence.

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gcagacgcgg tgaaggggggg gttcaccatc tcccgcgaca attccaagaa cacgctgtat	240
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ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac	180
gatcactoog tgaagggoog gttcaccato tooogogaca attocaagaa caogotgtat	240
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ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac	180
gatcactoog tgaagggoog gttoaccato tooogogaca attocaagaa caogotgtat	240
ctgcaaatga acageetgeg tgeegaggae aeegeggtat attaetgtge gatatataeg	300
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ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac	180
gatcactoog tgaagggoog gttcaccato tocogogaca attocaagaa caogotgtat	240
stgsaaatga asagostgog tgoogaggas acogoggtat attactgtgo gatatataog	300

ggtcgttggg agccttttgt ctactggggt cagggaaccc tggtcaccg	ctcgagc	357	
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tcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa	a cacgctgtat	240	
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ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgate	g tacatactac	180	
acacacteeg tgaagggeeg gtteaceate teeegegaca atteeaaga	a cacgctgtat	240	
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtg	gatatatact	300	
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acagacgcgg tgaaggggcg gttcaccatc tcccgcgaca attccaaga	a cacgctgtat	240	
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gcacactcog tgaagggoog gttcaccato tocogogaca attocaagaa caogotgtat	240
ctgcaaatga acageetgeg tgeegaggae acegeggtat attaetgtge gatatataeg	300
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ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac	180
gcacacteeg tgaagggeeg gtteaceate teeegegaca atteeaagaa eaegetgtat	240
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ctqcaaatqa acaqcctqcq tqccqaqqac accqcqqtat attactqtqc qatatatacq	300
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ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tagatactac	180
gatgactetg tgaagggeeg gtteaceate teeegegaea atteeaagaa eaegetgtat	240
ctgcaaatga acageetgeg tgeegaggae acegeggtat attaetgtge gatatataeg	300
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ccagggaagg gtctagagtg ggtctcacag atttcggata cgggtgatcg tagatactac	180
gatcactetg tgaagggeeg gtteaceate teeegegaea atteeaagaa eaegetgtat	240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg	300
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ccaqqqaaqq qtctaqaqtq qqtctcacaq attcqqata cqqqtqatcq taqatactac	180
gatgacqcqq tgaaqqqccq qttcaccatc tcccqcqaca attccaagaa cacqctqtat	240
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ccagggaagg gtctagagtg ggtctcacag attgcggata ctgctgatcg tagatactac	180
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ccagggaagg gtctagagtg ggtctcacag attgcggata cgggtgatcg tagatactac	180

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gatcactetg tgaagggeeg gtteaetate teeegegaea atteeaagaa eaegetgtat	240
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gcacacteeg tgaagggeeg gtteaceate teeegegaea atteeaagaa eaegetgtat	240
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ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 18	180
gcacacteeg tgaagggeeg gtteaceate teeegegaea atteeaagaa eaegetgtat 24	240
ctgcaaatga acageetgeg tgeegaggae acegeggtat attaetgtge gatatataeg 30	300
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358

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gggcgttggg tgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc	357
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ccagggaagg gtctagagtg ggtctcacag attgcggata ctgctgatcg tacatactac	180
gatcactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat	240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatact	300
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teetgtgeag eeteeggatt eacetttgtt aagtattega tggggtgggt eegeeagget	120
ccagggaagg gtctagagtg ggtctcacag attgcggata ctgctgatcg tacatactac	180
gatcacgcgg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat	240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatact	300
gggcgttggg tgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc	357
<210> SEQ ID NO 298 <211> LENGTH: 357 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence.	
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ccagggaagg gtctagagtg ggtctcacag attgcggata ctgctgatcg tagatactac	180
gcacacteeg tgaagggeeg gtteaceate teeegegaea atteeaagaa eaegetgtat	240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg	300
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<400> SEQUENCE: 299	

363

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teetgtgeag eeteeggatt eacetttgtt aagtattega tggggtgggt eegeeagget 1	20
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tagatactac 1	.80
gcacacgogg tgaagggoog gttcaccato tooogogaca attocaagaa caogotgtat 2	40
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 3	00
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teetgtgeag eeteeggatt eacetttgtt aagtattega tggggtgggt eegeeagget 1	20
ccagggaagg gtctagagtg ggtctcacag attgcggata ctgctgatcg tagatactac 1	80
gcacacgogg tgaagggoog gttcaccato tocogogaca attocaagaa caogotgtat 2	40
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 3	00
ggtcggtggg cgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 3	57
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teetgtgeag eeteeggatt eacetttgtt aagtattega tggggtgggt eegeeagget 1	20
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tagatactac 1	80
gatcacgcgg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 2	40
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tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 1	.20
ccagggaagg gtctagagtg ggtctcacag attgcggata ctgctgatcg tagatactac 1	80
gatcacgegg tgaagggeeg gtteaceate teeegegaea atteeaagaa eaegetgtat 2	40
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 3	00
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<210> SEQ ID NO 303 <211> LENGTH: 357 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEQUENCE: 303 gaggtgcagc tgttggagtc tggggggggc ttggtacagc ctgggggggtc cctgcgtctc 60 teetgtgeag eeteeggatt eacetttgtt aagtattega tggggtgggt eegeeagget 120 ccagggaagg gtctagagtg ggtctcacag attgcggata ctgctgatcg tagatactac 180 gatcactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240 ctgcaaatga acageetgeg tgeegaggae acegeggtat attaetgtge gatatataeg 300 ggteggtggg egeettttga gtaetggggt eagggaaeee tggteaeegt etegage 357 <210> SEQ ID NO 304 <211> LENGTH: 357 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEOUENCE: 304 gaggtgcagc tgctggagtc tggggggggc ttggtacagc ctggggggtc cctgcgtctc 60 tcctgtgcag cctccggatt cacctttttc aagtattcga tggggtgggt ccgccaggct 120 ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tagatactac 180 gatgacgcgg tgaagggccg gttcaccatc acccgcgaca attccaagaa cacgctgtat 240 ctgcaaatga acageetgeg tgeegaggae acegeggtat attactgtge gatatataeg 300 ggtcgttggg agccttttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357 <210> SEQ ID NO 305 <211> LENGTH: 163 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEQUENCE: 305 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu 10 1 Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser 25 Ser Gly Ala Pro Pro Pro Ser Gly Gly Gly Gly Gly Ser Gly Gly Gly 35 40 45 Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser 55 60 Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala 65 70 75 80 Ser Gln Trp Ile Gly Ser Gln Leu Ser Trp Tyr Gln Gln Lys Pro Gly 85 90 95 Lys Ala Pro Lys Leu Leu Ile Met Trp Arg Ser Ser Leu Gln Ser Gly 100 105 110 Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu 115 120 125

Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Ala

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130	135	5	140		
Gln Gly Ala . 145	Ala Leu Pro Arg 150	g Thr Phe Gly	Gln Gly 155	Thr Lys Val Glu 160	
Ile Lys Arg					
<pre><210> SEQ ID <211> LENGTH <212> TYPE: : <213> ORGANI. <220> FEATUR <223> OTHER</pre>	NO 306 : 489 DNA SM: Artificial E: INFORMATION: De	Sequence erived from a	Human Ge	ermline sequence.	
<400> SEQUEN	CE: 306				
catggtgaag g	aacatttac cagtg	jacttg tcaaaac	aga tgga	agagga ggcagtgco	4G 60
ttatttattg a	gtggettaa gaacg	ygagga ccaagta	aca aaac	acctec gecategge	gt 120
ggtggaggcg g	ttcaggcgg aggtg	gcagc ggcggtg	gcg ggto	ggacat ccagatgac	cc 180
cagtetecat c	ctccctgtc tgcat	ctgta ggagacc	gtg tcac	catcac ttgccgggc	ca 240
agtcagtgga t	tgggtctca gttat	cttgg taccage	aga aacc	agggaa agcccctaa	ag 300
ctcctgatca t	gtggegtte etegt	tgcaa agtgggg	tcc cato	acgttt cagtggcag	gt 360
ggatctggga c	agatttcac tctca	accatc agcagtc	tgc aacc	tgaaga ttttgctac	zg 420
tactactgtg c	tcagggtgc ggcgt	tgeet aggaegt	tcg gcca	agggac caaggtgga	aa 480
atcaaacgg					489
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His Gly Glu	Gly Thr Phe Thr	: Ser Asp Leu	Ser Lys	Gln Met Glu Glu	
1	5	10		15	
Glu Ala Val .	Arg Leu Phe Ile 20	e Glu Trp Leu 25	Lys Asn	Gly Gly Pro Ser 30	
Ser Gly Ala 3 35	Pro Pro Pro Ser	Gly Gly Gly 40	Gly Gly	Ser Gly Gly Gly 45	
Gly Ser Gly 50	Gly Gly Gly Ser 55	Asp Ile Gln	Met Thr 60	Gln Ser Pro Ser	
Ser Leu Ser . 65	Ala Ser Val Gly 70	v Asp Arg Val	Thr Ile 75	Thr Cys Arg Ala 80	
Ser Gln Trp	Ile Gly Ser Glr 85	n Leu Ser Trp 90	Tyr Gln	Gln Lys Pro Gly 95	
Lys Ala Pro	Lys Leu Leu Ile 100	e Met Trp Arg 105	Ser Ser	Leu Gln Ser Gly 110	
Val Pro Ser . 115	Arg Phe Ser Gly	/ Ser Gly Ser 120	Gly Thr	Asp Phe Thr Leu 125	
Thr Ile Ser 1 130	Ser Leu Gln Pro 135	Glu Asp Phe .	Ala Thr 140	Tyr Tyr Cys Ala	
Gln Gly Leu . 145	Arg His Pro Lys 150	Thr Phe Gly	Gln Gly 155	Thr Lys Val Glu 160	
Ile Lys Arg					

<210> SEQ ID NO 308

369

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<211> LENGTH: 489 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEQUENCE: 308 catggtgaag gaacatttac cagtgacttg tcaaaacaga tggaagagga ggcagtgcgg 60 ttatttattg agtggcttaa gaacggagga ccaagtagcg gggcacctcc gccatcgggt 120 ggtggaggcg gttcaggcgg aggtggcagc ggcggtggcg ggtcggacat ccagatgacc 180 cagteteeat ceteeetgte tgeatetgta ggagaeegtg teaceateae ttgeegggea 240 agtcagtgga ttgggtctca gttatcttgg taccagcaga aaccagggaa agcccctaag 300 ctcctgatca tgtggcgttc ctcgttgcaa agtggggtcc catcacgttt cagtggcagt 360 ggatetggga cagattteac teteaceate ageagtetge aacetgaaga ttttgetaeg 420 480 tactactgtg ctcagggttt gaggcatect aagaegtteg gecaagggae caaggtggaa 489 atcaaacqq <210> SEQ ID NO 309 <211> LENGTH: 163 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEQUENCE: 309 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu 1 5 10 15 Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser 20 25 30 Ser Gly Ala Pro Pro Pro Ser Gly Gly Gly Gly Gly Ser Gly Gly Gly 40 45 35 Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser 50 55 60 Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala 65 70 75 80 Ser Gln Trp Ile Gly Ser Gln Leu Ser Trp Tyr Gln Gln Lys Pro Gly 85 90 95 Lys Ala Pro Lys Leu Leu Ile Met Trp Arg Ser Ser Leu Gln Ser Gly 100 105 110 Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu 115 120 Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Ala 135 130 140 Gln Gly Leu Met Lys Pro Met Thr Phe Gly Gln Gly Thr Lys Val Glu 145 150 155 160 Ile Lys Arg <210> SEQ ID NO 310 <211> LENGTH: 489 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEQUENCE: 310

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371

ttatttattg agtggettaa gaacggagga ceaagtageg gggeacetee geeategggt

ggtggaggcg gttcaggcgg aggtggcagc ggcggtggcg ggtcggacat ccagatgacc

372

120

cagtetecat cetecetgte tgeatetgta ggagaeegtg teaceateae ttgeeggge	a 240
agtcagtgga ttgggtctca gttatcttgg taccagcaga aaccagggaa agcccctaa	g 300
ctcctgatca tgtggcgttc ctcgttgcaa agtggggtcc catcacgttt cagtggcag	360
ggatetggga cagattteae teteaceate ageagtetge aacetgaaga ttttgetae	g 420
tactactgtg ctcagggtct tatgaagcct atgacgttcg gccaaggggac caaggtggaa	a 480
atcaaacgg	489
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Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser 20 25 30	
Ser Gly Ala Pro Pro Pro Ser Gly Gly Gly Gly Gly Ser Gly Gly Gly Gly 35 40 45	
Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser 50 55 60	
Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Ser Cys Arg Ala65707580	
Ser Gln Trp Ile Gly Ser Gln Leu Ser Trp Tyr Gln Gln Lys Pro Gly 85 90 95	
Glu Ala Pro Lys Leu Leu Ile Met Trp Arg Ser Ser Leu Gln Ser Gly 100 105 110	
Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu 115 120 125	
Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Ala 130 135 140	
Gln Gly Ala Ala Leu Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu 145 150 155 160	
Ile Lys Arg	
<210> SEQ ID NO 312 <211> LENGTH: 489 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence.	
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ggtggaggeg gttcaggegg aggtggcage ggeggtggeg ggteggaeat ceagatgae	2 180
cagtetecat ecteetigte tgeatetgta ggagaeegtg teaceatete ttgeegggea	a 240
agtcagtgga ttgggtetea gttatettgg taccageaga aaccagggga ageeeetaa	g 300

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ctcctgatca tgtggcgttc ctcgttgcaa agtggggtcc catcacgttt cagtggcagt	360
ggatetggga cagattteae teteaceate ageagtetge aacetgaaga ttttgetaeg	420
tactactgtg ctcagggtgc ggcgttgcct aggacgttcg gccaagggac caaggtggaa	480
atcaaacgg	489
<210> SEQ ID NO 313 <211> LENGTH: 163 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence.	
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Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser 20 25 30	
Ser Gly Ala Pro Pro Pro Ser Gly Gly Gly Gly Gly Ser Gly Gly Gly 35 40 45	
Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser 50 55 60	
Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala 65 70 75 80	
Ser Arg Pro Ile Gly Thr Thr Leu Ser Trp Tyr Gln Gln Lys Pro Gly 85 90 95	
Lys Ala Pro Lys Leu Leu Ile Trp Phe Gly Ser Arg Leu Gln Ser Gly 100 105 110	
Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu 115 120 125	
Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Ala130135140	
Gln Ala Gly Thr His Pro Thr Thr Phe Gly Gln Gly Thr Lys Val Glu145150155160	
Ile Lys Arg	
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ggtggaggcg gttcaggcgg aggtggcagc ggcggtggcg ggtcggacat ccagatgacc	180
cagteteeat eeteeetgte tgeatetgta ggagaeegtg teaceateae ttgeegggea	240
agtegteega ttgggaegae gttaagttgg taecageaga aaccagggaa ageeectaag	300
ctcctgatct ggtttggttc ccggttgcaa agtgggggtcc catcacgttt cagtggcagt	360
ggatetggga cagattteae teteaceate ageagtetge aacetgaaga ttttgetaeg	420
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<213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence.						
<400> SEQUENCE: 315						
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Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser 20 25 30						
Ser Gly Ala Pro Pro Pro Ser Gly Gly Gly Gly Gly Ser Gly Gly Gly 35 40 45						
Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser 50 55 60						
Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala65707580						
Ser Arg Pro Ile Gly Thr Met Leu Ser Trp Tyr Gln Gln Lys Pro Gly 85 90 95						
Lys Ala Pro Lys Leu Leu Ile Leu Phe Gly Ser Arg Leu Gln Ser Gly 100 105 110						
Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu 115 120 125						
Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Ala 130 135 140						
Gln Ala Gly Thr His Pro Thr Thr Phe Gly Gln Gly Thr Lys Val Glu 145 150 155 160						
Ile Lys Arg						
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ggtggaggcg gttcaggcgg aggtggcagc ggcggtggcg ggtcggacat ccagatgacc						
cagteteeat eeteeetgte tgeatetgta ggagaeegtg teaceateae ttgeegggea						
agtogtooga ttgggaogat gttaagttgg taccagoaga aaccagggaa agoooctaag						
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ggatctggga cagatttcac tctcaccatc agcagtctgc aacctgaaga ttttgctacg						
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<400> SEQUENCE: 317

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu 1 5 10 15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser 20 25 30
Ser Gly Ala Pro Pro Ser Gly Gly Gly Gly Gly Ser Gly Gly Gly 35 40 45
Gly Ser Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser 50 55 60
Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala 65 70 75 80
Ser Arg Pro Ile Gly Thr Met Leu Ser Trp Tyr Gln Gln Lys Pro Gly 85 90 95
Lys Ala Pro Lys Leu Leu Ile Leu Ala Phe Ser Arg Leu Gln Ser Gly 100 105 110
Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu 115 120 125
Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Ala 130 135 140
Gln Ala Gly Thr His Pro Thr Thr Phe Gly Gln Gly Thr Lys Val Glu 145 150 155 160
Ile Lys Arg
<210> SEQ ID NO 318 <211> LENGTH: 489 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence.
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qqtqqaqqcq qttcaqqcqq aqqtqqcaqc qqcqqtqqcq qqtcqqacat ccaqatqacc 180
cagtetecat ectecetyte tycatetyta ggagaeegty teaceateae ttycegygea 240
agtcgtccga ttgggacgat gttaagttgg taccagcaga aaccagggaa agcccctaag 300
ctcctgatcc ttgctttttc ccgtttgcaa agtggggtcc catcacgttt cagtggcagt 360
ggatetggga cagattteae teteaceate ageagtetge aacetgaaga ttttgetaeg 420
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<210> SEQ ID NO 319 <211> LENGTH: 114 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence.
<400> SEQUENCE: 319
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Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Trp Ile Gly Ser Gln 20 25 30
Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile 35 40 45

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Met Trp Arg Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly 50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro 65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Ala Gln Gly Leu Arg His Pro Lys 85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Gly Gly Gly Gly 100 105 110
Ser Cys
<210> SEQ ID NO 320 <211> LENGTH: 345 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence.
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gggaaageee etaageteet gateatgtgg egtteetegt tgeaaagtgg ggteeeatea 180
cgtttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240
gaagattttg ctacgtacta ctgtgctcag ggtttgaggc atcctaagac gttcggccaa 300
gggaccaagg tggaaatcaa acggggtggc ggagggggtt cctgt 345
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<400> SEQUENCE: 321
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Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Trp Ile Gly Ser Gln 20 25 30
Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Ile 35 40 45
Met Trp Arg Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly 50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro 65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Ala Gln Gly Leu Arg His Pro Lys 85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala 100 105 110
Pro Ser Cys 115
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atca	ctto	jaa é	gggca	aagto	ca gi	ggat	tggg	g tct	ccagt	tat	cttç	ggta	cca 🤉	gcaga	aaacca	1:	20		
ggga	aago	eee o	ctaaç	geteo	ct ga	atcat	gtgg	g cgt	cteet	cgt	tgca	aaagi	ad d	ggtco	ccatca	1	B 0		
cgtt	tcag	gtg g	gcagt	ggat	tc to	gggad	cagat	t t t d	cacto	ctca	ccat	ccago	cag 1	cctgo	caacct	24	40		
gaag	gattt	tg d	ctaco	gtact	ca ci	gtgo	ctcag	g ggt	ttga	agge	atco	ctaa	gac g	gttco	ggccaa	30	00		
ggga	iccaa	agg t	ggaa	aatca	aa a	cggad	ccgto	e get	gcto	ccat	cttç	gt				34	45		
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<400	/> 5E	QUEP	NCE:	323	a 1	G	G]	a]	a]	T		G]	Deve	G]	G]				
1	vai	GIN	Leu	ьeu 5	GIU	ser	GIY	GIY	СГУ 10	Leu	vai	GIN	Pro	15	GIY				
Ser	Leu	Arg	Leu 20	Ser	Суа	Ala	Ala	Ser 25	Gly	Phe	Thr	Phe	Asn 30	Arg	Tyr				
Ser	Met	Gly 35	Trp	Leu	Arg	Gln	Ala 40	Pro	Gly	Lys	Gly	Leu 45	Glu	Trp	Val				
Ser	Arg 50	Ile	Asp	Ser	Tyr	Gly 55	Arg	Gly	Thr	Tyr	Tyr 60	Glu	Asp	Pro	Val				
Lys 65	Gly	Arg	Phe	Ser	Ile 70	Ser	Arg	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80				
Leu	Gln	Met	Asn	Ser 85	Leu	Arg	Ala	Glu	Asp 90	Thr	Ala	Val	Tyr	Tyr 95	Сүз				
Ala	Lys	Ile	Ser 100	Gln	Phe	Gly	Ser	Asn 105	Ala	Phe	Asp	Tyr	Trp 110	Gly	Gln				
Gly	Thr	Gln 115	Val	Thr	Val	Ser	Ser 120	Ala	Ser	Thr	Ser	Gly 125	Pro	Ser	Asp				
Ile	Gln 130	Met	Thr	Gln	Ser	Pro 135	Ser	Ser	Leu	Ser	Ala 140	Ser	Val	Gly	Asp				
Arg 145	Val	Thr	Ile	Thr	Cys 150	Arg	Ala	Ser	Arg	Pro 155	Ile	Gly	Thr	Thr	Leu 160				
Ser	Trp	Tyr	Gln	Gln 165	Lys	Pro	Gly	Lys	Ala 170	Pro	Lys	Leu	Leu	Ile 175	Trp				
Phe	Gly	Ser	Arg 180	Leu	Gln	Ser	Gly	Val 185	Pro	Ser	Arg	Phe	Ser 190	Gly	Ser				
Gly	Ser	Gly 195	Thr	Asp	Phe	Thr	Leu 200	Thr	Ile	Ser	Ser	Leu 205	Gln	Pro	Glu				
Asp	Phe 210	Ala	Thr	Tyr	Tyr	Cys 215	Ala	Gln	Ala	Gly	Thr 220	His	Pro	Thr	Thr				
Phe 225	Gly	Gln	Gly	Thr	Lys 230	Val	Glu	Ile	Гла	Arg 235									
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Glu Val Gl
n Leu Leu Glu Ser Gly Gly Gly Leu Val Gl
n Pro Gly Gly

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1	_	_	_	5		_	_	_	10	_	_		_	15	_	_	 _	_	_	 _
Ser	Leu	Arg	Leu 20	Ser	Суз	Ala	Ala	Ser 25	Gly	Phe	Thr	Phe	Asn 30	Arg	Tyr					
Ser	Met	Gly 35	Trp	Leu	Arg	Gln	Ala 40	Pro	Gly	Lys	Gly	Leu 45	Glu	Trp	Val					
Ser	Arg 50	Ile	Asp	Ser	Tyr	Gly 55	Arg	Gly	Thr	Tyr	Tyr 60	Glu	Asp	Pro	Val					
Lys 65	Gly	Arg	Phe	Ser	Ile 70	Ser	Arg	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80					
Leu	Gln	Met	Asn	Ser 85	Leu	Arg	Ala	Glu	Asp 90	Thr	Ala	Val	Tyr	Tyr 95	Суз					
Ala	Lys	Ile	Ser 100	Gln	Phe	Gly	Ser	Asn 105	Ala	Phe	Asp	Tyr	Trp 110	Gly	Gln					
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Ile	Gln 130	Met	Thr	Gln	Ser	Pro 135	Ser	Ser	Leu	Ser	Ala 140	Ser	Val	Gly	Asp					
Arg 145	Val	Thr	Ile	Thr	Cys 150	Arg	Ala	Ser	Arg	Pro 155	Ile	Gly	Thr	Thr	Leu 160					
Ser	Trp	Tyr	Gln	Gln 165	Гла	Pro	Gly	Lys	Ala 170	Pro	ГЛа	Leu	Leu	Ile 175	Trp					
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Phe 225	Gly	Gln	Gly	Thr	Lys 230	Val	Glu	Ile	Гла	Arg 235	Ala	Ala	Ala	Glu	Gln 240					
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gage	gtgca	agc 1	tgtt	ggagi	tc tç	99999	gagg	c ttç	ggta	cagc	ctg	39999	gtc (cctgo	gtctc	60				
tcct	gtgo	cag (cctc	cggai	tt ca	accti	ttaai	z agę	gtata	agta	tgg	ggtgg	gct (ccgco	aggct	120				
ccaç	gggaa	agg g	gtcta	agagi	tg g	gtct	cacg	g ati	gati	cctt	atg	gtcgt	gg 1	tacat	actac	180				
gaaq	gacco	ccg I	tgaa	gggc	cg gi	ttca	gcat	c to	ccgcé	gaca	atto	ccaaç	gaa (cacgo	tgtat	240				
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ccagggaagg gtctagagtg ggtctcacgg	attgattett atggtegtgg taeataetae	180
gaagaccccg tgaagggccg gttcagcatc	teeegegaca atteeaagaa caegetgtat	240
ctgcaaatga acagcctgcg tgccgaggac	accgccgtat attactgtgc gaaaatttct	300
cagtttgggt caaatgcgtt tgactactgg	ggtcagggaa cccaggtcac cgtctcgagc	360
gctagcacca gtggtccatc ggacatccag	atgacccagt ctccatcctc cctgtctgca	420
tetgtaggag accgtgteac cateaettge	cgggcaagtc gtccgattgg gacgacgtta	480
agttggtacc agcagaaacc agggaaagcc	cctaagctcc tgatctggtt tggttcccgg	540
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accatcagca gtctgcaacc tgaagatttt	gctacgtact actgtgcgca ggctgggacg	660
catectaega egtteggeea agggaeeaag	gtggaaatca aacgggcggc cgcagaacaa	720
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Ser Leu Arg Leu Ser Cys Ala Ala S 20 2	er Gly Phe Thr Phe Asn Arg Tyr 5	
Ser Met Gly Trp Leu Arg Gln Ala P 35 40	ro Gly Lys Gly Leu Glu Trp Val 45	
Ser Arg Ile Asp Ser Tyr Gly Arg G 50 55	ly Thr Tyr Tyr Glu Asp Pro Val 60	
Lys Gly Arg Phe Ser Ile Ser Arg A 65 70	sp Asn Ser Lys Asn Thr Leu Tyr 75 80	
Leu Gln Met Asn Ser Leu Arg Ala G 85	lu Asp Thr Ala Val Tyr Tyr Cys 90 95	
Ala Lys Ile Ser Gln Phe Gly Ser A 100 1	sn Ala Phe Asp Tyr Trp Gly Gln 05 110	
Gly Thr Gln Val Thr Val Ser Ser A 115 120	la Ser Thr Ser Gly Pro Ser Asp 125	
Ile Gln Met Thr Gln Ser Pro Ser S 130 135	er Leu Ser Ala Ser Val Gly Asp 140	
Arg Val Thr Ile Thr Cys Arg Ala S 145 150	er Arg Pro Ile Gly Thr Met Leu 155 160	
Ser Trp Tyr Gln Gln Lys Pro Gly L	ys Ala Pro Lys Leu Leu Ile Leu	

				165					170					175	
Phe G	ly	Ser	Arg 180	Leu	Gln	Ser	Gly	Val 185	Pro	Ser	Arg	Phe	Ser 190	Gly	Ser
Gly S	er	Gly 195	Thr	Asp	Phe	Thr	Leu 200	Thr	Ile	Ser	Ser	Leu 205	Gln	Pro	Glu
Asp P 2	he 10	Ala	Thr	Tyr	Tyr	Cys 215	Ala	Gln	Ala	Gly	Thr 220	His	Pro	Thr	Thr
Phe G 225	ly	Gln	Gly	Thr	Lys 230	Val	Glu	Ile	Lys	Arg 235					
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Ser M	et	Gly 35	Trp	Leu	Arg	Gln	Ala 40	Pro	Gly	Lys	Gly	Leu 45	Glu	Trp	Val
Ser A 5	rg 0	Ile	Asp	Ser	Tyr	Gly 55	Arg	Gly	Thr	Tyr	Tyr 60	Glu	Asp	Pro	Val
Lys G 65	ly	Arg	Phe	Ser	Ile 70	Ser	Arg	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80
Leu G	ln	Met	Asn	Ser 85	Leu	Arg	Ala	Glu	Asp 90	Thr	Ala	Val	Tyr	Tyr 95	Cys
Ala L	Yв	Ile	Ser 100	Gln	Phe	Gly	Ser	Asn 105	Ala	Phe	Asp	Tyr	Trp 110	Gly	Gln
Gly T	hr	Gln 115	Val	Thr	Val	Ser	Ser 120	Ala	Ser	Thr	Ser	Gly 125	Pro	Ser	Asp
Ile G 1	ln 30	Met	Thr	Gln	Ser	Pro 135	Ser	Ser	Leu	Ser	Ala 140	Ser	Val	Gly	Asp
Arg V 145	al	Thr	Ile	Thr	Cys 150	Arg	Ala	Ser	Arg	Pro 155	Ile	Gly	Thr	Met	Leu 160
Ser T	rp	Tyr	Gln	Gln 165	ГЛа	Pro	Gly	Гла	Ala 170	Pro	ГЛа	Leu	Leu	Ile 175	Leu
Phe G	ly	Ser	Arg 180	Leu	Gln	Ser	Gly	Val 185	Pro	Ser	Arg	Phe	Ser 190	Gly	Ser
Gly S	er	Gly 195	Thr	Aap	Phe	Thr	Leu 200	Thr	Ile	Ser	Ser	Leu 205	Gln	Pro	Glu
Asp P 2	he 10	Ala	Thr	Tyr	Tyr	Cys 215	Ala	Gln	Ala	Gly	Thr 220	His	Pro	Thr	Thr
Phe G 225	ly	Gln	Gly	Thr	Lys 230	Val	Glu	Ile	Lys	Arg 235	Ala	Ala	Ala	Glu	Gln 240
Lys L	eu	Ile	Ser	Glu 245	Glu	Asp	Leu	Asn							
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<220> FEATURE:

<223> OTHER INFORMATION: Derived from a Human Germline sequence.

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ccagggaagg	gtctagagtg	ggtctcacgg	attgattctt	atggtcgtgg	tacatactac	180
gaagaccccg	tgaagggccg	gttcagcatc	tcccgcgaca	attccaagaa	cacgctgtat	240
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jctagcacca	gtggtccatc	ggacatccag	atgacccagt	ctccatcctc	cctgtctgca	420
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lccatcagca	gtctgcaacc	tgaagatttt	gctacgtact	actgtgcgca	ggctgggacg	660
atcctacga	cgttcggcca	agggaccaag	gtggaaatca	aacgg		705
210> SEQ : 211> LENG 212> TYPE 213> ORGAJ 220> FEAT 223> OTHEI 400> SECU	ID NO 330 TH: 750 : DNA NISM: Artif: JRE: R INFORMATIC ENCE: 330	icial Sequer DN: Derived	nce from a Huma	an Germline	sequence.	
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caddaaadd	atctagagta	aatataaaa	ayytatayta	ataataataa	tagatagtag	180
aadaccccd	taaaaaacca	attcadcatc	teccacaca	attccaacaa	cacactatat	240
tagaeeeeg	acadectded	taccasaaa	accoccotat	attactotoc	gaaaatttet	300
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attaataaa	accycyccac	accactige	aataaaataa	tastattatt	taattaaaaa	400 E40
taassata	agcagaaacc	agggaaagee	agazatagat	atagaagaa	tttapatata	600
aastasaas	gggteecate	tappastttt	ggcagtggat	cuyyyacaya	ggatggaag	660
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ateetaega	egileggeea	agggaccaag	glggaaalca	aacggggegge	egeagaacaa	720
laacteatet	Cagaagagga	lClyaallaa				/50
210> SEQ 3 211> LENG 212> TYPE 213> ORGAI 220> FEAT 223> OTHE	ID NO 331 TH: 235 : PRT NISM: Artif: JRE: R INFORMATI(icial Seque DN: Derived	nce from a Huma	an Germline	sequence.	
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Ser Leu Arg	g Leu Ser Cy 20	ys Ala Ala :	Ser Gly Phe 25	Thr Phe Ası 30	n Arg Tyr	

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Ser	Arg 50	Ile	Asp	Ser	Tyr	Gly 55	Arg	Gly	Thr	Tyr	Tyr 60	Glu	Asp	Pro	Val
Lys 65	Gly	Arg	Phe	Ser	Ile 70	Ser	Arg	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80
Leu	Gln	Met	Asn	Ser 85	Leu	Arg	Ala	Glu	Asp 90	Thr	Ala	Val	Tyr	Tyr 95	Сув
Ala	Lys	Ile	Ser 100	Gln	Phe	Gly	Ser	Asn 105	Ala	Phe	Asp	Tyr	Trp 110	Gly	Gln
Gly	Thr	Gln 115	Val	Thr	Val	Ser	Ser 120	Ala	Ser	Thr	Ser	Gly 125	Pro	Ser	Азр
Ile	Gln 130	Met	Thr	Gln	Ser	Pro 135	Ser	Ser	Leu	Ser	Ala 140	Ser	Val	Gly	Aap
Arg 145	Val	Thr	Ile	Thr	Cys 150	Arg	Ala	Ser	Arg	Pro 155	Ile	Gly	Thr	Met	Leu 160
Ser	Trp	Tyr	Gln	Gln 165	Lys	Pro	Gly	Lys	Ala 170	Pro	Lys	Leu	Leu	Ile 175	Leu
Ala	Phe	Ser	Arg 180	Leu	Gln	Ser	Gly	Val 185	Pro	Ser	Arg	Phe	Ser 190	Gly	Ser
Gly	Ser	Gly 195	Thr	Asp	Phe	Thr	Leu 200	Thr	Ile	Ser	Ser	Leu 205	Gln	Pro	Glu
Asp 2	Phe 2 10	Ala	Thr	Tyr	Tyr	Cys 215	Ala	Gln	Ala	Gly	Thr 220	His	Pro	Thr	Thr
Phe 225	Gly	Gln	Gly	Thr	Lys 230	Val	Glu	Ile	Lys	Arg 235					
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Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Leu 165 170 175	
Ala Phe Ser Arg Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser 180 185 190	
Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu 195 200 205	
Asp Phe Ala Thr Tyr Tyr Cys Ala Gln Ala Gly Thr His Pro Thr Thr 2 10 215 220	
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agttggtacc agcagaaacc agggaaagcc cctaagctcc tgatccttgc tttttcccgt	540
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accatcagca gtctgcaacc tgaagatttt gctacgtact actgcgcgca ggctgggacg	660
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ccagggaagg gtctagagtg ggtctcacgg attgattctt atggtcgtgg tacatactac	180
gaagaccccg tgaagggccg gttcagcatc tcccgcgaca attccaagaa cacgctgtat	240
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cagtttgggt caaatgcgtt tgactactgg ggtcagggaa cccaggtcac cgtctcgagc	360
gctagcacca gtggtccatc ggacatccag atgacccagt ctccatcctc cctgtctgca	420
tctgtaggag accgtgtcac catcacttgc cgggcaagtc gtccgattgg gacgatgtta	480
agttggtacc agcagaaacc agggaaagcc cctaagctcc tgatccttgc tttttcccgt	540

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ttgcaaagtg gggtcccatc acgtttcagt ggcagtggat ctgggacaga tttcactctc 600
accatcagca gtctgcaacc tgaagatttt gctacgtact actgcgcgca ggctgggacg 660
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gaggagtttg gcaaccagtt ccaaaaggct gaaaccatcc ctgtcctcca tgagatgatc	180
cagcagatet teaatetett cagcacaaag gaeteatetg etgettggga tgagaeeete	240
ctagacaaat tctacactga actctaccag cagctgaatg acctggaagc ctgtgtgata	300
cagggggtgg gggtgacaga gactcccctg atgaaggagg actccattct ggctgtgagg	360
aaatacttcc aaagaatcac tctctatctg aaagagaaga aatacagccc ttgtgcctgg	420
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Gly Ser Thr Gly 20	
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Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp 20 25 30	
Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln 35 40 45	
Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe 50 55 60	
Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu 65 70 75 80	
Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu 85 90 95	
Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys 100 105 110	

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Glu	Asp	Ser 115	Ile	Leu	Ala	Val	Arg 120	Lys	Tyr	Phe	Gln	Arg 125	Ile	Thr	Leu	
Tyr	Leu 130	Lys	Glu	Lys	Lys	Tyr 135	Ser	Pro	Сув	Ala	Trp 140	Glu	Val	Val	Arg	
Ala 145	Glu	Ile	Met	Arg	Ser 150	Phe	Ser	Leu	Ser	Thr 155	Asn	Leu	Gln	Glu	Ser 160	
Leu	Arg	Ser	ГЛЗ	Glu 165	Thr	Val	Ala	Ala	Pro 170	Ser	Asp	Ile	Gln	Met 175	Thr	
Gln	Ser	Pro	Ser 180	Ser	Leu	Ser	Ala	Ser 185	Val	Gly	Asp	Arg	Val 190	Thr	Ile	
Thr	Cys	Arg 195	Ala	Ser	Gln	Trp	Ile 200	Gly	Ser	Gln	Leu	Ser 205	Trp	Tyr	Gln	
Gln	Lys 210	Pro	Gly	гла	Ala	Pro 215	Lys	Leu	Leu	Ile	Met 220	Trp	Arg	Ser	Ser	
Leu 225	Gln	Ser	Gly	Val	Pro 230	Ser	Arg	Phe	Ser	Gly 235	Ser	Gly	Ser	Gly	Thr 240	
Asp	Phe	Thr	Leu	Thr 245	Ile	Ser	Ser	Leu	Gln 250	Pro	Glu	Asb	Phe	Ala 255	Thr	
Tyr	Tyr	Cys	Ala 260	Gln	Gly	Ala	Ala	Leu 265	Pro	Arg	Thr	Phe	Gly 270	Gln	Gly	
Thr	Lys	Val 275	Glu	Ile	Lys	Arg	Ala 280	Ala	Ala	Glu	Gln	Lys 285	Leu	Ile	Ser	
Glu	Glu 290	Asp	Leu	Asn												
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atgo	gtag	jaa 1	LLCC	ttgi		CCLE	gteta	a aag	ggaco	gtc	acga	actto	cgg a	attec	ctcag	g 120
gaag	Jagti	und d	gaaad	caat		caaaa	agca	i gaa	acta	acco	ctgi	tette	jca (rgaaa	atgato	2 180
t ago	adau	at i	tota	racto		tat	adag	y gao	ata	.cay	atat	- ada	yya i	taa	actety attatt	- 200
cade	atat	aa d	raatt	acto	ja a	acto	recta	a ato	naaad	iaeg	atto	raatt	ige i	adda	ittag	360
aaat	actt	tc a	aqcqt	tatca	ac at	tqta	attta	a aad	qaaa	aqa	aata	actco	ccc a	atqto	qcatqo	420
gago	gtggt	ta 🤉	gagca	agaaa	at ta	atgag	gtco	tto	ctcto	ttt	ctad	cgaat	tt o	gcaag	gaatct	- : 480
ttga	agato	ta a	aggaa	aacco	gt co	getge	ctcca	a tct	gaca	atcc	agat	gaco	cca g	gtete	catco	c 540
tccc	tgto	tg «	catct	gtag	gg ag	gacco	gtgto	c acc	catca	actt	gcco	gggca	aag 1	tcagt	ggatt	: 600
gggt	ctca	igt 1	tatct	tggt	ta co	cagea	agaaa	a cca	aggga	aag	cccc	ctaaç	gct (cctga	atcato	g 660
tgga	gtto	ct d	cgttg	gcaaa	ag to	ggggt	ccca	a tca	acgtt	tca	gtgg	gcagt	agg a	atcto	ggaca	a 720
gatt	tcad	etc 1	tcaco	catca	ag ca	agtct	gcaa	a cct	gaag	gatt	ttgo	ctaco	gta (ctact	gtget	. 780
cago	ggtgo	gg (gttg	geeta	ag ga	acgtt	cggo	c caa	aggga	acca	aggt	cggaa	aat (caaad	gggcg	g 840
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<210> SEQ ID NO 386

415

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Leu	Leu	Ala	Gln 20	Met	Arg	Arg	Ile	Ser 25	Leu	Phe	Ser	Сув	Leu 30	Lys	Asp	
Arg	His	Asp 35	Phe	Gly	Phe	Pro	Gln 40	Glu	Glu	Phe	Gly	Asn 45	Gln	Phe	Gln	
Lys	Ala 50	Glu	Thr	Ile	Pro	Val 55	Leu	His	Glu	Met	Ile 60	Gln	Gln	Ile	Phe	
Asn 65	Leu	Phe	Ser	Thr	Lys 70	Asp	Ser	Ser	Ala	Ala 75	Trp	Asp	Glu	Thr	Leu 80	
Leu	Asp	Lys	Phe	Tyr 85	Thr	Glu	Leu	Tyr	Gln 90	Gln	Leu	Asn	Asp	Leu 95	Glu	
Ala	Суз	Val	Ile 100	Gln	Gly	Val	Gly	Val 105	Thr	Glu	Thr	Pro	Leu 110	Met	Lys	
Glu	Asp	Ser 115	Ile	Leu	Ala	Val	Arg 120	Lys	Tyr	Phe	Gln	Arg 125	Ile	Thr	Leu	
Tyr	Leu 130	Lys	Glu	Lys	Lys	Tyr 135	Ser	Pro	Сув	Ala	Trp 140	Glu	Val	Val	Arg	
Ala 145	Glu	Ile	Met	Arg	Ser 150	Phe	Ser	Leu	Ser	Thr 155	Asn	Leu	Gln	Glu	Ser 160	
Leu	Arg	Ser	Lys	Glu 165	Thr	Val	Ala	Ala	Pro 170	Ser	Asp	Ile	Gln	Met 175	Thr	
Gln	Ser	Pro	Ser 180	Ser	Leu	Ser	Ala	Ser 185	Val	Gly	Asp	Arg	Val 190	Thr	Ile	
Thr	Суз	Arg 195	Ala	Ser	Gln	Trp	Ile 200	Gly	Ser	Gln	Leu	Ser 205	Trp	Tyr	Gln	
Gln	Lys 210	Pro	Gly	Lys	Ala	Pro 215	Lys	Leu	Leu	Ile	Met 220	Trp	Arg	Ser	Ser	
Leu 225	Gln	Ser	Gly	Val	Pro 230	Ser	Arg	Phe	Ser	Gly 235	Ser	Gly	Ser	Gly	Thr 240	
Asp	Phe	Thr	Leu	Thr 245	Ile	Ser	Ser	Leu	Gln 250	Pro	Glu	Asp	Phe	Ala 255	Thr	
Tyr	Tyr	Суз	Ala 260	Gln	Gly	Ala	Ala	Leu 265	Pro	Arg	Thr	Phe	Gly 270	Gln	Gly	
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atgo	cgtaq	gaa 1	tttc	ttgi	t ci	cctt	gtcta	a aaq	ggaco	cgtc	acga	actt	cgg a	attco	cctcag	120
gaa	gagti	tg 🤉	gaaa	ccaat	t c	caaaa	aagca	a gaa	aacta	attc	ctg	tett	gca (cgaaa	atgatc	180
cago	caaat	at 1	tcaa	ttgi	t ti	ccta	caaaq	g gad	ctcat	cag	ccg	cttg	gga 1	tgaaa	actctg	240
a ont invod																
-------------	--															
-continued																

ttagataaa	t tcta	cactg	ja ac	ctata	atcaa	a caa	actga	aacg	atct	agag	ggc t	tgcg	gttatt	300		
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gggteteag	t tatci	ttggt	a co	cagca	igaaa	a cca	aggga	aaag	ccco	ctaag	get d	cctga	atcatg	660		
tggcgttcc	t cgtto	gcaaa	ng to	ggggt	ccca	a tca	acgtt	tca	gtg	gcagt	agg a	atcto	Iggaca	720		
gatttcact	c tcac	catca	ig ca	agtct	gcaa	a cct	gaag	gatt	ttgo	ctace	gta d	ctact	gtget	780		
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<400> SEQ	OENCE:	388	The	Uia	Cor	Lou	cly	Corr	7 * 0	7.200	The	Lou	Mot			
сув Авр Ц 1	eu Pro	5	1111	HIS	Ser	Leu	10	ser	Arg	Arg	1111	15	Met			
Leu Leu A	la Gln 20	Met	Arg	Arg	Ile	Ser 25	Leu	Phe	Ser	Сүз	Leu 30	Lys	Aap			
Arg His A 3	sp Phe 5	Gly	Phe	Pro	Gln 40	Glu	Glu	Phe	Gly	Asn 45	Gln	Phe	Gln			
Lys Ala G 50	lu Thr	Ile	Pro	Val 55	Leu	His	Glu	Met	Ile 60	Gln	Gln	Ile	Phe			
Asn Leu Pl 65	he Ser	Thr	Lys 70	Asp	Ser	Ser	Ala	Ala 75	Trp	Asp	Glu	Thr	Leu 80			
Leu Asp Ly	ys Phe	Tyr 85	Thr	Glu	Leu	Tyr	Gln 90	Gln	Leu	Asn	Asp	Leu 95	Glu			
Ala Cys Va	al Ile 100	Gln	Gly	Val	Gly	Val 105	Thr	Glu	Thr	Pro	Leu 110	Met	Lys			
Glu Asp So 11	er Ile 15	Leu	Ala	Val	Arg 120	Lys	Tyr	Phe	Gln	Arg 125	Ile	Thr	Leu			
Tyr Leu Ly 130	ys Glu	Lys	Lys	Tyr 135	Ser	Pro	Суз	Ala	Trp 140	Glu	Val	Val	Arg			
Ala Glu I 145	le Met	Arg	Ser 150	Phe	Ser	Leu	Ser	Thr 155	Asn	Leu	Gln	Glu	Ser 160			
Leu Arg Se	er Lys	Glu 165	Thr	Val	Ala	Ala	Pro	Ser	Asp	Ile	Gln	Met	Thr			
Gln Ser P:	ro Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly	Asp	Arg	Val	Thr	Ile			
Thr Cys A:	rg Ala	Ser	Gln	Trp	Ile	Gly	Ser	Gln	Leu	Ser	Trp	Tyr	Gln			
1: Gln Lys P:	95 ro Gly	Lys	Ala	Pro	200 Lys	Leu	Leu	Ile	Met	205 Trp	Arg	Ser	Ser			
210	or Cl	-	Dro	215	-	Dh c	5	<i>с</i> 1	220	-	e	C1	Thr			
Leu Gin S 225	er GIY	vai	Pro 230	ser	Arg	rne	ser	сту 235	Ser	сту	ser	сту	240			
Asp Phe T	hr Leu	Thr 245	Ile	Ser	Ser	Leu	Gln 250	Pro	Glu	Asp	Phe	Ala 255	Thr			

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Tyr Tyr Cys Ala Gln Gly Leu Arg His Pro Lys Thr Phe Gly Gln Gly	
275 280 285	
Glu Glu Asp Leu Asn 290	
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cagcaaatat tcaatttgtt ttctacaaag gactcatcag ccgcttggga tgaaactctg	240
ttagataaat tctacactga actatatcaa caactgaacg atctagaggc ttgcgttatt	300
cagggtgtag gagttactga aactccccta atgaaagaag attcaattct agccgttaga	360
aaatactttc agcgtatcac attgtattta aaggaaaaga aatactcccc atgtgcatgg	420
gaggtggtta gagcagaaat tatgaggtcc ttctctcttt ctacgaattt gcaagaatct	480
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gggtctcagt tatcttggta ccagcagaaa ccagggaaag cccctaagct cctgatcatg	660
tggcgttcct cgttgcaaag tggggtccca tcacgtttca gtggcagtgg atctgggaca	720
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Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp 20 25 30	
Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln 35 40 45	
Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe 50 55 60	
Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu 65 70 75 80	
Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu 85 90 95	
Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys 100 105 110	

Glu	Asp	Ser 115	Ile	Leu	Ala	Val	Arg 120	Lys	Tyr	Phe	Gln	Arg 125	Ile	Thr	Leu	
Tyr	Leu 130	Lys	Glu	Lys	Lys	Tyr 135	Ser	Pro	Сув	Ala	Trp 140	Glu	Val	Val	Arg	
Ala 145	Glu	Ile	Met	Arg	Ser 150	Phe	Ser	Leu	Ser	Thr 155	Asn	Leu	Gln	Glu	Ser 160	
Leu	Arg	Ser	Lys	Glu 165	Thr	Val	Ala	Ala	Pro 170	Ser	Asp	Ile	Gln	Met 175	Thr	
Gln	Ser	Pro	Ser 180	Ser	Leu	Ser	Ala	Ser 185	Val	Gly	Asp	Arg	Val 190	Thr	Ile	
Thr	Суз	Arg 195	Ala	Ser	Gln	Trp	Ile 200	Gly	Ser	Gln	Leu	Ser 205	Trp	Tyr	Gln	
Gln	Lys 210	Pro	Gly	Lys	Ala	Pro 215	Lys	Leu	Leu	Ile	Met 220	Trp	Arg	Ser	Ser	
Leu 225	Gln	Ser	Gly	Val	Pro 230	Ser	Arg	Phe	Ser	Gly 235	Ser	Gly	Ser	Gly	Thr 240	
Asp	Phe	Thr	Leu	Thr 245	Ile	Ser	Ser	Leu	Gln 250	Pro	Glu	Asp	Phe	Ala 255	Thr	
Tyr	Tyr	Сув	Ala 260	Gln	Gly	Leu	Arg	His 265	Pro	Lys	Thr	Phe	Gly 270	Gln	Gly	
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cago	caaat	at t	tcaat	ttgi	ct tt	ccta	caaaq	g gao	ctcat	cag	ccgo	ttg	gga 1	tgaaa	actctg	240
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cago	ıgtgt	ag g	gagti	cact	ga aa	actco	cccta	a ato	jaaag	gaag	atto	caati	cct a	ageco	gttaga	360
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ttga	agato	ta a	aggaa	aacco	gt co	getgo	eteca	a tct	gaca	atcc	agat	gaco	cca g	gtcto	ccatcc	540
tccc	tgto	etg d	catct	gtaq	gg ag	gacco	gtgto	c acc	catca	actt	gccó	addc:	aag 1	tcagt	ggatt	600
gggt	ctca	agt t	tatct	tggi	ta co	cagea	agaaa	a cca	ıggga	aaag	ccco	taa	get (cctga	atcatg	660
tggo	gtto	cct d	cgtto	gcaaa	ag to	ggggt	cccca	a tca	acgtt	tca	gtgg	gcagi	gg a	atcto	gggaca	720
gatt	tcad	etc t	tcaco	catca	ag ca	agtci	cgcaa	a cct	gaag	gatt	ttgo	tace	gta	ctact	gtget	780
cago	ygtti	ga g	ggcat	ccta	aa ga	acgti	cggo	c caa	aggga	acca	aggt	ggaa	aat (caaa	cgg	837
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<223> OTHER INFORMATION: Derived from a Human Germline sequence.

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

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

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

<400> SEQUENCE: 392

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu 115 120 125 Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu Arg Ser Lys Glu Thr Val Ala Ala Pro Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Trp Ile Gly Ser Gln Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Met Trp Arg Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Ala Gln Gly Leu Met Lys Pro Met Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Ala Ala Ala Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asn <210> SEQ ID NO 393 <211> LENGTH: 882 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEQUENCE: 393 tgcgacttgc cacagacaca tagtttggga tcaagaagaa cattgatgtt attagcacaa atgcgtagaa tttctttgtt ctcttgtcta aaggaccgtc acgacttcgg attccctcag qaaqaqtttq qaaaccaatt ccaaaaaqca qaaactattc ctqtcttqca cqaaatqatc cagcaaatat tcaatttgtt ttctacaaag gactcatcag ccgcttggga tgaaactctg ttaqataaat tctacactqa actatatcaa caactqaacq atctaqaqqc ttqcqttatt

425

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ttgagateta aggaaaeegt egetgeteea tetgaeatee agatgaeeea gteteeatee 540
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gggteteagt tatettggta eeageagaaa eeagggaaag eeeetaaget eetgateatg 660
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gatttcactc tcaccatcag cagtctgcaa cctgaagatt ttgctacgta ctactgtgct 780
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Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe 50 55 60
Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu 65 70 75 80
Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu 85 90 95
Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys 100 105 110
Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu 115 120 125
Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg 130 135 140
Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser 145 150 155 160
Leu Arg Ser Lys Glu Thr Val Ala Ala Pro Ser Asp Ile Gln Met Thr 165 170 175
Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile 180 185 190
Thr Cys Arg Ala Ser Gln Trp Ile Gly Ser Gln Leu Ser Trp Tyr Gln 195 200 205
Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Met Trp Arg Ser Ser 210 215 220
Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr 225 230 235 240
Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr 245 250 255

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Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln 35 40 45	
Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe 50 55 60	
Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu 65 70 75 80	
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Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu 115 120 125	

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Ser (Cys	Arg 195	Ala	Ser	Gln	Trp	Ile 200	Gly	Ser	Gln	Leu	Ser 205	Trp	Tyr	Gln	
Gln I	Lуз 210	Pro	Gly	Glu	Ala	Pro 215	Lys	Leu	Leu	Ile	Met 220	Trp	Arg	Ser	Ser	
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Arg	His	Asp 35	Phe	Gly	Phe	Pro	Gln 40	Glu	Glu	Phe	Gly	Asn 45	Gln	Phe	Gln				
Lys	Ala 50	Glu	Thr	Ile	Pro	Val 55	Leu	His	Glu	Met	Ile 60	Gln	Gln	Ile	Phe				
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Leu	Asp	Lys	Phe	Tyr 85	Thr	Glu	Leu	Tyr	Gln 90	Gln	Leu	Asn	Asp	Leu 95	Glu				
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Glu	Asp	Ser 115	Ile	Leu	Ala	Val	Arg 120	Lys	Tyr	Phe	Gln	Arg 125	Ile	Thr	Leu				
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Ala 145	Glu	Ile	Met	Arg	Ser 150	Phe	Ser	Leu	Ser	Thr 155	Asn	Leu	Gln	Glu	Ser 160				
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Gln	Lys 210	Pro	Gly	Lys	Ala	Pro 215	Lys	Leu	Leu	Ile	Trp 220	Phe	Gly	Ser	Arg				
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 Ser Ser Ala Ala Tr
p Asp Glu Thr Leu 65 70 75 80 Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gl
n Gln Leu Asn Asp Leu Glu 85 90 95 Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys 100 105 110 Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu 115 120 125 Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg

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130 135 140 Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser 145 150 155 160 Leu Arg Ser Lys Glu Thr Val Ala Ala Pro Ser Asp Ile Gln Met Thr 165 170 175 Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile 180 185 190 Thr Cys Arg Ala Ser Arg Pro Ile Gly Thr Thr Leu Ser Trp Tyr Gln 195 200 205 Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Trp Phe Gly Ser Arg 210 215 220 Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr 225 230 235 240 Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr 250 255 245 Tyr Tyr Cys Ala Gln Ala Gly Thr His Pro Thr Thr Phe Gly Gln Gly 260 265 270 Thr Lys Val Glu Ile Lys Arg 275 <210> SEQ ID NO 403 <211> LENGTH: 837 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEQUENCE: 403 tgcgacttgc cacagacaca tagtttggga tcaagaagaa cattgatgtt attagcacaa 60 atgcgtagaa tttctttgtt ctcttgtcta aaggaccgtc acgacttcgg attccctcag 120 gaagagtttg gaaaccaatt ccaaaaagca gaaactattc ctgtcttgca cgaaatgatc 180 cagcaaatat tcaatttgtt ttctacaaag gactcatcag ccgcttggga tgaaactctg 240 ttagataaat tctacactga actatatcaa caactgaacg atctagaggc ttgcgttatt 300 cagggtgtag gagttactga aactccccta atgaaagaag attcaattct agccgttaga 360 aaatactttc agcgtatcac attgtattta aaggaaaaga aatactcccc atgtgcatgg 420 gaggtggtta gagcagaaat tatgaggtcc ttctctcttt ctacgaattt gcaagaatct 480 ttgagateta aggaaacegt egetgeteea tetgacatee agatgaeeea gteteeatee 540 tccctgtctg catctgtagg agaccgtgtc accatcactt gccgggcaag tcgtccgatt 600 gggacgacgt taagttggta ccagcagaaa ccagggaaag cccctaagct cctgatctgg 660 tttqqttccc qqttqcaaaq tqqqqtccca tcacqtttca qtqqcaqtqq atctqqqaca 720 gatttcactc tcaccatcag cagtctgcaa cctgaagatt ttgctacgta ctactgtgcg 780 837 caggetggga egeateetae gaegttegge caagggaeea aggtggaaat caaaegg <210> SEQ ID NO 404 <211> LENGTH: 293 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence. <400> SEOUENCE: 404 Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met 5 1 10 15

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Arg	His	Asp 35	Phe	Gly	Phe	Pro	Gln 40	Glu	Glu	Phe	Gly	Asn 45	Gln	Phe	Gln
Lys	Ala 50	Glu	Thr	Ile	Pro	Val 55	Leu	His	Glu	Met	Ile 60	Gln	Gln	Ile	Phe
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Leu	Aap	Lys	Phe	Tyr 85	Thr	Glu	Leu	Tyr	Gln 90	Gln	Leu	Asn	Aap	Leu 95	Glu
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Glu	Asp	Ser 115	Ile	Leu	Ala	Val	Arg 120	Lys	Tyr	Phe	Gln	Arg 125	Ile	Thr	Leu
Tyr	Leu 130	ГЛа	Glu	ГЛа	Lya	Tyr 135	Ser	Pro	Сув	Ala	Trp 140	Glu	Val	Val	Arg
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Gln	Ser	Pro	Ser 180	Ser	Leu	Ser	Ala	Ser 185	Val	Gly	Asp	Arg	Val 190	Thr	Ile
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Gln	Lys 210	Pro	Gly	Гла	Ala	Pro 215	Lys	Leu	Leu	Ile	Leu 220	Phe	Gly	Ser	Arg
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cag	gctg	gga d	cgcat	tccta	ac ga	acgti	tcggo	c caa	aggga	acca	aggi	tggaa	aat d	caaad	gggggg	g 840
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Arg	His	Asp 35	Phe	Gly	Phe	Pro	Gln 40	Glu	Glu	Phe	Gly	Asn 45	Gln	Phe	Gln	
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Leu	Asp	Lys	Phe	Tyr 85	Thr	Glu	Leu	Tyr	Gln 90	Gln	Leu	Asn	Asp	Leu 95	Glu	
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Leu	Arg	Ser	Lys	Glu 165	Thr	Val	Ala	Ala	Pro 170	Ser	Asp	Ile	Gln	Met 175	Thr	
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Gln	Lys 210	Pro	Gly	Lys	Ala	Pro 215	Lys	Leu	Leu	Ile	Leu 220	Phe	Gly	Ser	Arg	
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Asp	Phe	Thr	Leu	Thr 245	Ile	Ser	Ser	Leu	Gln 250	Pro	Glu	Asp	Phe	Ala 255	Thr	
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Leu Arg Ser Lys Glu Thr Val Ala Ala Pro Ser Asp Ile Gln Met Thr 165 170 175	
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Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Leu Ala Phe Ser Arg 210 215 220	
Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr 225 230 235 240	
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Tyr Tyr Cys Ala Gln Ala Gly Thr His Pro Thr Thr Phe Gly Gln Gly 260 265 270	
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cagggtgtag gagttactga aactccccta atgaaagaag attcaattct agccgttaga	360
aaatactttc agcgtatcac attgtattta aaggaaaaga aatactcccc atgtgcatgg	420
gaggtggtta gagcagaaat tatgaggtcc ttctctcttt ctacgaattt gcaagaatct	480
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gatttcactc tcaccatcag cagtctgcaa cctgaagatt ttgctacgta ctactgcgcg	780
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Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asr 35 40 45	n Gln Phe Gln						
Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Glr 50 55 60	n Gln Ile Phe						
Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp 65 70 75	o Glu Thr Leu 80						
Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asr 85 90	n Asp Leu Glu 95						
Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro 100 105	D Leu Met Lys 110						
Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg 115 120 125	g Ile Thr Leu 5						
Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu 130 135 140	ı Val Val Arg						
Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu 145 150 155	ı Gln Glu Ser 160						
Leu Arg Ser Lys Glu Thr Val Ala Ala Pro Ser Asp Ile 165 170	e Gln Met Thr 175						
Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg 180 185	y Val Thr Ile 190						
Thr Cys Arg Ala Ser Arg Pro Ile Gly Thr Met Leu Ser 195 200 205	Trp Tyr Gln						
Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Leu Ala 210 215 220	a Phe Ser Arg						
Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly 225 230 235	v Ser Gly Thr 240						
Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp 245 250	9 Phe Ala Thr 255						
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teeetgtetg catetgtagg agacegtgte accateaett geegggeaag tegteegatt	600
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Met Trp Arg Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly 50 55 60	
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro65707580	
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<212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Derived from a Human Germline sequence.

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Thr Val Ala Ala Pro Ser 1 5

The invention claimed is:

1. An anti-serum albumin (SA) immunoglobulin single variable domain variant of SEQ ID NO: 421, wherein the variant comprises a CDR1 amino acid sequence as shown in SEQ ID NO: 344, a CDR2 amino acid sequence as shown in SEQ ID NO: 345, and a CDR3 amino acid sequence as shown in SEQ ID NO: 346.

2. An anti-serum albumin (SA) immunoglobulin single variable domain variant of SEQ ID NO: 421, wherein the ²⁰ variant comprises an amino acid sequence that is identical to the amino acid sequence of SEQ ID NO: 2.

3. The variant of claim 1, wherein the variant comprises a binding site that specifically binds human SA with a dissociation constant (KD) of from about 0.1 to about 10000 25 nM, optionally from about 1 to about 6000 nM, as determined by surface plasmon resonance.

4. The variant of claim **1**, wherein the variant comprises a binding site that specifically binds human SA with an off-rate constant (K_d) of from about 1.5×10^{-4} to about 0.1 ³⁰ sec⁻¹, optionally from about 3×10^{-4} to about 0.1 sec⁻¹ as determined by surface plasmon resonance.

5. The variant of claim 1, wherein the variant comprises a binding site that specifically binds human SA with an on-rate constant (K_a) of from about 2×10⁶ to about 1×10⁴ ³⁵ M^{-1} sec⁻¹, optionally from about 1×10⁶ to about 2×10⁴ M^{-1} sec⁻¹ as determined by surface plasmon resonance.

6. The variant of claim **1**, wherein the variant comprises a binding site that specifically binds Cynomolgus monkey SA with a dissociation constant (KD) of from about 0.1 to ⁴⁰ about 10000 nM, optionally from about 1 to about 6000 nM, as determined by surface plasmon resonance.

7. The variant of claim 1, wherein the variant comprises a binding site that specifically binds Cynomolgus monkey SA with an off-rate constant (K_d) of from about 1.5×10^{-4} to about 0.1 sec⁻¹, optionally from about 3×10^{-4} to about 0.1 sec⁻¹ as determined by surface plasmon resonance.

8. The variant of claim **1**, wherein the variant comprises a binding site that specifically binds Cynomolgus monkey SA with an on-rate constant (K_a) of from about 2×10^6 to about 1×10^4 M⁻¹ sec⁻¹, optionally from about 1×10^6 to about 5×10^3 M⁻¹ sec⁻¹ as determined by surface plasmon resonance.

9. A multispecific ligand comprising an anti-SA variant of claim **1** and a binding moiety that specifically binds a target antigen other than SA.

10. The anti-serum albumin (SA) immunoglobulin single variable domain variant of claim **1**, wherein the variable domain is conjugated to an NCE drug.

11. A composition comprising a variant of claim **1** and a pharmaceutically acceptable diluent, carrier, excipient or vehicle.

12. A nucleic acid comprising a nucleotide sequence encoding a variant according to claim **1**.

13. A nucleic acid comprising the nucleotide sequence of SEQ ID NO: 7.

14. A vector comprising the nucleic acid of claim 12.

15. An isolated host cell comprising the vector of claim 14.

16. A nucleic acid comprising a nucleotide sequence encoding a variant according to claim **2**.

* * * * *